Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital
Foreword

The second report of session 2004-5 of The House of Commons Health Committee ‘The Prevention of Venous Thromboembolism in Hospitalised Patients’ opens with these worrying statistics: Each year 25,000 people in the UK die from venous thromboembolism. This figure includes both patients admitted for medical care of serious illnesses, as well as, those admitted for surgery. The report goes on to state that this is a larger number of deaths than are attributable to breast cancer, AIDS and road traffic accidents combined. It is 25 times the number of people who die as a result of MRSA infection 286.

The sudden killer is pulmonary embolism (PE). That is a thrombus (or blood clot) which forms in the lower limb or pelvic veins and then comes loose and is carried in the blood to lodge in the lungs. Acute massive pulmonary embolism often kills immediately. If the patient survives the immediate haemodynamic consequences, death may still ensue in the days or weeks that follow. Survivors of the initial event may eventually recover after a protracted hospital course including some time in intensive care.

Deep vein thrombosis (DVT) is in itself a cause of substantial morbidity and may lead to the development of post thrombotic syndrome (PTS) with chronic swelling and ulceration of the legs amongst its manifestations. Add this burden of morbidity to the estimated 25,000 deaths and it becomes a massive health problem. This is the perception of the situation as presented to the Health Committee, the CMO by expert advisors and patient representatives.

Many of these deaths are in patients admitted for medical care but some have gone into hospital for a planned surgical operation such as joint replacement, gynaecological surgery or gall bladder removal intended to improve their quality of life, or for a cancer operation with the hope of cure. Characteristically it is several weeks after surgery, when recovery is in sight that this tragedy strikes. Our guideline covers all patients admitted to hospital and includes patients having surgery in day-case facilities. The magnitude of risk of venous thromboembolism (VTE) is dependent upon factors inherent in the operation and factors related to the individual patient. It is the combination of these factors which defines certain patients as at increased risk of VTE. A key part of this guidance is systematic risk assessment of all patients either on admission in the case of emergencies or prior to admission for planned surgery. This evaluation must be repeated regularly during a hospital stay because the balance of risks of bleeding and of VTE change as the condition of the patient changes. The part of our work relating to risk assessment has been done in close collaboration with the Department of Health and the Chief Medical Officer’s VTE Working Group as part of the national VTE prevention strategy.
Surgeons have been acutely aware of the dangers of VTE and have been central to research from the 1970s and 1980s. Physical methods (such as graduated compression/anti-embolism stockings, foot impulse and intermittent pneumatic compression devices) and pharmacological treatments (such as heparin and warfarin) have been studied in a plethora of randomised trials. Both physical and pharmacological treatments have been shown to reduce the incidence of DVT under study conditions. The difficulty is knowing how to implement prophylaxis in practice. Will reduction of DVTs translate into reduced death rates from PE?

There is a question over whether the incidence of PE bears a reasonably consistent numerical relationship to the more frequent clinical event of DVT. We have not simply accepted this as an assumption but, where data sets allow both to be counted, we have tested the hypothesis. There appears to be a reasonably consistent association. However, this putative relationship between detectable lower limb DVT and fatal PE may break down in special cases such as knee replacement. The next question is whether reducing the incidence of DVT (the more numerous and more readily studied outcome) will result in a proportionate reduction in potentially fatal PE. Again we have tried to test this extrapolation against the data. We have conducted analyses where data are sufficient such as in studies of unfractionated heparin versus no prophylaxis: and found a similar reduction in fatal PEs. A note of caution must remain however. We generally lack evidence for reduction in all-cause mortality which would require very large trials.

The pharmacological methods introduce another consideration. They carry with them a new risk - that of bleeding. It is major bleeding events which are counted in the RCTs. We have to give guidance concerning the method of VTE prophylaxis which steers the safest course between the competing risks posed by thrombosis on the one hand and bleeding on the other.

Major bleeding is clearly a threat to life but under some circumstances, a low volume bleed can be a very major complication. A few millilitres of bleeding into the brain, or compressing the spinal cord within the vertebral canal can cause death or permanent neurological damage. Small volumes of bleeding into a joint can cause the operation to fail and the patient will be worse off than before.

It is a clinical problem which requires a meticulously researched and analysed evidence base. The potential health gains for the optimal strategy are great. An individual team will have patients who suffer PE and patients whose recovery is complicated by a treatment related bleed. The clinical difficulty is that both fatal pulmonary embolism and major bleeding have low event rates affecting fewer than one in a hundred patients. We cannot emphasise too strongly that it is evidence from the best available randomised controlled trials that we must use to quantify these competing risks. Clinical impressions cannot adequately capture the trade off between risk and benefit, particularly where both relate to infrequent clinical events or where the manifestations are delayed. It has been well shown that if clinicians base decisions for future patients on a recent adverse event in their own experience, those decisions are not likely to be in the best interest of future patients.

The impossibility of basing a policy on clinical experience makes it essential to rely on evidence based guidance. It is appropriate that this guidance is made available for individual clinicians and their teams to use in framing locally implemented prophylactic policies. Hence VTE prophylaxis is an ideal subject for an evidence based guideline. The complex task has been undertaken in collaboration between the scientific staff at the NCC-AC, and the medical professionals of the Guideline Development Group (GDG).
There are important changes expected in anticoagulation if the oral agents recently licensed or currently undergoing evaluation prove to be safe and consistently effective. We have been cautious in our recommendations, but if during the lifetime of this guideline they fulfill the hope that many doctors have for them, they will simplify practice that at present relies on daily injections of an anticoagulant, although there will need to be consideration of their drug interactions.

A summary of our recommendations:

Mechanical methods have been proven to be effective in surgical patients and do not add the risk of bleeding. We have recommended these methods for patients at risk of bleeding and in combination with pharmacological methods for many groups of patients. However during our work on this guidance a large study in stroke patients did not show any beneficial effect of stockings in stroke patients but did show an increase in skin complications associated with their use. This influenced our recommendations.

In patients at higher risk of VTE, the use of pharmacological methods is cost effective. In surgical patients these are often to be used in combination with mechanical prophylaxis such as stockings as this was the case in many of the RCTs on which we rely.

There will be patients who are already on antiplatelet medication; there will also be some for whom aspirin may be recommended in the perioperative period for the reduction of risk of heart attack and stroke. This may present a therapeutic conflict: clinicians will be concerned about the risk of bleeding. It should be noted that while aspirin does reduce the risk of VTE to some extent, we have not recommended it as a form of VTE prophylaxis. Aspirin has an important role in cardiovascular perioperative risk reduction, but this is outside our scope. It might be tempting to see antiplatelet therapy as a convenient prophylactic “two for one”. To use this as a clinical justification for omitting recommended VTE pharmacological prophylaxis risks is not recommended because the protective effective of aspirin against VTE is insufficient.

Although there are many trials, we still found ourselves with uncertainties. For example, the true present day rate of DVT and PE is very hard to ascertain. Many more patients have less invasive surgery. Surgical patients get out of bed sooner. High emphasis is placed on early mobilisation and early discharge from hospital. Prophylaxis (both mechanical and pharmacological) is widely used, but practice varies and implementation is probably patchy. There is a strong sense that DVT and PE are less of a problem than they used to be in surgical patients but maybe it is hidden from the view of clinicians by early discharge rather than being truly reduced because 80% of DVT are subclinical and the average DVT occurs on the 7th postoperative day, long after the patient has left hospital.

High quality monitoring of adverse events will be needed to ensure that these recommendations are as safe as they can be and we emphasise strongly the need to implement the research recommendations. These research recommendations specifically target the area where we found the biggest potential consequence from uncertainty. We also welcome the recommendation of the House of Commons Health Committee: “Systems must be put in place to ensure that the NICE VTE guidelines are implemented” 286. Once implemented, we need to monitor adverse events, both bleeding and venous thromboembolism to ensure that guidance is steering the safest course between those competing risks to all patients admitted to hospital.
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Chair, Guideline Development Group
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Guideline review panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring its quality. The panel includes members from the following perspectives.

Mr Peter Robb (Chair)  Consultant ENT Surgeon, Epsom and St Helier University Hospitals and The Royal Surrey County NHS Trusts

Dr Christine Hine  Consultant in Public Health (Acute Commissioning), Bristol and South Gloucestershire PCTs

Mr Greg Rogers  General Practitioner, Kent

Mr John Seddon  Lay Member
Stakeholder involvement

Anticoagulation Europe
ArjoHuntleigh
Barts and the London NHS Trust
Bayer HealthCare
Boehringer Ingelheim Ltd
Bristol-Myers Squibb Pharmaceuticals Limited
British Association of Day Surgery
British Association of Knee Surgery
British Association of Spine Surgeons (BASS)
British Association Of Stroke Physicians (BASP)
British Cardiovascular Society
British Elbow and Shoulder Society (BEES)
British Hip Society
British Orthopaedic Association
British Society for Haematology
British Society for Surgery of the Hand
Chelsea/Westminster hospital
Christie Hospital NHS Foundation Trust
Colchester Hospital University NHS Foundation Trust
Cornwall Isles of Scilly Community Health Services
Covidien (UK) Commercial Ltd
(Formerly: Tyco Healthcare (UK) Commercial Ltd)
Department of Health
GlaxoSmithKline
Griffiths & Nielsen Ltd
Harrogate and District NHS Foundation Trust
Intavent Orthofix
King’s College Hospital NHS Foundation Trust
Luton & Dunstable Hospital NHS Foundation Trust
Mid Essex Hospitals Trust
Milton Keynes Hospital Foundation Trust
North Middlesex University Hospital Paediatric Intensive Care Society
Pfizer Limited
Plymouth teaching Primary Care Trust
Poole Hospital NHS Foundation Trust
Queen Elizabeth Hospital
Royal Brompton & Harefield NHS Trust
Royal College of Midwives
Royal College of Nursing
Royal College of Obstetricians & Gynaecologists
Royal College of Pathologists
Salisbury NHS Foundation Trust
Sanofi Aventis
SBNS (Society of British Neurological Surgeons)
Sedgefield PCT (Now County Durham PCT)
Sheffield Teaching Hospital NHS Foundation Trust
Sherwood Forest Hospitals NHS Foundation Trust
Society of Vascular Nurses
St. Helens & Knowsley Teaching Hospitals NHS Trust
The Society and College of Radiographers
Trafford Healthcare NHS Trust
UK Thromboprophylaxis Forum
University Hospital Birmingham
University Hospital of North Staffordshire NHS Trust
University of Hertfordshire
Vascular Society of Great Britain and Ireland
Whittington Hospital
Wirral University Teaching Hospital NHS Trust
### Abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACS</td>
<td>Acute Coronary Syndrome</td>
</tr>
<tr>
<td>AES</td>
<td>Anti-embolism stockings</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BNF</td>
<td>British National Formulary</td>
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<td>CCA</td>
<td>Cost-consequences analysis</td>
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<tr>
<td>CCT</td>
<td>Controlled clinical trial</td>
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<tr>
<td>CEA</td>
<td>Cost-effectiveness analysis</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CPM</td>
<td>Continuous passive motion</td>
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<tr>
<td>CRT</td>
<td>Catheter related thrombosis</td>
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<td>CTEPH</td>
<td>Chronic thromboembolic pulmonary hypertension</td>
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<tr>
<td>CUA</td>
<td>Cost-utility analysis</td>
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<tr>
<td>CVC</td>
<td>Central venous catheters</td>
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<tr>
<td>DH</td>
<td>Department of Health</td>
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<tr>
<td>DVT</td>
<td>Deep-vein thrombosis</td>
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<td>FID</td>
<td>Foot impulse devices</td>
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<tr>
<td>FP</td>
<td>Forest Plot</td>
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<tr>
<td>GCS</td>
<td>Graduated compression stocking</td>
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<td>GDG</td>
<td>Guideline Development Group</td>
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<tr>
<td>GP</td>
<td>General Practitioner</td>
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<tr>
<td>GPRD</td>
<td>General Practice Research Database</td>
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<td>GRADE</td>
<td>Guidelines Recommendations Assessment Development Evaluation</td>
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<td>GRP</td>
<td>Guideline Review Panel</td>
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<tr>
<td>HD</td>
<td>High dose</td>
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<td>HES</td>
<td>Hospital Episode Statistics</td>
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<td>HIT</td>
<td>Heparin-induced thrombocytopenia</td>
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<tr>
<td>HRQL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>HTA</td>
<td>Health technology assessment</td>
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<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
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<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
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<tr>
<td>IPCD</td>
<td>Intermittent pneumatic compression devices</td>
</tr>
<tr>
<td>INB</td>
<td>Incremental net benefit</td>
</tr>
<tr>
<td>INR</td>
<td>International normalized ratio</td>
</tr>
<tr>
<td>IPCD</td>
<td>Intermittent pneumatic compression devices</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LD</td>
<td>Low dose</td>
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<tr>
<td>LMWH</td>
<td>Low molecular weight heparin</td>
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</table>
LOS Length of stay
LY Life-year
MB Major Bleeding
MHRA Medicines and Healthcare Products Regulatory Agency
NCC-AC National Collaborating Centre for Acute Care
NCGC National Clinical Guideline Centre for Acute and Chronic Conditions
(Formerly known as the National Collaborating Centre for Acute Care)
NHS National Health Service
NICE National Institute for Health and Clinical Excellence
NMA Network meta-analysis
NNT Number needed to treat
OAC Oral anticoagulants
OR Odds ratio
PASA NHS Purchasing and Supply Agency
PE Pulmonary embolism
PHT Chronic thromboembolic pulmonary hypertension
PICO Framework incorporating patients, interventions, comparisons, outcomes
PPIP Patient and Public Involvement Programme
PSA Probabilistic sensitivity analysis
PTS Post-thrombotic syndrome
QALY Quality-adjusted life year
RCT Randomised controlled trial
RR Relative risk
sc Subcutaneous
SR Systematic review
UKOSS United Kingdom Obstetric Surveillance System
UFH Unfractionated heparin
VKA Vitamin K antagonist
vs Versus
VTE Venous thromboembolism
## Glossary of terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td><strong>Absolute effect</strong></td>
<td>The difference in the risk of an event between two groups (one subtracted from the other) in a comparative study.</td>
</tr>
<tr>
<td><strong>Absolute risk reduction (Risk difference)</strong></td>
<td>See absolute effect</td>
</tr>
<tr>
<td><strong>Abstract</strong></td>
<td>Summary of a study, which may be published alone or as an introduction to a full scientific paper.</td>
</tr>
<tr>
<td><strong>Acute medical admission</strong></td>
<td>A medical admission concerned with the immediate and early specialist management of adult patients suffering from a wide range of medical conditions who present to, or from within, hospitals, requiring urgent or emergency care.</td>
</tr>
<tr>
<td><strong>Adherence</strong></td>
<td>The extent to which the patient’s behaviour matches the prescriber’s recommendations. Adherence emphasises the need for agreement and that the patient is free to decide whether or not to adhere to the doctor’s recommendation.</td>
</tr>
<tr>
<td><strong>Adjustment</strong></td>
<td>A statistical procedure in which the effects of differences in composition of the populations being compared (or treatment given at the same time) have been minimised by statistical methods.</td>
</tr>
<tr>
<td><strong>Algorithm (in guidelines)</strong></td>
<td>A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
<td>The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.</td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td>Any agent used to prevent the formation of blood clots. These include oral agents, such as warfarin, and others which are injected into a vein or under the skin, such as heparin.</td>
</tr>
<tr>
<td><strong>Anti-embolism stockings</strong></td>
<td>Hosiery which, when worn on the leg, exerts graduated compression on the leg surface and is intended to reduce the incidence of deep vein thrombosis. These should not be confused with “graduated compression stockings” which have a different pressure profile and are not used for the prevention of venous thromboembolism.</td>
</tr>
<tr>
<td><strong>Applicability</strong></td>
<td>The degree to which the results of an observation, study or review...</td>
</tr>
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</table>
are likely to hold true in a particular clinical practice setting.

**Appraisal of Guidelines, Research and Evaluation (AGREE)**

An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreecollaboration.org). The AGREE instrument, developed by the group, is designed to assess the quality of clinical guidelines.

**Arm (of a clinical study)**

Sub-section of individuals within a study who receive one particular intervention, for example placebo arm.

**Association**

Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.

**Audit**

See ‘Clinical audit’.

**Baseline**

The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.

**Bias**

Systematic (as opposed to random) deviation of the results of a study from the ‘true’ results that is caused by the way the study is designed or conducted.

**Blinding (masking)**

Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.

**Capital costs**

Costs of purchasing major capital assets (usually land, buildings or equipment). Capital costs represent investments at one point in time.

**Carer (caregiver)**

Someone other than a health professional who is involved in caring for a person with a medical condition.

**Case-control study**

Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.

**Case series**

Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.

**Chronic thromboembolic pulmonary hypertension**

Abnormally elevated blood pressure within the pulmonary circuit (pulmonary artery).

**Clinical audit**

A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.

**Clinical efficacy**

The extent to which an intervention is active when studied under controlled research conditions.

**Clinical effectiveness**

The extent to which an intervention produces an overall health benefit in routine clinical practice.
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<thead>
<tr>
<th>Term</th>
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<tr>
<td>Clinical impact</td>
<td>The effect that a guideline recommendation is likely to have on the treatment or treatment outcomes, of the target population.</td>
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<tr>
<td>Clinical question</td>
<td>In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.</td>
</tr>
<tr>
<td>Clinician</td>
<td>A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.</td>
</tr>
<tr>
<td>Cluster</td>
<td>A closely grouped series of events or cases of a disease or other related health phenomena with well-defined distribution patterns, in relation to time or place or both. Alternatively, a grouped unit for randomisation.</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>A regularly updated electronic collection of evidence-based medicine databases, including the Cochrane Database of Systematic Reviews.</td>
</tr>
<tr>
<td>Cochrane Review</td>
<td>A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.</td>
</tr>
<tr>
<td>Cohort study</td>
<td>A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.</td>
</tr>
<tr>
<td>Comparability</td>
<td>Similarity of the groups in characteristics likely to affect the study results (such as health status or age).</td>
</tr>
<tr>
<td>Compliance</td>
<td>The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as ‘adherence’ or ‘concordance’.</td>
</tr>
<tr>
<td>Concordance</td>
<td>This is a recent term whose meaning has changed. It was initially applied to the consultation process in which prescriber and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine-taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.</td>
</tr>
<tr>
<td>Conference proceedings</td>
<td>Compilation of papers presented at a conference.</td>
</tr>
<tr>
<td>Confidence interval (CI)</td>
<td>A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.</td>
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</table>
Confounding
In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the ‘confounding variable’) that can influence the outcome independently of the intervention under study.

Consensus methods
Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.

Control group
A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) – in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.

Controlled clinical trial (CCT)
A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.

Cost benefit analysis
A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.

Cost-consequences analysis (CCA)
A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.

Cost-effectiveness analysis (CEA)
An economic study design in which consequences of different interventions are measured using a single outcome, usually in ‘natural’ units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

Cost-effectiveness model
An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.

Cost-utility analysis (CUA)
A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).

Continuous passive motion
Where a joint is moved continuously, either by another person bending it or by a machine.

Credible interval
The Bayesian equivalent of a confidence interval.
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<tr>
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<tr>
<td>Decision analysis</td>
<td>A systematic way of reaching decisions, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.</td>
</tr>
<tr>
<td>Decision analytic techniques</td>
<td>A way of reaching decisions, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees that direct the clinician through a succession of possible scenarios, actions and outcomes.</td>
</tr>
<tr>
<td>Decision problem</td>
<td>A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform.</td>
</tr>
<tr>
<td>Deep-vein thrombosis (DVT)</td>
<td>Venous thrombosis that occurs in the “deep veins” in the legs, thighs, or pelvis.</td>
</tr>
<tr>
<td>Discounting</td>
<td>Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.</td>
</tr>
<tr>
<td>Distal</td>
<td>Refers to a part of the body that is farther away from the centre of the body than another part.</td>
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<tr>
<td>Dominance</td>
<td>An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.</td>
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<tr>
<td>Dosage</td>
<td>The prescribed amount of a drug to be taken, including the size and timing of the doses.</td>
</tr>
<tr>
<td>Double blind/masked study</td>
<td>A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment nor intervention the subject is receiving. The purpose of blinding is to protect against bias.</td>
</tr>
<tr>
<td>DVT</td>
<td>See 'Deep-vein thrombosis'.</td>
</tr>
<tr>
<td>Drop-out</td>
<td>A participant who withdraws from a clinical trial before the end.</td>
</tr>
<tr>
<td>Economic evaluation</td>
<td>Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.</td>
</tr>
<tr>
<td>Effect (as in effect measure, treatment effect, estimate of effect, effect size)</td>
<td>The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.</td>
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<tr>
<td>Effectiveness</td>
<td>See 'Clinical effectiveness'.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>See 'Clinical efficacy'.</td>
</tr>
<tr>
<td>Elective</td>
<td>Name for clinical procedures that are regarded as advantageous to the patient but not urgent.</td>
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<tr>
<td>Electrical stimulation</td>
<td>Designed to increase venous blood flow velocity out of the leg to...</td>
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</tbody>
</table>
Venous Thromboembolism Prophylaxis

reduce the incidence of post-surgical venous thrombosis.

**Emergency admission**
When admission is unpredictable and at short notice because of clinical need.

**Epidemiological study**
The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.

**Equity**
Fair distribution of resources or benefits.

**Evidence**
Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).

**Evidence table**
A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.

**Exclusion criteria (literature review)**
Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.

**Exclusion criteria (clinical study)**
Criteria that define who is not eligible to participate in a clinical study.

**Expert consensus**
See ‘Consensus methods’.

**Extended dominance**
If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.

**Extrapolation**
In data analysis, predicting the value of a parameter outside the range of observed values.

**Follow up**
Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.

**Foot impulse devices (FID)**
The foot impulse device is designed to stimulate the leg veins (venous pump) artificially by compressing the venous plexus and mimicking normal walking and reducing stasis in immobilised patients.

**Generalisability**
The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.

**Gold standard**
See ‘Reference standard’.

**Goodness-of-fit**
How well a statistical model or distribution compares with the
<table>
<thead>
<tr>
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<th>Definition</th>
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<tbody>
<tr>
<td>Graduated compression stockings (GCS)</td>
<td>Stockings manufactured to provide compression around legs at gradually increasing pressures. There are two different standards for graduated compression stockings, the British Standard and the European Standard. These are different to anti-embolism stockings which are used for the prevention of venous thromboembolism.</td>
</tr>
<tr>
<td>Grey literature</td>
<td>Reports that are unpublished or have limited distribution, and are not included in the common bibliographic retrieval systems.</td>
</tr>
<tr>
<td>Harms</td>
<td>Adverse effects of an intervention.</td>
</tr>
<tr>
<td>Health economics</td>
<td>The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.</td>
</tr>
<tr>
<td>Health-related quality of life (HRQL)</td>
<td>A combination of an individual’s physical, mental and social well-being; not merely the absence of disease.</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia (HIT)</td>
<td>Low blood platelet count resulting from the administration of heparin (or heparin-like agents). Despite having a low platelet count, patients with this condition are at high risk of their blood clotting.</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.</td>
</tr>
<tr>
<td>HIT</td>
<td>See ‘Heparin-induced thrombocytopenia’.</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.</td>
</tr>
<tr>
<td>Hypothesis</td>
<td>A supposition made as a starting point for further investigation.</td>
</tr>
<tr>
<td>Inclusion criteria (literature review)</td>
<td>Explicit criteria used to decide which studies should be considered as potential sources of evidence.</td>
</tr>
<tr>
<td>Incremental analysis</td>
<td>The analysis of additional costs and additional clinical outcomes with different interventions.</td>
</tr>
<tr>
<td>Incremental cost</td>
<td>The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention</td>
</tr>
<tr>
<td>Incremental cost effectiveness ratio (ICER)</td>
<td>The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.</td>
</tr>
<tr>
<td>Incremental net</td>
<td>The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be</td>
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</tbody>
</table>
**Venous Thromboembolism Prophylaxis**

**benefit (INB)** calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.

**Index** In epidemiology and related sciences, this word usually means a rating scale, for example, a set of numbers derived from a series of observations of specified variables. Examples include the various health status indices, and scoring systems for severity or stage of cancer.

**Indication (specific)** The defined use of a technology as licensed by the Medicines and Healthcare products Regulatory Agency (MHRA).

**Intention-to-treat analysis (ITT analysis)** An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.

**Intermediate outcomes** Outcomes that are related to the outcome of interest but may be more easily assessed within the context of a clinical study: for example, blood pressure reduction is related to the risk of a stroke.

**Intermittent pneumatic compression devices (IPCD)** A method of prophylaxis that comprises the use of inflatable garments wrap ped around the legs, inflated by a pneumatic pump. The pump provides intermittent cycles of compressed air which alternately inflates and deflates the chamber garments, enhancing venous return.

**Internal validity** The degree to which the results of a study are likely to approximate the 'truth' for the participants recruited in a study (that is, are the results free of bias?). It refers to the integrity of the design and is a prerequisite for applicability (external validity) of a study's findings. See 'External validity'.

**Intervention** Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.

**Intraoperative** The period of time during a surgical procedure.

**Length of stay (LOS)** The total number of days a participant stays in hospital.

**Licence** See 'Product licence'.

**Life year (LY)** A measure of health outcome which shows the number of years of remaining life expectancy.

**Life-years gained** Average years of life gained per person as a result of the intervention.

**Mechanical** Physical (as opposed to chemical) agent used, in this context, to reduce likelihood of thrombosis. Mechanical methods of DVT prophylaxis work to combat venous stasis and include: anti-embolism stockings/ Graduated compression stockings (GCS), intermittent pneumatic compression devices (IPCD), foot impulse devices, also known as foot pumps (FID).
**Medical devices**
All products, except medicines, used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or handicap.

**Medicines and Healthcare Products Regulatory Agency (MHRA)**
The Executive Agency of the Department of Health protecting and promoting public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely.

**Meta-analysis**
A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.

**Multivariate model**
A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.

**Narrative summary**
Summary of findings given as a written description.

**Network Meta-analysis (NMA)**
Statistical technique for combining all direct and indirect evidence into one analysis (see Section 3.10 for details on methods).

**Number needed to treat (NNT)**
The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.

**Observational study**
Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.

**Odds ratio (OR)**
A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The ‘odds’ is the ratio of events to non-events.

**Off-label**
A drug or device used treat a condition or disease for which it is not specifically licensed.

**Older people**
People over the age of 65 years.

**Operating costs**
Ongoing costs of carrying out an intervention, excluding capital costs.

**Opportunity cost**
The opportunity cost of investing in a healthcare intervention is the loss of other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.

**Outcome**
Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See ‘Intermediate outcome’.

**P values**
The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference.
between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be ‘statistically significant’.

**PE**  
See ‘Pulmonary embolism’.

**Peer review**  
A process where research is scrutinised by experts that have not been involved in the design or execution of the studies.

**Perioperative**  
The period from admission through surgery until discharge, encompassing pre-operative and post-operative periods.

**Placebo**  
An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.

**Placebo effect**  
A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.

**Post-thrombotic (Post-phlebitic) Syndrome**  
Chronic pain, swelling, and occasional ulceration of the skin of the leg that occur as a consequence of previous venous thrombosis.

**Postoperative**  
Pertaining to the period after patients leave the operating theatre, following surgery.

**Preoperative**  
Pertaining to the period before surgery commences.

**Primary care**  
Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians.

**Primary research**  
Study generating original data rather than analysing data from existing studies (which is called secondary research).

**Product licence**  
An authorisation from the MHRA to market a medicinal product.

**Prognosis**  
A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.

**Prophylaxis**  
A measure taken for the prevention of a disease.

**Prospective study**  
A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.

**Proximal**  
Refers to a part of the body that is closer to the centre of the body than another part.

**Pulmonary embolism (PE)**  
A blood clot that breaks off from the deep veins and travels round the circulation to block the pulmonary arteries (arteries in the lung). Most deaths arising from DVT are caused by PE.

**Pulmonary hypertension**  
See ‘Chronic thromboembolic pulmonary hypertension’.

**Qualitative research**  
Research concerned with subjective outcomes relating to social,
emotional and experiential phenomena in health and social care.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td>See ‘Health-related quality of life’.</td>
</tr>
<tr>
<td>Quality-adjusted life-year (QALY)</td>
<td>An index of survival that is adjusted to account for the patient’s quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.</td>
</tr>
<tr>
<td>Quantitative research</td>
<td>Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census which counts people and households.</td>
</tr>
<tr>
<td>Quick Reference Guide</td>
<td>An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.</td>
</tr>
<tr>
<td>Randomisation</td>
<td>Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.</td>
</tr>
<tr>
<td>Randomised controlled trial (RCT)</td>
<td>A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.</td>
</tr>
<tr>
<td>Relative risk (RR)</td>
<td>The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).</td>
</tr>
<tr>
<td>Remit</td>
<td>The brief given by the Department of Health and Welsh Assembly Government at the beginning of the guideline development process. This defines core areas of care that the guideline needs to address.</td>
</tr>
<tr>
<td>Resource implication</td>
<td>The likely impact in terms of finance, workforce or other NHS resources.</td>
</tr>
<tr>
<td>Retrospective study</td>
<td>A retrospective study deals with the present/past and does not involve studying future events. This contrasts with studies that are prospective.</td>
</tr>
<tr>
<td>Review of the literature</td>
<td>An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their findings. It may or may not be systematically researched and developed.</td>
</tr>
<tr>
<td>Secondary benefits</td>
<td>Benefits resulting from a treatment in addition to the primary, intended outcome.</td>
</tr>
</tbody>
</table>
| Selection bias (also allocation bias) | A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of
patients protects against this bias.

**Selection criteria**
Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.

**Sensitivity (of a search)**
The proportion of relevant studies identified by a search strategy expressed as a percentage of all relevant studies on a given topic. It describes the comprehensiveness of a search method (that is, its ability to identify all relevant studies on a given topic). Highly sensitive strategies tend to have low levels of specificity and vice versa.

**Sensitivity analysis**
A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.

One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.

Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated.

Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified.

Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).

**Significantly Reduced Mobility**
Defined by the GDG as: 'patients who are bed bound, unable to walk unaided or likely to spend a substantial proportion of their day in bed or in a chair'.

**Stakeholder**
Those with an interest in the use of a technology under appraisal or a guideline under development. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.

**Statistical power**
The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.

**Synthesis of evidence**
A generic term to describe methods used for summarising (comparing and contrasting) evidence into a clinically meaningful conclusion in order to answer a defined clinical question. This can include systematic review (with or without meta-analysis), qualitative and narrative summaries.
<table>
<thead>
<tr>
<th><strong>Systematic review</strong></th>
<th>Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombophilia</strong></td>
<td>The genetic or acquired prothrombotic states that increase the tendency to venous thromboembolism. It is a condition which leads to a tendency for a person’s blood to clot inappropriately.</td>
</tr>
<tr>
<td><strong>Thromboprophylaxis</strong></td>
<td>A measure taken to reduce the risk of thrombosis.</td>
</tr>
<tr>
<td><strong>Time horizon</strong></td>
<td>The time span used in the NICE appraisal which reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence.</td>
</tr>
<tr>
<td><strong>Treatment allocation</strong></td>
<td>Assigning a participant to a particular arm of the trial.</td>
</tr>
<tr>
<td><strong>Treatment options</strong></td>
<td>The choices of intervention available.</td>
</tr>
<tr>
<td><strong>Utility</strong></td>
<td>A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or ‘perfect’ health). Health states can be considered worse than death and thus have a negative value.</td>
</tr>
<tr>
<td><strong>Venous thromboembolism (VTE)</strong></td>
<td>The blocking of a blood vessel by a blood clot dislodged from its site of origin. It includes both DVT and PE.</td>
</tr>
<tr>
<td><strong>Venous thrombosis (VT)</strong></td>
<td>A condition in which a blood clot (thrombus) forms in a vein.</td>
</tr>
</tbody>
</table>
1 Introduction

1.1 The need for this guideline

Venous thromboembolism (VTE) is a term used to include the formation of a blood clot (a thrombus) in a vein which may dislodge from its site of origin to travel in the blood, a phenomenon called embolism. A thrombus most commonly occurs in the deep veins of the legs; this is called deep vein thrombosis. A dislodged thrombus that travels to the lungs is known as a pulmonary embolism.

VTE includes/encompasses a range of clinical presentations. Venous thrombosis may be completely asymptomatic or it may cause pain and swelling in the leg. Part or all of the thrombus/clot can come free and travel to the lung as a potentially fatal pulmonary embolism. Symptomatic venous thrombosis carries a considerable burden of morbidity, sometimes long-term due to chronic venous insufficiency. This in turn can cause venous ulceration and development of a post-thrombotic limb (characterised by chronic pain, swelling and skin changes).

VTE is an important cause of death in hospitalised patients, and treatment of non-fatal symptomatic VTE and related long-term morbidities is associated with a considerable cost to the health service.

In 2004–05, there were around 64,000 finished consultant episodes (that is, periods of care under a consultant within an NHS trust) with a diagnosis of VTE. In 2005, VTE was registered as the underlying cause of death in more than 6500 patients, although this figure is likely to be an underestimate of the true incidence.

The incidence of VTE in different groups of hospital patients varies greatly in the literature. The risk of PE in the absence of prophylaxis has been estimated at 5% following surgery in the highest risk groups, and around 1% in acutely ill medical patients (Chapter 5).

The risk of developing VTE depends on the condition and/or procedure for which the patient is admitted and on any predisposing risk factors (such as age, obesity and concomitant conditions). Both of these types of risk will be assessed within the guideline.

This guideline examines the risk of venous thromboembolism and assesses the evidence for the effectiveness of primary preventative measures. It provides recommendations on the most clinically and cost effective measures to reduce the risk of venous thromboembolism, whilst considering the potential risks of the various VTE prophylaxis options and patient preferences.
There is no current worldwide consensus on which patients should receive thromboprophylaxis. The inconsistent use of prophylactic measures for VTE has been widely reported. A UK survey suggested that 71% of patients assessed to be at medium or high risk of developing DVT did not receive any form of pharmacological or mechanical thromboprophylaxis.

This guideline incorporates the published NICE guideline ‘Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery’ (NICE clinical guideline 46). This single piece of guidance covers all patients admitted to hospital.

We start by examining the risk factors for developing VTE (both hospital related and patient related), followed by a review of the evidence of clinical and cost effectiveness for each of the prophylactic methods that we are considering. We continue by examining the data relating to specific patient groups, taking into account the overall effectiveness of the various methods and make recommendations for these specific groups.

1.2 Assumptions made in this guideline

This guideline recommends primary VTE prophylaxis on the basis of their effectiveness in reducing the risk of DVT (both symptomatic and asymptomatic), acknowledging that this is a ‘surrogate’ endpoint which is frequently employed in randomised controlled trials (RCTs).

There are several difficulties with considering only pulmonary embolism (PE) as an outcome:

1. PE is a rare event, and therefore large trials (or numbers of trials) are needed to demonstrate an effect.

2. Few trials that report PE have made the diagnosis using objective methods (clinical diagnosis being unreliable).

3. Many trials that report PE as an outcome measure have also assessed all included patients for DVT. Trial protocols usually dictate that patients in whom a DVT is detected are removed from the trial and anticoagulation is given, and hence a PE may be prevented that would have occurred in the usual clinical setting.

DVT is a usual precursor of both fatal PE and post-thrombotic syndrome (PTS), although the aetiology and development of the diseases have not yet been fully elucidated. Although asymptomatic DVT is, by definition, covert these thrombi can become pulmonary embolisms and are a clinically useful endpoint for a trial. We therefore consider it appropriate to evaluate both asymptomatic and symptomatic DVT when looking at the effectiveness of prophylactic strategies. Clinical detection of DVT is unreliable and also fails to detect asymptomatic events, hence we have only included trials that assess all patients for DVT using objective methods.

DVT, therefore, is accepted as a suitable endpoint by this guideline which will evaluate trials where patients are assessed for DVT.
1.3 What are clinical practice guidelines?

Our clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care though primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific clinical questions.

Clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process
- The scope is prepared by the National Clinical Guideline Centre- Acute and Chronic Conditions (NCGC), formerly the National Collaborating Centre for Acute Care (NCC-AC)
- The NCGC establish a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline
- The final guideline is produced

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
• the **NICE guideline** presents the recommendations from the full version in a format suited to implementation by health professionals and NHS bodies

• the **quick reference guide** presents recommendations in a suitable format for health professionals

• information for the public ("understanding NICE guidance") is written using suitable language for people without specialist medical knowledge.

This version is the full version. This and the other versions can be downloaded from the NICE website [www.NICE.org.uk](http://www.NICE.org.uk).

1.4 **The National Clinical Guideline Centre - Acute and Chronic Conditions**  
(formerly the National Collaborating Centre for Acute Care)

This guideline was commissioned by NICE and developed by the National Collaborating Centre for Acute Care (now called the National Clinical Guidelines Centre - Acute and Chronic Conditions). The centre is funded by NICE and comprises a partnership between a variety of academic, professional and patient-based organisations. As a multidisciplinary centre we draw upon the expertise of the healthcare professions and academics and ensure the involvement of patients in our work. Further information on the centre and our partner organisations can be found at our website [http://www.rcplondon.ac.uk/clinical-standards/ncgc/](http://www.rcplondon.ac.uk/clinical-standards/ncgc/).

1.5 **Remit of the guideline**

The following remit was received from the Department of Health and the Welsh Assembly Government in March 2007 as part of NICE's 14th wave programme of work.

1.6 **What the guideline covers**

This guideline covers adults (18 years and older) admitted to hospital as inpatients or formally admitted to a hospital bed for day-case procedures, including:

• surgical inpatients

• inpatients with acute medical illness (for example, myocardial infarction, stroke, spinal injury, severe infection or exacerbation of chronic obstructive pulmonary disease)

• trauma inpatients

• patients admitted to intensive care units

• cancer inpatients

• people undergoing long-term rehabilitation in hospital

• patients admitted to a hospital bed for day-case medical or surgical procedures.

The scope for this guideline can be found in Appendix A.
1.7 What the guideline does not cover

This guideline does not cover:

- People under the age of 18.
- People attending hospital as outpatients.
- People presenting to emergency departments without admission.
- Elderly or immobile people cared for at home, or in external residential accommodation, unless admitted to hospital.
- Patients admitted to hospital with a diagnosis of, or suspected diagnosis of, DVT or PE.

1.8 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Clinical Excellence funds the National Clinical Guideline Centre- Acute and Chronic Conditions, NCGC (formerly the National Collaborating Centre for Acute Care, NCC-AC) and thus supported the development of this guideline. The Guideline Development Group was convened by the NCC-AC and chaired by Professor Tom Treasure in accordance with guidance from the National Institute for Health and Clinical Excellence (NICE).

The group met every 6-8 weeks during the development of the guideline. At the start of the guideline development process all Guideline Development Group members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent Guideline Development Group meetings, members declared arising conflicts of interest, which were also reported (Appendix B). Members are either required to withdraw completely or for part of the discussion if their declared interest makes it appropriate, however this was not deemed necessary for any group members on this guideline.

A separate orthopaedic subgroup was set up in March 2008 to provide specific expert guidance on VTE prophylaxis for patients having orthopaedic surgery. This group, was chaired by Professor Tom Treasure and comprised seven consultant orthopaedic surgeons representing a range of orthopaedic specialties along with a patient representative and a nursing representative. The group met 5 times and all members declared conflicts of interests at all meetings (recorded in Appendix B). This orthopaedic subgroup group reviewed the evidence for orthopaedic surgery and provided expert opinion and draft recommendations to the main GDG. The full GDG had the responsibility for final approval of all recommendations in the guideline.

Staff from the NCGC provided methodological support and guidance for the development process. They undertook systematic searches, retrieval and appraisal of the
evidence and drafted the guideline. The glossary to the guideline contains definitions of terms used by staff and the Guideline Development Group.
2 Summary of recommendations

Below are the recommendations that the Guideline Development Group (GDG) selected as the key priorities for implementation followed by the full list of recommendations.

2.1 Key priorities for implementation

The GDG identified ten key priorities for implementation. The decision was made after voting by the GDG. They selected recommendations that would:

- Have a high impact on outcomes that are important to patients (A)
- Have a high impact on reducing variation in care and outcomes (B)
- Lead to a more efficient use of NHS resources (C)
- Promote patient choice (D)
- Promote equalities. (E)

In doing this the GDG also considered which recommendations were particularly likely to benefit from implementation support. They considered whether a recommendation:

- Requires changes in service delivery (W)
- Requires retraining of professionals or the development of new skills and competencies (X)
- Affects and needs to be implemented across various agencies or settings (complex interactions) (Y)
- May be viewed as potentially contentious, or difficult to implement for other reasons (Z)

For each key recommendation listed below, the selection criteria and implementation support points are indicated by the use of the letters shown in brackets above.
Assess all patients on admission to identify those who are at increased risk of venous thromboembolism (VTE).

(Selection Criteria: A, B, C; Implementation support: W, X Y)

Regard medical patients as being at increased risk of VTE if they:
- have had or are expected to have significantly reduced mobility for 3 days or more or
- are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.

(Selection Criteria: A, B, C; Implementation support: W, X Y)

Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more risk factors shown in Box 1.

(Selection Criteria: A, B, C; Implementation support: W, X Y)

Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.

*Consult the summary of product characteristics for the pharmacological prophylaxis being used or planned for further details.

(Selection Criteria: A, B, C, E; Implementation support: X, Y)

Reassess patients’ risk of bleeding and VTE within 24 hours of admission and whenever the clinical situation changes, to:
- ensure that the methods of VTE prophylaxis used are suitable
- ensure that VTE prophylaxis is being used correctly
- identify adverse events resulting from VTE prophylaxis.

(Selection Criteria: A, B, C, E; Implementation support: W, X, Y)

Encourage patients to mobilise as soon as possible.
Offer pharmacological VTE prophylaxis to general medical patients assessed to be at increased risk of VTE (see section 2.2.1). Choose any one of:
- fondaparinux sodium
- LMWH*
- UFH (for patients with renal failure).

Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

*At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.

Before starting VTE prophylaxis, offer patients and/or their families or carers verbal and written information on:
- the risks and possible consequences of VTE
- the importance of VTE prophylaxis and its possible side effects
- the correct use of VTE prophylaxis (for example, anti-embolism stockings, foot impulse or intermittent pneumatic compression devices)
- how patients can reduce their risk of VTE (such as keeping well hydrated and, if possible exercising and becoming more mobile)

As part of the discharge plan, offer patients and/or their families or carers verbal and written information on:
- the signs and symptoms of deep vein thrombosis and pulmonary embolism
- the correct and recommended duration of use of VTE prophylaxis at home (if discharged with prophylaxis)
- the importance of using VTE prophylaxis correctly and continuing treatment for the recommended duration (if discharged with prophylaxis)
- the signs and symptoms of adverse events related to VTE prophylaxis (if discharged with prophylaxis)
- the importance of seeking help and who to contact if they have any problems using the prophylaxis (if discharged with prophylaxis)
- the importance of seeking medical help if deep vein thrombosis, pulmonary embolism or another adverse event is suspected.
2.2 The complete list of clinical practice recommendations

2.2.1 Assessing the risks of VTE and bleeding

- Assess all patients on admission to identify those who are at increased risk of venous thromboembolism (VTE).

- Regard **medical patients** as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more or
  - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.

- Regard **surgical patients and patients with trauma** as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
  - acute surgical admission with inflammatory or intra-abdominal condition
  - expected significant reduction in mobility
  - one or more of the risk factors shown in Box 1.

---

**Box 1 Risk factors for VTE**

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilies
- Obesity (body mass index [BMI] over 30 kg/m²)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).
Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.

*At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH.

Box 2 Risk factors for bleeding

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalized ratio [INR] higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10⁹/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand’s disease)

Reassess patients’ risk of bleeding and VTE within 24 hours of admission, and whenever the clinical situation changes, to:

- ensure that the methods of VTE prophylaxis being used are suitable
- ensure that VTE prophylaxis is being used correctly
- identify adverse events resulting from VTE prophylaxis.

2.2.2 Reducing the risk of VTE – general recommendations

- Do not allow patients to become dehydrated unless clinically indicated.
- Encourage patients to mobilise as soon as possible.
- Do not regard aspirin or other antiplatelet agents as adequate prophylaxis for VTE.
- Consider offering temporary inferior vena caval filters to patients who are at very high risk of VTE (such as patients with a previous VTE event or an active...
malignancy) and for whom mechanical and pharmacological VTE prophylaxis are contraindicated.

2.2.3 Using VTE prophylaxis

2.2.3.1 Mechanical VTE prophylaxis

➢ Base the choice of mechanical VTE prophylaxis on individual patient factors including clinical condition, surgical procedure and patient preference. Choose any one of:

- anti-embolism stockings (thigh or knee length)
- foot impulse devices
- intermittent pneumatic compression devices (thigh or knee length).

Anti-embolism stockings

➢ Do not offer anti-embolism stockings to patients who have:

- suspected or proven peripheral arterial disease
- peripheral arterial bypass grafting
- peripheral neuropathy or other causes of sensory impairment
- any local conditions in which stockings may cause damage e.g. fragile ‘tissue paper’ skin, dermatitis, gangrene or recent skin graft
- known allergy to material of manufacture
- cardiac failure
- severe leg oedema or pulmonary oedema from congestive heart failure
- unusual leg size or shape
- major limb deformity preventing correct fit.

Use caution and clinical judgement when applying anti-embolism stockings over venous ulcers or wounds.

➢ Ensure that patients who need anti-embolism stockings have their legs measured and that the correct size of stocking is provided. Anti-embolism stockings should be fitted and patients shown how to use them by staff trained in their use.

➢ Ensure that patients who develop oedema or postoperative swelling have their legs re-measured and anti-embolism stockings refitted.

➢ If arterial disease is suspected, seek expert opinion before fitting anti-embolism stockings.
Use anti-embolism stockings that provide graduated compression and produce a calf pressure of 14-15mmHg.

Encourage patients to wear their anti-embolism stockings day and night until they no longer have significantly reduced mobility.

Remove anti-embolism stockings daily for hygiene purposes and to inspect skin condition. In patients with a significant reduction in mobility, poor skin integrity or any sensory loss, inspect the skin two or three times per day, particularly over the heels and bony prominences.

Discontinue the use of anti-embolism stockings if there is marking, blistering or discolouration of the skin, particularly over the heels and bony prominences, or if the patient experiences pain or discomfort. If suitable, offer a foot impulse or intermittent pneumatic compression device as an alternative.

Show patients how to use anti-embolism stockings correctly and ensure they understand that this will reduce their risk of developing VTE.

Monitor the use of anti-embolism stockings and offer assistance if they are not being worn correctly.

Foot impulse devices and intermittent pneumatic compression devices

Do not offer foot impulse or intermittent pneumatic compression devices to patients with a known allergy to the material of manufacture.

Encourage patients on the ward who have foot impulse or intermittent pneumatic compression devices to use them for as much of the time as is possible and practical, both when in bed and when sitting in a chair.

2.2.3.2 Pharmacological VTE prophylaxis

Base the choice of pharmacological agents on local policies and individual patient factors, including clinical condition (such as renal failure) and patient preferences.

2.2.4 Reducing the risk of VTE in medical patients

Offer pharmacological VTE prophylaxis to general medical patients assessed to be at increased risk of VTE (see section 2.2.1). Choose any one of:

- fondaparinux sodium
- LMWH*
- UFH (for patients with renal failure).

Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

*At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should
consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.

**Patients with stroke**

- Do not offer anti-embolism stockings for VTE prophylaxis to patients who are admitted for stroke.

- Consider offering prophylactic-dose LMWH* (or UFH for patients with renal failure) if:
  - a diagnosis of haemorrhagic stroke has been excluded, and
  - the risk of bleeding (haemorrhagic transformation of stroke or bleeding into another site) is assessed to be low, and
  - the patient has one or more of:
    - major restriction of mobility
    - previous history of VTE
    - dehydration
    - comorbidities (such as malignant disease).

Continue until the acute event is over and the patient's condition is stable.

*At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.

- Until the patient can have pharmacological VTE prophylaxis, consider offering a foot impulse or intermittent pneumatic compression device.

**Patients with cancer**

- Offer pharmacological VTE prophylaxis to patients with cancer who are assessed to be at increased risk of VTE (see section 2.2.1). Choose any one of:
  - fondaparinux sodium
  - LMWH*
  - UFH (for patients with renal failure).

Start pharmacological VTE prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

*At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should
consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented. LMWH.

➢ Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with cancer having oncological treatment who are ambulant.

**Patients with central venous catheters**

➢ Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with central venous catheters who are ambulant.

➢ Consider offering pharmacological VTE prophylaxis with LMWH* (or UFH for patients with renal failure) to patients with central venous catheters who are at increased risk of VTE (See section 2.2.1).

*At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.

**Patients in palliative care**

➢ Consider offering pharmacological VTE prophylaxis to patients in palliative care who have potentially reversible acute pathology. Take into account potential risks and benefits and the views of the patient and their family and/or carers. Choose any one of:

- Fondaparinux sodium
- LMWH*
- UFH (for patients with renal failure).

*At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.

➢ Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients admitted for terminal care or those commenced on an end-of-life care pathway.

➢ Review decisions about VTE prophylaxis for patients in palliative care daily, taking into account the views of the patient, their family and/or carers and the multidisciplinary team.

**Medical patients in whom pharmacological prophylaxis is contraindicated**

➢ Consider offering mechanical VTE prophylaxis to medical patients in whom pharmacological prophylaxis is contraindicated. Choose any one of:

- anti-embolism stockings (thigh or knee length)
SUMMARY OF RECOMMENDATIONS

- foot impulse devices
- intermittent pneumatic compression devices (thigh or knee length)

2.2.5 Reducing the risk of VTE in surgical patients

2.2.5.1 General recommendations for all surgical patients

- Advise patients to consider stopping oestrogen-containing oral contraceptives or hormone replacement therapy 4 weeks before elective surgery. If stopped, provide advice on alternative contraceptive methods.

- Assess the risks and benefits of stopping pre-existing established antiplatelet therapy 1 week before surgery. Consider involving the multidisciplinary team in the assessment.

- Consider regional anaesthesia for individual patients, in addition to other methods of VTE prophylaxis, as it carries a lower risk of VTE than general anaesthesia. Take into account the patients’ preferences, their suitability for regional anaesthesia and any other planned method of VTE prophylaxis.

- If regional anaesthesia is used, plan the timing of pharmacological VTE prophylaxis to minimise the risk of epidural haematoma. If antiplatelet or anticoagulant agents are being used, or their use is planned, refer to the summary of product characteristics for guidance about the safety and timing of these in relation to the use of regional anaesthesia.

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients undergoing a surgical procedure with local anaesthesia by local infiltration with no limitation of mobility.

2.2.5.2 Recommendation for specific surgical patient groups

Cardiac surgery

- Offer VTE prophylaxis to patients undergoing cardiac surgery who are not having other anticoagulation therapy and are assessed to be at increased risk of VTE (see section 2.2.1)

  - Start mechanical VTE prophylaxis at admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.
- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

**Gastrointestinal, gynaecological, urological and thoracic surgery**

- **Offer VTE prophylaxis to patients undergoing bariatric surgery**

  - Start mechanical VTE prophylaxis at admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length).

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:
  - fondaparinux sodium
  - LMWH
  - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

- **Offer VTE prophylaxis to patients undergoing gastrointestinal surgery who are assessed to be at increased risk of VTE (see section 2.2.1)**

  - Start mechanical VTE prophylaxis at admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length).

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.
• Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:
  - fondaparinux sodium
  - LMWH
  - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Offer VTE prophylaxis to patients undergoing **gynaecological, thoracic or urologic surgery** who are assessed to be at increased risk of VTE (see section 2.2.1)

• Start mechanical VTE prophylaxis at admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

• Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Extend pharmacological prophylaxis to 28 days postoperatively for patients who have had major cancer surgery in the abdomen or pelvis.

**Neurological (cranial or spinal)**

➢ Offer VTE prophylaxis to patients undergoing **cranial or spinal surgery** who are assessed to be at increased risk of VTE (see section 2.2.1)

• Start mechanical VTE prophylaxis from admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).
Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

- Do not offer pharmacological VTE prophylaxis to patients with ruptured cranial or spinal vascular malformations (for example, brain aneurysms) or acute traumatic or non-traumatic haemorrhage until the lesion has been secured or the condition is stable.

**Orthopaedic- elective hip replacement**

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing **elective hip replacement surgery**:

  - Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors:
    - anti-embolism stockings (thigh or knee length), used with caution (see section 2.2.3.1)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

  - Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of:
    - dabigatran etexilate, starting 1-4 hours after surgery*
    - fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established
    - LMWH, starting 6–12 hours after surgery
    - rivaroxaban, starting 6-10 hours after surgery$
    - UFH (for patients with renal failure), starting 6–12 hours after surgery.
Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used.

* Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157 (2008).476

$ Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).479

Orthopaedic- elective knee replacement

Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing **elective knee replacement surgery**.

- Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors:
  - anti-embolism stockings (thigh or knee length), used with caution (see section 2.2.3.1)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of:
  - dabigatran etexilate, starting 1-4 hours after surgery*
  - fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established
  - LMWH, starting 6-12 hours after surgery
  - rivaroxaban, starting 6-10 hours after surgery$
  - UFH (for patients with renal failure), starting 6-12 hours after surgery.

Continue pharmacological VTE prophylaxis for 10-14 days, according to the summary of product characteristics for the individual agent being used.

* Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have
undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157(2008).

Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).

Orthopaedic- hip fracture

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing hip fracture surgery.

  - Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors:
    - anti-embolism stockings (thigh or knee length), used with caution (see section 2.2.3.1)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length).

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

  - Provided there are no contraindications, add pharmacological VTE prophylaxis. Choose any one of:
    - fondaparinux sodium, starting 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2)
    - LMWH, starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.
    - UFH (for patients with renal failure), starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.

  Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used.

  - Fondaparinux sodium is not recommended for use preoperatively for patients undergoing hip fracture surgery. If it has been used preoperatively it should be stopped 24 hours before surgery and started 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2).

Other orthopaedic
Consider offering combined VTE prophylaxis with mechanical and pharmacological methods to patients having orthopaedic surgery (other than hip fracture, hip replacement or knee replacement) based on an assessment of risks (see section 2.2.1) and after discussion with the patient. Start mechanical VTE prophylaxis at admission. Choose one of the following, based on individual patient factors:

- anti-embolism stockings (thigh or knee length), used with caution (see section 2.2.3.1)
- foot impulse devices
- intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Start pharmacological VTE prophylaxis 6–12 hours after surgery. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

Do not routinely offer VTE prophylaxis to patients undergoing upper limb surgery. If a patient is assessed to be at increased risk of VTE (see section 2.2.1) refer to recommendation for other orthopaedic surgery (above).

Vascular

Offer VTE prophylaxis to patients undergoing vascular surgery who are not having other anticoagulant therapy and are assessed to be at increased risk of VTE (see section 2.2.1). If peripheral arterial disease is present, seek expert opinion before fitting anti-embolism stockings.

- Start mechanical VTE prophylaxis at admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis for patients who have a low risk of bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
  - LMWH
VENOUS THROMBOEMBOLISM PROPHYLAXIS

- UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patients no longer has significantly reduced mobility (generally 5-7 days).

Day surgery

➢ Offer VTE prophylaxis to patients undergoing day surgery who are assessed to be at increased risk of VTE (see section 2.2.1)

• Start mechanical VTE prophylaxis at admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

• Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:
  - fondaparinux
  - LMWH
  - UFH (for patients with renal failure)

If the patient is expected to have significantly reduced mobility after discharge, continue pharmacological VTE prophylaxis, generally for 5-7 days.

➢ Offer VTE prophylaxis to patients undergoing surgery other than that covered in section 2.2.5.2 who are assessed to be at increased risk of VTE (see recommendation 2.2.1).

• Start mechanical VTE prophylaxis at admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

• Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
2.2.6 Other patient groups

**Major trauma**

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients with major trauma. Regularly reassess the patient's risks of VTE and bleeding.
  - Start mechanical VTE prophylaxis at admission or as early as clinically possible. Choose any one of:
    - anti-embolism stockings (thigh or knee length) used with caution (see section 2.2.3.1)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)
  - If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see Box 2) and the bleeding risk has been established as low, add pharmacological VTE prophylaxis and continue until the patient no longer has significantly reduced mobility. Choose one of:
    - LMWH
    - UFH (for patients with renal failure).
  - Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

**Spinal injury**

- Offer combined VTE prophylaxis with mechanical and pharmacological methods for patients with spinal injury. Regularly reassess the patient's risks of VTE and bleeding.
  - Start mechanical VTE prophylaxis at admission or as early as clinically possible. Choose any one of:
    - anti-embolism stockings (thigh or knee length) used with caution (see section 2.2.3.1)
    - foot impulse devices
  - Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.
- intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility

- If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see Box 2) and the bleeding risk has been established as low, add pharmacological VTE prophylaxis. Choose one of:

  - LMWH

  - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility

**Lower limb plaster casts**

- Consider offering pharmacological VTE prophylaxis for patients with lower limb plaster casts after evaluating the risks (see section 2.2.1) and benefits based on clinical discussion with the patient. Offer LMWH (or UFH for patients with renal failure) until lower limb plaster cast removal.

**Pregnancy and up to 6 weeks post partum**

- Consider offering VTE prophylaxis with LMWH (or UFH for patients with renal failure) to women who are pregnant or have given birth within the previous 6 weeks who are admitted to hospital but are not undergoing surgery and have one or more of the following risk factors:

  - expected to have significantly reduced mobility for 3 or more days
  - active cancer or cancer treatment
  - age over 35 years
  - critical care admission
  - dehydration
  - excess blood loss or blood transfusion
  - known thrombophilias
  - obesity (pre-pregnancy or early pregnancy BMI over 30 kg/m²)
  - one or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
  - personal or a first degree relative with a history of VTE
• pregnancy related risk factor (such as ovarian hyperstimulation, hyperemesis gravidarum, multiple pregnancy and pre-eclampsia)

• varicose veins with phlebitis.

➢ Consider offering combined VTE prophylaxis with mechanical methods and LMWH (or UFH for patients with renal failure) to women who are pregnant or have given birth within the previous 6 weeks who are undergoing surgery, including caesarean section.

➢ Offer mechanical and/or pharmacological VTE prophylaxis to women who are pregnant or have given birth within the previous 6 weeks only after assessing the risks and benefits and discussing these with the patient and with healthcare professionals who have knowledge of the proposed method of VTE prophylaxis during pregnancy and post partum. Plan when to start and stop pharmacological VTE prophylaxis to minimise the risk of bleeding.

Critical Care

➢ Assess all patients on admission to the critical care unit for their risks of VTE (see section 2.2.1) and bleeding (see Box 2). Reassess patients’ risks of VTE and bleeding daily and more frequently if their condition is changing rapidly.

➢ Offer VTE prophylaxis to patients admitted to the critical care unit based on the reason for admission, taking into account:

  • any planned interventions
  • the use of other therapies that may increase the risk of complications.

➢ Review decisions about VTE prophylaxis for patients in critical care daily and more frequently if their condition is changing rapidly. Take into account the known views of the patient, comments from their family and/or carers and the multidisciplinary team.

Patients already having antiplatelet agents or anticoagulants on admission or needing them for treatment

➢ Consider offering additional mechanical or pharmacological VTE prophylaxis to patients who are having antiplatelet agents to treat other conditions and who are assessed to be at increased risk of VTE (see section 2.2.1). Take into account the risk of bleeding (see Box 2) and of comorbidities such as arterial thrombosis.

  • If the risk of VTE outweighs the risk of bleeding, consider offering pharmacological VTE prophylaxis according to the reason for admission.

  • If the risk of bleeding outweighs the risk of VTE, offer mechanical VTE prophylaxis.

➢ Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are taking vitamin K antagonists and who are within their therapeutic range, providing anticoagulant therapy is continued.
Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are having full anticoagulant therapy (for example, fondaparinux sodium, LMWH or UFH).

2.2.7 Patient information and planning for discharge

Patient information

Be aware that heparins are of animal origin and this may be of concern to some patients*. For patients who have concerns about using animal products, consider offering synthetic alternatives based on clinical judgement after discussing their suitability, advantages and disadvantages with the patient.


Before starting VTE prophylaxis, offer patients and/or their families or carers verbal and written information on:

- the risks and possible consequences of VTE
- the importance of VTE prophylaxis and its possible side effects
- the correct use of VTE prophylaxis (for example, anti-embolism stockings, foot impulse or intermittent pneumatic compression devices).
- how patients can reduce their risk of VTE (such as keeping well hydrated and, if possible exercising and becoming more mobile)

Planning for discharge

As part of the discharge plan, offer patients and/or their families or carers verbal and written information on:

- the signs and symptoms of deep vein thrombosis and pulmonary embolism
- the correct and recommended duration of use of VTE prophylaxis at home (if discharged with prophylaxis)
- the importance of using VTE prophylaxis correctly and continuing treatment for the recommended duration (if discharged with prophylaxis)
- the signs and symptoms of adverse events related to VTE prophylaxis (if discharged with prophylaxis)
- the importance of seeking help and who to contact if they have any problems using the prophylaxis (if discharged with prophylaxis)
- the importance of seeking medical help if deep vein thrombosis, pulmonary embolism or other adverse events are suspected.
➤ Ensure that patients who are discharged with anti-embolism stockings:
   • understand the benefits of wearing them
   • understand the need for daily hygiene removal
   • are able to remove and replace them, or have someone available who
     will be able to do this for them
   • know what to look for such as skin marking, blistering or discolouration,
     particularly over the heels and bony prominences
   • know who to contact if there is a problem.

➤ Ensure that patients who are discharged with pharmacological and/or mechanical
VTE prophylaxis are able to use it correctly, or have arrangements made for
someone to be available who will be able to help them.

➤ Notify the patient’s GP if the patient has been discharged with pharmacological
and/or mechanical VTE prophylaxis to be used at home.

2.3 Recommendations for research

2.3.1 Assessment of risk for VTE

The Guideline Development Group (GDG) recommended the following research
question:

➤ What is the absolute risk of VTE among different groups of hospital patients and
can the risk be reliably estimated on admission to hospital to ensure that
appropriate patients are offered VTE prophylaxis?

Why this is important

One of the most difficult areas the Guideline Development Group faced when
developing the guideline was to identify the absolute risk of VTE among specific patient
groups in relation to the reason for admission. A new, large pragmatic cohort study
and/or record linkage study using Hospital Episode Statistics and the General Practice
Research Database is proposed. This would allow all people admitted to hospital to be
studied to identify those who develop VTE, including people who are diagnosed with VTE
in primary care after discharge from hospital. Information on baseline patient-related
factors, procedures and duration of stay, complications, prophylactic therapies and
concomitant drug use should be collected and analysed. It should allow the identification
of independent risk factors for VTE and the development and subsequent validation of a
risk model to estimate the absolute risk of VTE in individual patients. This research would
allow clearer identification of those patients at risk of VTE and those in whom the risk is
so low that the bleeding risk of pharmacological VTE prophylaxis would add overall
hazard.
2.3.2 VTE prophylaxis for general medical patients

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of pharmacological prophylaxis, mechanical prophylaxis and combined pharmacological and mechanical prophylaxis for reducing the risk of VTE in medical patients?

Why this is important

Only a small number of trials with medical patients were identified and generally the inclusion criteria were narrow, for example, patients with an acute medical illness, with a hospital stay of more than 5 days, and often with severely limited mobility. Further research into less severely ill patient groups would be beneficial.

The evidence concerning mechanical prophylaxis in medical patients is sparse. There have been a few small trials of patients with coronary syndrome but the only large, randomised controlled trial was of patients with stroke. This trial showed that routine care plus thigh-length anti-embolism stockings did not confer significantly more protection against VTE than routine care alone and was associated with significantly more harm. All of these trials included large proportions of patients who were taking aspirin, which may have influenced the results.

New trial(s) should investigate the benefits of reducing the risk of VTE balanced against the risk of bleeding. The trial(s) should compare pharmacological prophylaxis alone, mechanical prophylaxis alone, and combined mechanical and pharmacological prophylaxis. The benefit of extended-duration prophylaxis in medical patient groups may also be investigated.

2.3.3 VTE prophylaxis for patients with lower limb plaster casts

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of pharmacological prophylaxis for reducing the risk of VTE in patients with lower limb plaster casts?

Why this is important

A number of randomised controlled trials have been published reporting the use of VTE prophylaxis in patients with lower limb plaster casts. However, within these trials there has been a range of patients including patients with soft tissue injuries and no operation, those with operated and unaoperated fractures and patients having elective procedures. The incidence of VTE in the published trials that did not use VTE prophylaxis ranges from 4%–40%. The implications of providing pharmacological prophylaxis for all patients with lower limb plaster casts are potentially considerable with respect to cost. Trials stratifying patients by reason for plaster cast would be useful to determine which patients should be recommended for prophylaxis.

2.3.4 VTE prophylaxis for patients after stroke

The GDG recommended the following research question:

- What is the overall risk/benefit of low molecular weight heparin and/or fondaparinux sodium in respect of both stroke outcome and the development of VTE for patients with acute stroke?
Why this is important

Patients with either ischaemic or haemorrhagic stroke have a risk of both VTE and bleeding into the brain. ‘Stroke: diagnosis and management of acute stroke and transient attack [TIA]’ (NICE clinical guideline 68, published July 2008) recommends the use of aspirin for treatment of ischaemic stroke but does not recommend anticoagulants. There is recent evidence to suggest that prophylactic-doses of anticoagulants in addition to aspirin reduce the risk of VTE in patients with ischaemic stroke but there are no data showing an effect of these anticoagulants on the stroke itself. Do they increase the risk of haemorrhagic transformation and so increase neurological damage? This research should include patients with haemorrhagic or ischaemic strokes to identify which patients would benefit from additional pharmacological prophylaxis.

2.3.5 Incidence of post-thrombotic syndrome after venous thromboembolism

The GDG recommended the following research question:

- What is the incidence, loss of quality of life and cost associated with post-thrombotic syndrome after potentially preventable deep vein thrombosis?

Why this is important

During development of the guideline it became apparent that the incidence of post-thrombotic syndrome, particularly after asymptomatic deep vein thrombosis, was not well reported. This study should use standard, validated definitions to identify the incidence of post-thrombotic syndrome both when a deep vein thrombosis has occurred as a result of a hospital admission and in the absence of hospital-acquired deep vein thrombosis. The study also should aim to identify the costs to the NHS of treating post-thrombotic syndrome.
3 Methodology

3.1 Incorporation and update of NICE clinical guideline 46

The remit for this guideline was received from the Department of Health:

*To prepare a clinical guideline on the prevention of VTE in all patients admitted to hospital.*

The National Collaborating Centre for Acute Care published a guideline in 2007 on reducing the risk of venous thromboembolism (VTE) in surgical inpatients^473^. As part of the development of the current guideline, the surgical guideline was incorporated. The previous guideline^473^ is therefore superseded by this guideline and will be withdrawn.

As part of the incorporation of the surgical guideline, questions on the effectiveness of prophylaxis methods, anaesthesia and patient views & information were updated. This included re-running the searches, systematically reviewing new literature and developing and running network meta-analyses and economic models for appropriate sub-populations. The sections which were not updated were section 5.3.2 (absolute risk of VTE after surgical procedures from clinical registry data) and section 5.3.3 (absolute risk of VTE from prospective cohort studies). In addition an update search for individual patient risk factors VTE in surgical patients was not run (section 5.7), although a search was conducted for individual patient risk factors for medical patients.

The key methodology differences between this guideline and the guideline for surgical inpatients are summarised below:

- A different guideline development group was convened to provide clinical guidance into the evidence review. Some members of the guideline development group for the surgical guideline were included on the current GDG, and a list of all members for both parts of the guideline can be seen in the section titled ‘Guideline Development Group membership and Acknowledgements’.

- Some outdated or uncommon interventions (e.g. dextran, heparinoids, electrical stimulation) were excluded. These were included in the previous guideline but have not been reported in this updated version.

- Although the main outcomes (DVT, PE and major bleeding) were the same in the previous surgical and the current guideline, the different guideline development groups included slightly different criteria for identifying the outcomes. In addition some of the outcomes that the current development
group considered as important (e.g. all cause mortality) were not identified as key outcomes by the guideline development group from the previous surgical guideline. Details of the differences in outcomes considered between previous surgical guideline and the current guideline are presented for each outcome in section 3.5.

- The evidence for each patient population separately was considered separately. In the previous surgical guideline the evidence for different surgical populations was combined.

- Updated methods for network meta-analysis (Section 3.10).

- Updated economic model (chapter 4)

### 3.2 Guideline methodology

The guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in "The guidelines manual". The versions of the guideline manual used for each stage of guideline development are detailed in Table 3-1:

#### Table 3-1: Version of NICE guideline used

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoping for NICE Clinical guideline 46 (Surgery)</td>
<td>2005</td>
</tr>
<tr>
<td>Development of NICE Clinical guideline 46 (Surgery)</td>
<td>2006</td>
</tr>
<tr>
<td>Scoping and development of current clinical guideline for all hospital patients</td>
<td>2007</td>
</tr>
<tr>
<td>Validation of current clinical guideline for all hospital patients</td>
<td>2009</td>
</tr>
</tbody>
</table>

### 3.3 Developing the clinical questions

Clinical questions were developed to guide the literature searching process and to facilitate the development of recommendations by the guideline development group.

The clinical questions were initially drafted by the review team and were refined and validated by the guideline development group. The questions were based on the scope (Appendix A).

#### 3.3.1 Questions on effectiveness of interventions to reduce the risk of VTE

The clinical questions were:

- What is the effectiveness of X vs Y in reducing the incidence of VTE?

Where X and Y are the prophylaxis methods in the list of interventions below. Every possible combination was compared.

a) Graduated elastic compression stockings / anti-embolism stockings (GCS)

b) Intermittent pneumatic compression (IPCD) devices
c) Foot pumps or foot impulse devices (FID)

d) Vena caval filters

e) Aspirin or antiplatelet therapy

f) Low-dose unfractionated heparin administered subcutaneously (UFH)

g) Low molecular weight heparin (LMWH)

h) The synthetic pentasaccharide, Fondaparinux

i) Vitamin K Antagonists (For example, warfarin, coumarin)

j) Early mobilisation

k) Foot elevation

l) Hydration

m) New oral anticoagulants licensed during the guideline development period.*

n) Placebo or no intervention

* During the development of the guideline two new oral anticoagulants; dabigatran (direct thrombin inhibitor) and rivaroxaban (direct factor Xa inhibitor) were considered by NICE as part of their health technology appraisal (HTA) programme. The NICE HTA report for dabigatran was published in September 2008. The appraisal on rivaroxaban was published in April 2009, and was incorporated into our guideline after the stakeholder consultation.

The effectiveness of combinations of methods of prophylaxis (For example, a combination of a mechanical and a pharmacological intervention or two mechanical devices) were also considered versus no prophylaxis, versus single methods or versus other combinations.

3.3.2 Additional considerations on the use of the above interventions

In addition to the questions of effectiveness of prophylaxis (section 3.3.1) we examined more detail regarding prophylaxis in the following areas:

- Extending pharmacological prophylaxis beyond the hospitalised period.

- Potential variations in effectiveness by fixed or adjusted dose vitamin K antagonists (e.g. warfarin)

- The pre or post operative administration of pharmacological prophylaxis (LMWH)

- The length of mechanical devices anti-embolism stocking or intermittent pneumatic compression devices (e.g. knee-length vs. over the knee)
3.3.3 Anaesthesia

The following clinical questions relating to anaesthesia were examined:

- What is the effectiveness of regional anaesthesia vs general anaesthesia in reducing the incidence of postoperative VTE?
- Does adding a regional to a general anaesthetic reduce the risk of postoperative VTE?

3.3.4 Risk factors

We developed questions to address risk factors for VTE associated with surgical procedure, medical conditions and for individual patient risk characteristics:

- Which surgical procedures carry a high risk of deep vein thrombosis (DVT)/Pulmonary Embolism (PE)?
- Which medical conditions carry a high risk of DVT/PE?
- Which individual patient factors (for both surgical and medical patients) are risk factors for developing DVT/PE?

3.3.5 Patient information and communication

We examined the following clinical questions:

- What specific information about the prophylaxis methods or VTE should be provided to patients who require VTE prophylaxis?
- Does providing patients who were admitted to hospital with information about VTE or VTE prophylaxis methods:
  - reduce the number of DVTs and pulmonary embolisms?
  - affect any of the other outcomes listed or patient adherence?

3.3.6 Patient views and preferences

We searched for evidence of patient views (effectiveness and acceptability) and preferences regarding all the interventions listed in section 3.3.1.

3.4 Patients covered by this guideline

We searched for studies of adults (age 18 years and older) admitted to hospital for any reason. A more detailed list of patient groups that are included or excluded from the guideline can be found in the scope (Appendix A).

3.5 Outcomes

3.5.1 Primary outcomes

3.5.1.1 All cause mortality
This was identified as an important outcome. The evidence for all cause mortality was extracted from any new studies that were reviewed. These data had not been extracted for the previous version of the guideline and it was not possible to extract data for all cause mortality from all of the surgical areas already reviewed.

3.5.1.2 **Deep-vein thrombosis (DVT)**

DVT (symptomatic and asymptomatic) identified by one of the following methods:

- Radioiodine (125I) fibrinogen uptake
- Venography
- Doppler ultrasound
- Magnetic resonance imaging (MRI)

In order to detect all asymptomatic DVTs the inclusion criteria required that all patients included in the study were screened using one or more of the methods above. Studies that only assessed patients with clinical suspicion of DVT were not included for this outcome.

The following methods of diagnosing DVT were excluded as they were considered to be unreliable (unless used in conjunction with one of the methods outlined above):

- D-dimer blood assay test alone
- Impedance plethysmography (for the medical guideline this test was accepted if it was used as a ‘rule out’ tool for screening all patients providing the DVT events were subsequently confirmed using one of the objective methods.)
- Clinical examination alone

3.5.1.3 **Pulmonary embolism (PE)**

PE determined by one or more of the following methods

- Pulmonary angiogram
- Ventilation/perfusion scan (pulmonary scintigraphy)
- CT pulmonary angiogram
- Echocardiography (medical guideline only)
- Autopsy
- Clinical suspicion confirmed by one of the preceding methods

The following methods of diagnosing PE were excluded as they were considered to be unreliable:
• Chest X-ray alone
• Clinical examination alone

For the studies reviewed for the surgical guideline all pulmonary embolisms were included as the outcome measure and in the medical section only symptomatic pulmonary embolisms were included. This was because the Guideline Development Group agreed that symptomatic pulmonary embolism was more commonly reported in studies.

3.5.1.4 Major bleeding events

A bleeding events were considered to be “major” on the basis of the authors’ own established criteria, or if the results reported corresponded to one of the definitions below.

A major bleeding event is defined as a bleeding event that results in one or more of the following:

• death,
• a decrease in haemoglobin concentration of 2g/dl or more,
• transfusion of at least 2 units of blood,
• bleeding from a retroperitoneal, intracranial, or intraocular site
• a serious or life-threatening clinical event,
• a surgical or medical intervention.

We included papers that met our quality criteria if they reported at least one of the following outcomes:

• DVT,
• PE.

3.5.2 Secondary outcomes

The following secondary outcomes were also included in our review where reported:

• post-thrombotic syndrome (PTS),
• chronic thromboembolic pulmonary hypertension (CTEPH),
• heparin-induced thrombocytopenia (HIT),
• neurological events,
• quality of life,
• survival,
3.5.3 Important methodological issues relating to the outcomes

- Pulmonary emboli, major bleeds, spinal haematomas and heparin-induced thrombocytopenia are rare events, consequently, large numbers of patients are required to obtain an estimate of effect.

- Very few trials assess all patients for pulmonary embolism using objective methods.

- Where trials assess both DVT and pulmonary embolism, protocols usually dictate that patients in whom a DVT is detected are withdrawn and started on anticoagulant therapy which may prevent further progression of the disease. This may result in an underestimation of the PE rate as many of these patients (particularly those with asymptomatic DVT) would not have been picked up in standard practice.

- Chronic thromboembolic pulmonary hypertension and post thrombotic syndrome are long term events that may occur many years after the initial thrombotic event. The follow up period in trials is unlikely to be long enough to identify these events.

- Very few trials reported any of the secondary outcomes.

3.6 Clinical literature search

The aim of the literature search was to find evidence within the published literature in order to answer the clinical questions identified. We searched clinical databases using filters (or hedges), using relevant medical subject headings and free-text terms. Non-English studies and abstracts were not reviewed. Searches were conducted to update the previous guideline.

Each database was searched up to 10 December 2008. We performed one initial search and then two update searches nearer the end of guideline development period. No papers after this date were considered. After the first draft of the guideline had been returned after stakeholder consultation a new study presenting results of the effectiveness of stockings in stroke patients was published in June 2009. This study reported new evidence on the use of stockings in stroke patients. The GDG decided the study should be included and felt that recommendations concerning the use of stockings should be reconsidered. To ensure all stockings studies published since the last searches in December 2008 were identified the search for evidence on stockings was updated to 9 June 2009.

The search strategies can be found in Appendix C.

The following databases were searched:

- The Cochrane Library up to Issue 4 2008
- Medline 1950-2008 (OVID)
- Embase 1980-2008 (OVID)
- Cinahl 1982-2008 (NLH Search 2.0)
- Health Economic and Evaluations Database (HEED) up to December 2008

There was no systematic attempt to search for grey literature or unpublished literature although all stakeholder references were followed up. We searched for guidelines and reports via relevant websites including those listed below.

- Members of the Guidelines International Network’s web sites (http://www.gi-n.net/)
- National Institute of Health and Clinical Excellence (NICE) (www.nice.org.uk)
- National Library for Health (NLH) (http://www.library.nhs.uk/)
- National Institutes of Health Consensus Development Program (consensus.nih.gov)
- New Zealand Guidelines Development Group (NZGG) (http://www.nzgg.org.nz/)
- Scottish Intercollegiate Guideline Network (SIGN) (www.sign.ac.uk)

3.7 Hierarchy of clinical evidence

There are many different methods of ranking the evidence and there has been considerable debate about which system is best. We used the system, developed by the Scottish Intercollegiate Guidelines Network (SIGN), and outlined in the NICE guidelines manual[480], shown in Table 3-2.

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1-</td>
<td>Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High-quality systematic reviews of case–control or cohort studies. High-quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well-conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2-</td>
<td>Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies (For example, case reports, case series)</td>
</tr>
</tbody>
</table>
For each clinical question the highest level of evidence was sought. Where an appropriate systematic review, meta-analysis or randomised controlled trial was identified, we did not search for studies of a weaker design. Studies assessed as being levels 1- and 2- were excluded.

### 3.8 Literature reviewing process

References identified by the systematic literature search were screened for appropriateness by title and abstract by an information scientist and systematic reviewer. Studies were selected that reported one or more VTE outcome (DVT, PE) determined by objective/reliable methods. We did not select studies that reported only major bleeding outcomes, but where an included systematic review reported such studies, they were not removed. The guideline development group also suggested further references and we assessed these in the same way.

Selected studies were ordered and assessed in full by a systematic reviewer using agreed inclusion/exclusion criteria specific to the guideline topic, and using NICE methodology quality assessment checklists appropriate to the study design. These are described in the NICE guidelines manual.\(^{480}\)

#### 3.8.1 Literature review for patient view studies.

Information of patient views regarding thromboprophylaxis and adherence are often more appropriately studied using non-RCT designs (i.e qualitative studies, surveys of patients in observational studies). Unlike interventional studies, there is no established hierarchy of evidence to answer questions on patient views; observational or qualitative designs are not necessarily of lower quality than RCTs. Therefore, no study design limitation was included in the search and review of evidence. Relevant studies where the methods were clearly reported, appropriately designed to answer the study questions and met the quality assessment were included.

Qualitative studies were quality assessed using checklists from the NICE guideline manual\(^{480}\) and only studies rated as ‘+’ or ‘++’ were included.

The questionnaires used in the various patient view studies found in our searches did not report on how they were designed and validated. This is a major methodological limitation for all studies using questionnaires in this guideline.

It is also important to note that both RCTs and observational studies of patient adherence come with potential biases and limitations. For example, the informed consent process and strict inclusion criteria of RCTs may contribute to better informed or motivated patients. In addition, participation in RCTs is usually associated with closer monitoring and better level of support. This may result in higher adherence than may be expected in routine practice. Adherence may also be higher in studies where patients were checked hourly for adherence or where self-reports were used. However, when a range of results are observed in different study designs and settings, these provide a useful
indication of the types of issues that might be expected from the interventions in usual practice.

3.9 Methods for combining direct evidence

Where possible, meta-analyses were conducted to combine the results of studies addressing the same clinical question using Cochrane’s Review Manager Software. Random effects method (Der Simonian and Laird model) was used to calculate risk ratios (relative risk) of an event occurring, that is, all cause mortality, DVT, PE or major bleeding. Statistical heterogeneity was assessed by considering the chi-squared and the I-squared test. Significant heterogeneity was noted for any study where the I-squared value was >50%, or the I-squared value was between 25% and 50% and the chi-squared value was p <0.1. We carried out sensitivity analyses to identify studies whose results were heterogeneous to the overall result. Any such studies were further assessed to identify any clinical or methodological causes. We avoided removing these studies from the meta-analyses unless we identified a serious methodological flaw, as removal would introduce bias into the systematic review.

Where combining results of trials in a meta-analysis was not appropriate a narrative synthesis of studies was undertaken.

3.10 Methods for combining direct and indirect evidence

It is difficult to determine the most effective prophylaxis strategy from the results of conventional meta-analyses of direct evidence for three reasons:

1) Some pairs of alternative strategies have not been directly compared in an RCT (for example, aspirin vs. fondaparinux).

2) Sometimes the direct evidence does not provide enough data and we need to support it with indirect evidence.

3) There are frequently multiple overlapping comparisons (For example, heparin vs. no prophylaxis, heparin vs. stockings and stockings vs no prophylaxis), that potentially give inconsistent estimates of effect.

To overcome these problems, we conducted a network meta-analysis (NMA) that simultaneously pools together all the data. This allowed us to rank the different prophylaxis interventions in order of efficacy at reducing DVTs and PEs and in order of risk of major bleeding. For each of these two outcomes, it gives us a single estimate of effect (with confidence intervals) for each intervention compared with no prophylaxis.

The advantages of a network meta-analysis are that

- It enables the ranking of different interventions
- It facilitates cost-effectiveness analysis
- It never breaks randomisation
- It doesn’t discard any randomised evidence
• It is useful for diagnosing inconsistency/heterogeneity between evidence comparisons (3.10.3).

NMA does require an additional assumption over conventional meta-analysis. In the case of a fixed-effects NMA, it assumes that intervention A has the same effect on patients in trials of AvsB as it does in trials of AvsC, etc. In the case of random-effects NMA, the assumption is that intervention A has the same effect distribution across trials of AvsB as it does across trials of AvsC, etc.

3.10.1 Study inclusion criteria

The following interventions were excluded from the network meta-analysis:

• dextran, danaparoid, antiplatelet drugs other than aspirin, fixed-dose vitamin K antagonists—since these are unlicensed, dated, and not likely to be recommended

• different anaesthetic regimes, since most of the surgical studies patients had a mixture of types of anaesthesia

• hydration, physiotherapy, continuous passive motion, foot elevation, electrical stimulation and vena caval filters, where there was insufficient RCT evidence.

• A combination of two types of mechanical prophylaxis was not included in the base case analysis because the data are from only a few small trials and the GDG did not consider this evidence to be robust.

Randomised controlled trials (RCTs) that evaluated two or more of the following interventions were included in the network meta-analysis (NMA):

• aspirin (low-dose & high-dose), dabigatran, rivaroxaban, fondaparinux, heparin (UFH/LMWH), adjustable-dose vitamin K antagonists (VKA-adj)

• graduated compression / anti-embolism stockings (GCS), intermittent pneumatic compression / foot impulse devices (IPCD/FID)

• nil (i.e. no prophylaxis or placebo)

• combinations of one drug and one mechanical device

• combinations of UFH and aspirin

Our analysis was also restricted to those populations and outcomes where there was a substantial amount of RCT data. Thus we chose the following population subgroups:

• hip fracture surgery,

• total hip replacement,

• total knee replacement,
general surgery (including gastrointestinal, gynaecological, laparoscopic, thoracic and urological surgery),

- general medical admissions.

And the following outcomes:

- DVT (asymptomatic+symptomatic) – from studies that screened the whole leg,
- symptomatic pulmonary embolism,
- major bleeding.

Analysis of major bleeding was carried out by pooling the data across all 5 population subgroups, since the data were sparse.

We also looked at all-cause mortality but only for two populations: hip fracture surgery and general medical admissions. Data were not collected for other populations (see Section 3.5.1.1). The event rates were expected to be low for these populations that it was deemed unlikely to allow for useful comparison. Pooling across populations is not appropriate given that both bleeding and pulmonary embolism effects contribute to mortality.

In all our network meta-analyses we considered foot impulse devices and intermittent pneumatic compression devices to be the same class of intervention. This is because of the range of different devices, the lack of evidence to consider them separately (especially in combination with different drugs) and because preliminary analysis suggested that they have a very similar effect. Graduated compression / anti-embolism stockings were kept as a distinct category since the biological mechanism is quite different and because there was some evidence of differential effects when compared with the other types of mechanical prophylaxis.

There are no biological reasons to believe that the presence of mechanical prophylaxis would influence the risk of major bleeding. Therefore, for the major bleeding NMA, mechanical only strategies are categorised as “Nil”. Likewise combination strategies are categorised according to their drug component only. We assume that the major bleeding rate for mechanical only strategies is the same as for the Nil strategy.

We included studies where the baseline was admission or surgery and where the interventions lasted up to three weeks (termed ‘standard duration’). Trials that started post-discharge were not included in the network meta-analysis. Where there was a choice of follow-up periods, we used the one that was furthest from baseline.

### 3.10.2 The model

We performed a hierarchical Bayesian NMA method\textsuperscript{411} using the software WinBUGS. This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term ‘network’ better describes the data structure, whereas ‘mixed treatments’ could easily be misinterpreted as referring to combinations of treatments.
We adapted a program on the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mixed-treatment-comparisons.html. Last accessed 20th January 2009). The model accounts for the correlation between arms in three-arm trials. We had no four-arm trials in our analysis.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each population subgroup we have produced a diagram of the evidence network to show which interventions have been included. Trials with zero events in each arm were excluded since these do not contain evidence relevant to the analysis. This explains, in part at least, why there are far fewer trials in our NMAs of pulmonary embolism compared with our NMAs of DVT.

The model takes the form of a random effects logistic regression model. The model parameters are estimated by Markov Chain Monte Carlo Simulation. Being a Bayesian analysis, the evidence distribution is weighted by a distribution of our prior beliefs. We have used non-informative prior distributions to maximise the weighting given to the data. These priors are normally distributed with a mean of zero and standard deviation of 10,000.

For each analysis we conducted a burn-in of 60,000 simulations to allow convergence and then a further 60,000 simulations to give us our output. Convergence was assessed by examining the history, kernel density and autocorrelation plots. We also checked the Monte Carlo error statistic. An alternative set of starting values were used to ensure that the results were not sensitive to these parameters.

We tested the goodness of fit of the model by calculating the residual deviance. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

Since the model is a logistic regression, the output parameters are odds ratios. For ease of interpretation we have converted these to relative risks (RR) using the following formula:

$$RR = \frac{OR}{(1 - P_0) + (P_0 \times OR)}$$

where $P_0$ is the risk of the event in the control arm. We estimated the RR for each of the 60,000 simulations, treating $P_0$ as a constant. The point estimate of the RR was taken to be the median of the 60,000 simulations and the 95% confidence intervals for the RR were taken to be the 2.5th and 97.5th centiles from the distribution of the RR.

### 3.10.3 Dealing with inconsistency

Supposing that there are trials of C vs B that give a relative risk (RR) of 0.8 and trials of B vs A that give a RR of 0.5 (Figure 3-1) then this implies that a comparison of C vs A would give a RR of 0.4 (0.8 x 0.5). But if the actual trials of C vs A indicate a RR of 0.5 then there is some kind of inconsistency within our data network. A network meta-analysis would re-estimate the RRs for all three comparisons using the all data pooled together.
There are two causes of this inconsistency. The first is chance, and if this is the case then the network meta-analysis results are more precise, since they pool more data than conventional estimates. The second is that there are differences in the trials included in the different comparisons. Differences that might potentially lead to inconsistency include:

- Different populations (sex, age, risk factors)
- Different interventions (doses, stocking length)
- Different measures of outcome (fibrinogen uptake, venography)
- Different follow-up periods (7-10 days, 14 days, 3 months)

This heterogeneity is a problem for NMA and needs to be dealt with by subgroup analysis and sometimes by re-defining inclusion criteria.

We identified the presence of heterogeneity by subjectively comparing the NMA odds ratio estimates with odds ratios derived from direct comparison estimates. Then we sought to identify the cause of this heterogeneity by examining the details of the study design, population, interventions and outcomes of the relevant trials.

### 3.11 Health economic methods

It is important to investigate whether health services are cost-effective (that is, value for money). If a particular prophylaxis or treatment strategy were found to yield little health gain relative to the resources used, then it would be advantageous to re-deploy resources to other activities that yield greater health gain.

In the previous NICE guideline we found great inconsistency in the economic evaluations in the published literature. This was mainly because the evaluations varied in the clinical studies they included and because they used crude methods to deal with indirect evidence. Furthermore most of the published studies did not evaluate cost-effectiveness using NICE’s reference case. Therefore in this guideline an original cost-effectiveness analysis was performed which compared a variety of different prophylactic strategies for a number of different hospital population subgroups.

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**Figure 3-1: Inconsistency between trial comparisons**

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addition, a systematic review of the economic literature was conducted for populations or interventions not covered by the original cost-effectiveness analysis.

The criteria applied for an intervention to be considered cost-effective were either:

a) The intervention dominated other relevant strategies (that is, it is both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or

b) The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy (and compared with no prophylaxis).

The full economic evaluation of any strategy has to be in comparison with another strategy. Hence we refer to:

- incremental cost: the mean cost of one strategy minus the mean cost of a comparator study
- QALYs gained: the mean QALYs associated one strategy minus the mean QALYs of a comparator study
- incremental cost-effectiveness ratio: the incremental cost divided by the respective QALYs gained
- incremental net benefit (INB): the (monetary) value of a strategy compared with an alternative strategy for a given cost-effectiveness threshold (For example: £20,000 per QALY gained).

In our own cost-effectiveness analysis (Chapter 4), we use the following formula to estimate the INB of each strategy:

\[ \text{INB} = (\text{QALYs gained compared with no prophylaxis } \times \text{£20,000}) - \text{the incremental cost compared with no prophylaxis}. \]

This indicates that we will invest up to £20,000 to gain one additional QALY. The strategy that has the highest INB is the optimal (that is, most cost-effective) strategy. Strategies that have a negative INB are not cost-effective even compared with no prophylaxis.

3.11.1 Literature review for health economics

We obtained published economic evidence from a systematic search of the following databases:

- The Cochrane Library up to Issue 4 2008
- Medline 1950-2008 (OVID)
- Embase 1980-2008 (OVID)
- Health Economic and Evaluations Database (HEED) up to December 2008
The information specialists used the same search strategy as for the clinical questions, using an economics filter in the place of a systematic review or randomised controlled trial filter. Each database was searched from its start date up to December 2008. Papers identified after this date were not considered. Search strategies can be found in Appendix C.

Each search strategy was designed to find any applied study estimating the cost or cost-effectiveness of an included prophylaxis intervention. A health economist reviewed the abstracts. Relevant references in the bibliographies of reviewed papers were also identified and reviewed.

Papers were excluded from the review and evidence tables if:

- The population and interventions were covered by an original guideline cost-effectiveness analysis.
- The study did not contain any original data on cost or cost-effectiveness (that is, it was a review or a clinical paper).
- The analysis was not incremental and was not described adequately to allow incremental analysis (so studies reporting only average cost-effectiveness ratios were excluded unless they provided data to allow the calculation of incremental cost-effectiveness ratios).
- Cost analyses were excluded if the results were not presented in a way that would allow the incremental cost per patient to be extracted or derived.

Where a comparison had a large number of evaluations (for example, LMWH vs UFH), we excluded those based on cohort studies and those based on simple models (that is, neither a meta-analysis nor a formal decision analytic model).

Included papers were reviewed by a health economist. In the evidence tables costs are reported as given in the paper. However, where costs were in a currency other than pounds sterling, the results were converted to pounds sterling using the relevant purchasing power parity for the study year.

We have included studies from all over the world in our review, however, we use overseas studies with caution since resource use and especially unit costs vary considerably. Particular caution is applied to studies with predominantly private health insurance (for example, USA or Switzerland) where unit costs may be much higher than in the UK and to developing countries where costs may be much lower.

Each study was categorised as one of the following: cost analysis, cost-effectiveness analysis, cost-utility analysis (that is, cost-effectiveness analysis with effectiveness measured in terms of QALYs), or cost consequences analysis. We did not find any ‘cost benefit analyses’ (studies that put a monetary value on health gain).

Models are analogous to systematic reviews as they are pooling evidence from a number of different studies and therefore if well-conducted they should out-rank studies based on a single RCT. Statistical significance is not usually applicable to models and uncertainty is explored using sensitivity analysis instead. Hence the results reported in our economics evidence tables and write-up may not necessarily imply statistical significance.
In our own cost-effectiveness analysis we rigorously explore the effects of sample variation using Monte Carlo simulation (Chapter 4).

Where QALYs were not estimated, we used thresholds of £20,000 per life-year gained, or £400,000 per life saved.

We state that cost-effectiveness is ‘indeterminable’ in cases where outcomes are expressed only in terms of VTEs rather than overall health outcomes and where one intervention is both more costly and more effective.

3.11.2 Cost-effectiveness modelling

The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the model.
- The model was based on a network meta-analysis derived from the systematic review of clinical evidence.
- Model assumptions were reported fully and transparently (Chapter 4).
- The results were subject to thorough sensitivity analysis and limitations discussed.
- Costs were calculated from a health services perspective.

3.12 Development of recommendations

Over the course of the guideline development process the GDG was presented with the following:

- Evidence tables and narrative summaries of the clinical evidence reviewed. All evidence tables are in Appendix D
- Forest plots of direct meta-analyses (Appendix E).
- Forest plots of network meta-analyses (Chapters 9-12, 23).
- A description of the methods for, and results of, the cost-effectiveness analysis (Chapter 4 and Chapters 9-12, 23).

Although evidence was reviewed for every population, network meta-analysis and cost effectiveness analyses were only conducted for 5 populations, general medical patients, general surgical patients, hip fracture surgery, total hip replacement and total knee replacement. For these populations the recommendations were derived directly from the results of the analyses. If the decision was taken not to recommend the most cost effective strategy the GDG clearly explained their reasoning for this.

For populations which did not have cost effectiveness models conducted, recommendations were based on the direct evidence available for that population and from extrapolating the results from cost-effectiveness models in other populations. The link between evidence and the subsequent recommendations is explained in the relevant sections.
We used a modified version of the nominal group technique of consensus development to agree the final recommendations.

3.13 Research recommendations

When we identified areas for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as the importance to patients or the population, national priorities, and the potential impact on the NHS and future NICE guidance. The individual chapters contain a summary of the research recommendations and the justification for the top five priority research recommendations are presented in Appendix F.

3.14 Prioritisation of recommendations for implementation

To assist users of the guideline in deciding the order in which to implement the recommendations, the guideline development group identified ten key priorities for implementation. The decision was made after discussion and voting by the GDG. They selected recommendations that would:

- have a high impact on outcomes that are important to patients,
- have a high impact on reducing variation in care and outcomes,
- lead to a more efficient use of NHS resources,
- promote patient choice,
- promote equalities.

3.15 Validation of guideline

Registered stakeholders were given the opportunity to comment on the draft guideline, which was posted on the NICE website. A Guideline Review Panel also reviewed the guideline and checked that stakeholders’ comments had been addressed.

A second consultation was conducted because the results of a large randomised controlled trial was published after the first consultation. As a result of the second consultation, some changes were made for the General Medical Patients (Chapter 23) and Stroke Patients (Chapter 24) recommendations.

3.16 Related NICE guidance

NICE has developed the following guidance (details available from www.nice.org.uk):

- Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults476 (Publication date September 2008)
- Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults479 (Publication date April 2009)
3.17 Updating the guideline

NICE clinical guidelines are updated as needed so that recommendations take into account important new information. We check for new evidence 3 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.
4 Development of cost-effectiveness model

4.1 General approach

Our aim in constructing the model was to determine the most cost-effective thromboprophylaxis strategy for different hospital population subgroups. The efficacy of each prophylaxis strategy is based on the results of the trials in our systematic review.

4.1.1 Interventions

The thromboprophylaxis interventions we compared in the model are those which we evaluated in our network meta-analysis (Section 3.10 above), which was based on the RCTs included in our clinical review. Trials that evaluated the following interventions were excluded from the network meta-analysis:

- dextran, danaparoid, antiplatelet drugs other than aspirin, fixed-dose vitamin K antagonists—since these are unlicensed, dated, and not likely to be recommended
- different anaesthetic regimes, since most of our studies patients had a mixture of types of anaesthesia
- hydration, physiotherapy, continuous passive motion, foot elevation, electrical stimulation and vena caval filters, where there was insufficient RCT evidence.
- A combination of two types of mechanical prophylaxis was not included in the base case analysis because the data were from only a few small trials and the Guideline Development Group did not consider this evidence to be robust.

Interventions included in the network meta-analysis:

- aspirin (low dose & high dose), dabigatran, fondaparinux, unfractionated heparin (UFH), Low molecular weight heparin (LMWH), adjustable-dose vitamin K antagonists (VKA), rivaroxaban
- graduated compression / anti-embolism stockings (GCS), intermittent pneumatic compression / foot impulse devices (IPCD/FID)
- nil (i.e. no prophylaxis or placebo)
- combinations of one drug and one mechanical device
4.1.2 Population

We conducted a cost-effectiveness analysis for each of five population subgroups:

- hip fracture surgery
- total hip replacement
- total knee replacement
- general surgery (including other internal surgery)
- general medical admissions

The cost-effectiveness of post-discharge / extended duration prophylaxis was considered separately for hip replacement patients, hip fracture and general surgery patients (Section 4.7).

4.1.3 Outcomes

The primary outcomes are quality-adjusted life-years (QALYs) gained and incremental cost.

The model employed a baseline cost-effectiveness threshold of £20,000 per QALY gained, complying with the reference case advocated by NICE, such that costs were estimated from an NHS and personal social services perspective. Future costs and QALYs are discounted at 3.5%.

4.1.4 The model

The model consists of a simple decision tree (Figure 4-2). The tree is repeated for each prophylaxis strategy. Each endpoint of the tree implies a particular cost and a particular health outcome (QALYs). For each prophylaxis strategy, the mean QALYs are calculated by summing across all the tree endpoints, the QALYs multiplied by the probability of reaching that endpoint. For different prophylaxis strategies the probabilities will be different and hence the mean costs and mean QALYs will be different also.

A separate model is constructed for each of the population subgroups stated above. Further models were developed for each of the post-discharge / extended duration population subgroups (Section 4.7).

VTEs and major bleeding events are modelled for the acute period (this is determined by the RCT follow-up, typically only 10-14 days) but QALYs and health service costs arising...
from these events are modelled over the patient’s lifetime, including treatment of post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH).

**Figure 4-2: Decision tree**

*PE=pulmonary embolism; PTS=post-thrombotic syndrome, PHT=chronic thromboembolic pulmonary hypertension; symp=symptomatic.*
4.2 Relative risks

The between-strategy differences in costs and effects are driven by each strategy’s relative risk (RR) reduction for VTE, and its relative risk increase for major bleeding. For example, the number of DVTs occurring under the LMWH strategy is the baseline risk of DVT (in the absence of prophylaxis) multiplied by the DVT RR reduction for LMWH compared with no prophylaxis.

4.2.1 VTE

We use the relative risks from our network meta-analysis of DVT risk (Section 3.10 Methods of combining indirect evidence). These relative risks were estimated in a separate network meta-analysis for each of the five population subgroups. The network meta-analysis uses a simulation approach and therefore for each RR we have a set of (60,000) results. Throughout the guideline, the point estimate for each RR reported is a median of 60,000 simulations. For our probabilistic analysis (see 4.8.1) we sampled 10,000 times from the set of 60,000 relative risks. For our deterministic analysis (i.e. based on point estimates) we used the mean of the 60,000 RRs. We chose the mean (rather than the median, which was used to report the network meta-analysis point estimate - 3.10.2) so that the deterministic results would be as similar as possible to the probabilistic results.

In the model we apply these RR reductions for DVT overall to symptomatic DVT, non-fatal pulmonary embolism, fatal pulmonary embolism, post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension as well as asymptomatic DVT. Thus, if a certain strategy was shown to reduce DVTs by 60% then in the model the incidence of fatal pulmonary embolism etc is also reduced by 60%.

We had conducted separate network meta-analyses for pulmonary embolism. However, these were based on sparse data and therefore the Guideline Development Group decided that the DVT RRs would be more robust estimates of the relative effects of prophylaxis on pulmonary embolism. Hence the pulmonary embolism relative risks were used only in a sensitivity analysis.

4.2.2 Bleeding

We use the mean relative risks (RR) from our network meta-analysis of major bleeding risk (Section 3.10 Methods of combining indirect evidence). These relative risks were pooled across all population subgroups because the data were so sparse that the Guideline Development Group felt that the estimates of major bleeding increase for specific population subgroups would not be sufficiently precise. However, subpopulation-specific estimates were used in a sensitivity analysis.

In the model we apply these RR increases for major bleeding overall to fatal bleeds and strokes as well as non-fatal major bleeding.

We assume that the major bleeding rate for mechanical only strategies is the same as for the nil strategy (i.e. mechanical prophylaxis has no effect on bleeding). This is reasonable on biological grounds.

In the post-discharge analyses the relative risk for major bleeding from the RCTs was less than one for LMWH (implying that LMWH reduces bleeding), although not significantly.
We believe it implausible that LMWH would decrease bleeding and therefore, in these instances for the deterministic analysis we assumed a RR of 1. For the probabilistic analysis we used the RCT point estimate and its standard error.

Similarly the network meta-analysis indicated a substantial reduction in bleeding associated with high-dose aspirin, albeit with wide confidence intervals. Again this seemed highly implausible. We set the major bleeding RR in the model to 1 for both the deterministic and probabilistic analysis. However, we did use the network meta-analysis estimate in a sensitivity analysis. The Guideline Development Group believed that the base case estimate of 1 was still a substantial under-estimate and a higher estimate of 1.3 was also used in a sensitivity analysis from a conventional meta-analysis.

In most cases the network meta-analysis mean RR was very similar to the median RR from the same analysis. In the case of dabigatran in knee replacement surgery it was slightly different. Although the median 0.87 implied a slight reduction in bleeding, the mean 1.001 implied a very slight increase. Since the median was not less than one, we made no adjustment for dabigatran (unlike aspirin) in the base case. We conducted a sensitivity analysis increasing the risk to the same level as LMWH.

4.2.3 Other complications

The only complications of prophylaxis included in these models are major bleeding (section 4.2.2) and HIT (section 4.3.2), both of which are complications of pharmacological prophylaxis. We believe that these are the most important complications but are aware that there may be others that are also important but difficult to quantify. Mechanical prophylaxis is not without complications. For example a study\textsuperscript{158} in stroke patents (section 24.2) found a significant increase in adverse events related to the use of GCS, such as skin breaks, ulcers, blisters or skin necrosis. However, this is a special group of patients and the results are unlikely to be transferrable to other populations. Trials in other populations have not found significant complications and therefore we have not included in our model treatment costs or utility decrements associated with such complications. We do have some survey evidence (section 6.6.1) that reports some patients find stockings uncomfortable (knee-length: 11%; full-length: 21%)\textsuperscript{43}. This suggests that there is some disutility (i.e. reduced quality of life) associated with stockings but this disutility is difficult to quantify and might be negligible compared with the patient’s underlying condition, especially as the disutility is transient. Perhaps of more concern is that the discomfort might cause patients to wear the stockings incorrectly (especially thigh-length stockings) – this might mean that the effectiveness estimated in trial conditions will not be replicated in practice – but for this reason we have included in our model the cost of nurse time for checking that stockings are fitted correctly (section 4.4.1). The extent to which any of these complications applies to other forms of mechanical prophylaxis is also unclear.

| Table 4-3: Baseline risk and other parameters that vary by population subgroup |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Source          | Hip Fracture surgery | Total hip replacement (THR) | Total knee replacement (TKR) | General surgery | General medical |
| Mean age (years) | a) HES 2005-6\textsuperscript{159} | 82(a) | 70(a) | 70 (a) | 60(b) | 74(b) |
## Venous Thromboembolism Prophylaxis

<table>
<thead>
<tr>
<th>Source</th>
<th>Hip Fracture surgery</th>
<th>Total hip replacement (THR)</th>
<th>Total knee replacement (TKR)</th>
<th>General surgery</th>
<th>General medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Male</td>
<td>a) HES 2005-6 [199] b) RCTs from our systematic review</td>
<td>23%(a)</td>
<td>38%(a)</td>
<td>42% (a)</td>
<td>50%(b)</td>
</tr>
<tr>
<td>Standardised Mortality Ratio (g)</td>
<td>a) Seagroatt (1994) [599] b) Ramiah (2007) [543] c) Nunley 2003 [494] d) assumed e) Herman Lingen 2001 [277] (f)</td>
<td>461% (a) (1 year)</td>
<td>Men: 85% (b)</td>
<td>Women: 98% (b) (10 years)</td>
<td>52% (c) (1 year)</td>
</tr>
<tr>
<td>Proportion of DVTs that are symptomatic (Ratio of symptomatic DVTs to all DVTs)</td>
<td>a) assumed to be same as THR b) Quinlan (2007) [542] c) RCTs from our systematic review (all patient combined excl TKR &amp; THR)</td>
<td>21.0%(a)</td>
<td>21.0%(b)</td>
<td>5.0%(b)</td>
<td>6.2%(c) (=40/644)</td>
</tr>
<tr>
<td>Major bleeding fatality rate(h)</td>
<td>a) Muntz (2004) [467] systematic review of thrombo-prophylaxis RCTs b) RCTs from our systematic review</td>
<td></td>
<td>0.8%(a) (=5/632)</td>
<td></td>
<td>14.3%(b) (=8/56)</td>
</tr>
<tr>
<td>Pulmonary embolism fatality rate (i)</td>
<td>RCTs in our systematic review</td>
<td>31.0% (=9/29)</td>
<td>6.0% (=11/184)</td>
<td></td>
<td>44.7% (=17/38)</td>
</tr>
<tr>
<td>Re-operation rate after major bleed</td>
<td>a) From a review of recent fondaparinux and dabigatran trials [36,175,377,476,651] b) Muntz (2004) [467]</td>
<td></td>
<td>13%(a)</td>
<td>21%(b)</td>
<td></td>
</tr>
<tr>
<td>Baseline risk in the absence of prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT risk</td>
<td>No prophylaxis/placebo arms of RCTs from our systematic review (Table 5-17 and Table 5-19)</td>
<td>39.8%</td>
<td>45.0%</td>
<td>60.0%</td>
<td>20.9%</td>
</tr>
<tr>
<td>Symptomatic pulmonary embolism (PE) risk</td>
<td>a) No prophylaxis/placebo arms of RCTs from our systematic review (Table 5-17 and Table 5-19) b) An estimate as no studies have presented results for symptomatic PE in the absence of prophylaxis(i).</td>
<td>7.9% (a)</td>
<td>3.4% (a)</td>
<td>1.0% (b)</td>
<td>1.3% (a)</td>
</tr>
<tr>
<td>Major bleeding risk</td>
<td>No prophylaxis/placebo arms of RCTs from our systematic review (Table 5-20 and Table 5-21)</td>
<td>3.2%</td>
<td>1.6%</td>
<td>1.9%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>
(f) Rate calculated from the mortality rate for general medical patients at 1 year (Herman Lingen (2001) 277) divided by death rate in the general population matched for age and gender. (Office of National statistics 2005)500.

(g) Standardised Mortality Ratio = Ratio of the death rate in the population subgroup under investigation compared with the death rate in the general population, adjusting for age and sex.

(h) Fatal major bleeds divided by all major bleeds

(i) Fatal PEs divided by all symptomatic PEs

(j) Symptomatic pulmonary embolism in cohort studies with prophylaxis range from 0.2-1.9% 422,474,678,689

4.3 Baseline risks

Effectiveness and cost-effectiveness are dependent on the change in absolute risk rather than just the relative risk (RR) changes. To estimate absolute risk changes, the model multiplies the RR changes by the baseline risk. We estimated baseline risk of DVT, symptomatic pulmonary embolism and major bleed, from the no prophylaxis arms of the RCTs in our clinical review (Chapter 5 Risk, risk reduction and harm).

Chapter 5 also summarises other differences between population subgroups that are captured by the model. Age, sex and standardised mortality ratio contribute to the estimates of life expectancy and subsequently the magnitude of QALYs gained from averting a fatal pulmonary embolism and the magnitude of QALYs lost from incurring a fatal bleeding event. The baseline risk of events affects the magnitude of total treatment costs (or savings) and the magnitude of total QALYs gained (or lost).

4.3.1 Post-thrombotic syndrome, Chronic thromboembolic pulmonary hypertension and stroke

Some probabilities were assumed, in the absence of evidence, not to vary between population subgroups (Total hip replacement, general medical patient etc.). To estimate the incidence of these symptomatic events we looked for good quality systematic reviews, RCTs or cohort studies for each parameter. We found them primarily by looking at the methods of the economic evaluations retrieved in our systematic reviews but also completed highly specific searches of PubMED to identify other good quality data.
In the case of post-thrombotic syndrome (PTS) after a symptomatic DVT we used the 5-year incidence from a case series of 528 patients. We assumed the incidence of preventable PTS after symptomatic pulmonary embolism to be the same as after a symptomatic DVT. In the case of preventable PTS after an asymptomatic DVT we used the incidence from a meta-analysis of 10 cohort studies of over 1200 patients. This study estimated the incidence of preventable PTS to be 8% by comparing the exposure arm rate with the control arm. The Guideline Development Group felt that this was a significant underestimate and specifically that some of the episodes of PTS observed in the control arm were also attributable to an unidentified DVT occurring during the same episode. The group was split between using the 8% incidence or the 21% rate observed in the exposure arm. So for the base case we used the mid-point of 15%; the other figures were used in sensitivity analyses.

The 2-year incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after a symptomatic pulmonary embolism was estimated to be around 1%. However the number of these cases that would be due to a single event and hence would be preventable from a single course of prophylaxis might be half this. Hence we estimate the incidence of preventable CTEPH to be between 0.5% and 1%. In the base case analysis we used the mid-point 0.75%; the other figures were used in sensitivity analyses.

Some major bleeding episodes will have long-term health consequences, notably if the bleed is intracranial or spinal (for simplicity we use the term ‘Stroke’) (Figure 4-2: Decision tree). We estimated the proportion of bleeds that would fall in to this category to be about 3%, using data from a systematic review of bleeding in VTE prophylaxis RCTs (Chapter 5).

### Table 4-4: Symptomatic event rates irrespective of population subgroup

<table>
<thead>
<tr>
<th>Event</th>
<th>Probability</th>
<th>Source</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of major bleeds that lead to chronic morbidity (i.e. non-fatal strokes)</td>
<td>3% (a)</td>
<td>Muntz (2004) and personal communication from Muntz &amp; Scott (2006)</td>
<td>Systematic review of thromboprophylaxis RCTs</td>
</tr>
<tr>
<td>5-year post-thrombotic syndrome rate after symptomatic VTE</td>
<td>25%</td>
<td>Prandoni (1997)</td>
<td>Meta-analysis of cohort studies (n=364). Follow-up was 2-10 years</td>
</tr>
<tr>
<td>5-year post-thrombotic syndrome rate after asymptomatic VTE</td>
<td>15%</td>
<td>Expert opinion – see main text (section 4.3.1). Derived from Wille-Jørgensen (2005)</td>
<td>Meta-analysis of cohort studies (n=364). Follow-up was 2-10 years</td>
</tr>
<tr>
<td>2-year chronic thromboembolic pulmonary hypertension rate after symptomatic pulmonary embolism</td>
<td>0.75% (0.5%-1%)</td>
<td>Expert opinion – main text (section 4.3.1). Derived from Miniati (2006)</td>
<td>Cohort study of patients with proven pulmonary embolism (n=320) compared with those without (n=514).</td>
</tr>
</tbody>
</table>

(a) Major bleeds were classified by site of bleeding. The sites were gastrointestinal, surgical site, “other: brain/spine”, “other: not brain/spine”, and “other: not specified”. The stroke rate was estimated as the product of the following two components:

i) The ratio of all “other site” to all sites = 83/378

ii) The ratio of “other: brain/spine” to (“other: brain/spine” + “other: not brain/spine” = 2/(2+11)

The denominator of ii) is smaller than the numerator of i) because in the majority of cases the exact site was not recorded.
Table 4-5: Incidence of heparin induced thrombocytopenia (HIT) from VTE prophylaxis

<table>
<thead>
<tr>
<th></th>
<th>Orthopaedic Surgery</th>
<th>General surgery</th>
<th>General medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>5%</td>
<td>5%</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td>392</td>
<td>Assumed same as orthopaedic</td>
<td>223</td>
</tr>
<tr>
<td>LMWH</td>
<td>0.5%</td>
<td>0.5%</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td>392</td>
<td>Assumed same as orthopaedic</td>
<td>536</td>
</tr>
</tbody>
</table>

4.3.2 Heparin induced thrombocytopenia

The thromboembolic events associated with heparin induced thrombocytopenia (HIT) should be already included within the trial data going into the model, at least partially, hence it is not explicitly included in the base case analysis. However, we do consider some additional costs and health losses associated with HIT in a sensitivity analysis (see 0). There were little data on heparin-induced thrombocytopenia in the RCTs and we have not conducted a systematic review of HIT incidence. We have therefore used the figures cited in the British Committee for Safety in Haematology (BCSH) guideline on the management of HIT. We have also looked at a meta-analysis although this doesn’t differentiate by category of patient. We use these estimates from this paper (LMWH 0.2%, UFH 2.6%) as an alternative sensitivity analysis.

For surgical patients the sub-tree is the same except that the incidence of HIT is 0.5% instead of 0.8% - see Table 4-5.

Figure 4-3: Heparin induced thrombocytopenia (HIT) sub-tree

The BCSH guidelines recommend danaparoid or lepirudin for the treatment of HIT. We used danaparoid since this was more easily costed, being a fixed dose. A search of PubMed revealed a single paper that evaluated the outcomes after HIT for patients treated with danaparoid.
Figure 4-3 shows a sub-tree that indicates the course of HIT used to determine the costs and lost QALYs attributable to HIT. HIT was assumed to affect only UFH or LMWH but not any of the other drug or mechanical strategies.

4.4 Resource use & cost

4.4.1 Prophylaxis

The unit costs of mechanical prophylaxis are given in Table 4-6. Equipment was assumed to have a life expectancy of five years. Drug prices were taken from the current British National Formulary BNF for the recommended thrombo-prophylactic-dose (Table 4-7).

In deciding on the duration of prophylaxis we wanted to reflect the average duration of prophylaxis in the RCTs in our review such that there is consistency between the effect size and intervention cost in the model. However, we also wanted to reflect the licensed dose. We compiled this information in a table and then set a duration that was specific to the population subgroup but constant across the different strategies being compared for that subgroup (Table 4-8). These ranged between 7 and 10 days – longer duration prophylaxis is considered separately 4.7.

We added the cost of nurse time and monitoring tests for each intervention (Table 4-9).

We had difficulty in finding costs for foot impulse device sleeves. In the base case analysis we assumed the same cost as for an IPCD sleeve. After stakeholder consultation, one manufacturer informed us that a typical contract would supply the equipment rent-free and charge £40 for a sleeve to be used for 7 days (£20 for one suitable for use over 2 days). This information arrived too late to be used in our base case analysis but was used in a sensitivity analysis.

Table 4-6: Mechanical prophylaxis unit costs

<table>
<thead>
<tr>
<th>Component of mechanical prophylaxis</th>
<th>Cost</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-embolism stockings – 2 pairs per patient</td>
<td>£6.36 per pair</td>
<td>PASA (2009 Catalogue)</td>
</tr>
<tr>
<td>Intermitent pneumatic compression (equipment )</td>
<td>£471.80</td>
<td>PASA (2009 Catalogue)</td>
</tr>
<tr>
<td>Intermitent pneumatic compression (sleeves) - 1 pair per patient</td>
<td>£26.12</td>
<td>PASA (2009 Catalogue)</td>
</tr>
<tr>
<td>Foot impulse device (equipment)</td>
<td>£2,228</td>
<td>Submitted by manufacturer</td>
</tr>
<tr>
<td>Foot impulse device (pads)</td>
<td>£26.12</td>
<td>Assumed the same as for IPCD sleeves</td>
</tr>
</tbody>
</table>

BNF=British National Formulary, PASA=NHS Purchasing and Supplies Agency
### Table 4-7: Pharmacological prophylaxis – information and prices from the British National Formulary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Injections per day</th>
<th>Drug cost per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>5000 units subcutaneous every 8 hours</td>
<td>3</td>
<td>£2.76</td>
</tr>
<tr>
<td>LMWH (Medical)</td>
<td>Average of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dalteparin 5000 units subcutaneous daily</td>
<td>1</td>
<td>£3.51</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 4000 units subcutaneous daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH (General Surgery)</td>
<td>Average of high dose (see dose for major orthopaedic surgery) and moderate dose:</td>
<td>1</td>
<td>£3.34</td>
</tr>
<tr>
<td></td>
<td>Dalteparin 2500 units subcutaneous daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 2000 units subcutaneous daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tinzaparin 3500 units subcutaneous daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH (Major orthopaedic surgery)</td>
<td>Average of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dalteparin 3500 units subcutaneous daily</td>
<td>1</td>
<td>£3.84</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 4000 units subcutaneous daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tinzaparin 4500 units subcutaneous daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux sodium</td>
<td>2.5mg subcutaneous daily</td>
<td>1</td>
<td>£6.66</td>
</tr>
<tr>
<td>Vitamin K antagonist (Warfarin)</td>
<td>Dose is adjustable.</td>
<td>N/A</td>
<td>£0.04</td>
</tr>
<tr>
<td></td>
<td>[Assumed average of 4mg per day]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (High dose)</td>
<td>Aspirin is not licensed specifically for thromboprophylaxis [A typical aspirin dose from the RCTs in our review is 1000mg]</td>
<td>N/A</td>
<td>£0.19</td>
</tr>
<tr>
<td>Aspirin (Low dose)</td>
<td>Aspirin is not licensed specifically for thromboprophylaxis [A typical aspirin dose from the RCTs in our review is 300mg]</td>
<td>N/A</td>
<td>£0.06</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>220mg daily</td>
<td>N/A</td>
<td>£4.20</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>10mg daily</td>
<td>N/A</td>
<td>£4.50</td>
</tr>
</tbody>
</table>

### Table 4-8: Duration of prophylaxis, by population subgroup

<table>
<thead>
<tr>
<th>Drug</th>
<th>HFS</th>
<th>THR</th>
<th>TKR</th>
<th>GS</th>
<th>GM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bemiparin (Zibor)</td>
<td>8 - 11</td>
<td>8 - 11</td>
<td>8 - 11</td>
<td>8 - 11</td>
<td>N/A</td>
</tr>
<tr>
<td>Dalteparin (Fragmin)</td>
<td>6 - 8</td>
<td>36</td>
<td>6 - 8</td>
<td>6 - 8</td>
<td>Not time limited</td>
</tr>
<tr>
<td>Enoxaparin (Clexane)</td>
<td>8 - 11</td>
<td>8 - 11</td>
<td>8 - 11</td>
<td>8 - 11</td>
<td>6 - 14</td>
</tr>
<tr>
<td>Tinzaparin (Innohep)</td>
<td>8 - 11</td>
<td>8 - 11</td>
<td>8 - 11</td>
<td>8 - 11</td>
<td>N/A</td>
</tr>
<tr>
<td>Fondaparinux (Arixtra)</td>
<td>Longer than 6-10</td>
<td>Longer than 6-10</td>
<td>6 - 10</td>
<td>6 - 10</td>
<td>6 - 14</td>
</tr>
<tr>
<td>Dabigatran* (Pradaxa)</td>
<td>N/A</td>
<td>28 - 35</td>
<td>10</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>N/A</td>
<td>35</td>
<td>14</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Average duration of prophylaxis in RCTs in our clinical review (excluding extended duration)
duration of prophylaxis costed in the model excluding extended duration prophylaxis (derived from all of the above)

| Any drug / Device | 10 | 10 | 10 | 7 | 10 |

4.4.2 VTE treatment

To devise resource use protocols for diagnosing and treating VTEs, we examined the British Thoracic Society guidelines on the management of pulmonary embolism and British Committee for Standards in Haematology (BCSH) guidance on the prophylaxis and treatment of DVT. Members of the VTE (surgical) Guideline Development Group helped develop treatment protocols that could be costed. We have sought to develop protocols that would be considered achievable good practice currently in the NHS. Unit costs were taken from standard NHS sources: NHS reference costs, British National Formulary, NHS Electronic Drug Tariff, NHS Purchasing and Supplies Agency, Unit Costs of Health and Social Care 2007 (Table 4-10).

In clinical practice there would be no treatment cost associated with asymptomatic DVT. We have assumed that the incremental treatment cost of fatal pulmonary embolism (and fatal bleeding) is £0 - on the one hand treatment of the event would generate additional health service costs but on the other hand the treatment costs for the illness they were admitted will be curtailed.
In the absence of more detailed information, we have assumed that the cost of treating a VTE (or major bleeding episode) does not vary by which population subgroup the patient was from (hip fracture, general surgery, etc).

4.4.3 Post-thrombotic syndrome & chronic thromboembolic pulmonary hypertension

For post-thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension (CTEPH) and stroke, the treatment pathways are varied and complex and therefore we took from the literature, costs estimated from relevant cohort studies of patients (Table 4-11). We found these sources primarily by looking at the methods of the economic evaluations retrieved in our systematic reviews but also did quick searches of HEED and PubMed to see if there we could find other good quality data.

Table 4-10: VTE diagnosis and treatment costs

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic DVT</th>
<th>Non-fatal Symptomatic pulmonary embolism</th>
<th>Source for resource use</th>
<th>Unit cost</th>
<th>Source for unit cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doppler ultrasound</td>
<td>1</td>
<td>-</td>
<td>Published guidelines</td>
<td>£64 per test</td>
<td>NHS reference costs 2006/07 161 (RA24Z)</td>
</tr>
<tr>
<td>CT pulmonary angiogram</td>
<td>- 1</td>
<td></td>
<td>Published guidelines</td>
<td>£101 per test</td>
<td>NHS reference costs 2006/07 161 (RA08Z)</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>- 1</td>
<td></td>
<td>Expert opinion</td>
<td>£29 per test</td>
<td>NHS reference costs 2006/07 (RA28Z)</td>
</tr>
<tr>
<td>ECG</td>
<td>- 1</td>
<td></td>
<td>Expert opinion</td>
<td>£27 per test</td>
<td>NHS reference costs 2006/07 161 (DA01)</td>
</tr>
<tr>
<td>D-dimer</td>
<td>1 1</td>
<td></td>
<td>Expert opinion</td>
<td>£12 per test</td>
<td>NHS Health Technology Assessment report on diagnostic strategies for DVT 228</td>
</tr>
<tr>
<td>Emergency admission</td>
<td>1 1</td>
<td></td>
<td>Expert opinion</td>
<td>£38</td>
<td>NHS reference costs 2006/07 161 (V8112)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>7 days</td>
<td>7 days</td>
<td>Published guidelines</td>
<td>£8.02 per day</td>
<td>Mean of treatment dose regimens - BNF July 2008 313</td>
</tr>
<tr>
<td>Full blood count</td>
<td>2 2</td>
<td></td>
<td>Expert opinion</td>
<td>£5.74 per test</td>
<td>NHS reference costs 2006/07 161 (including £2.82 phlebotomist cost)</td>
</tr>
<tr>
<td>Vitamin K antagonist</td>
<td>3 months x 69% (distal) 6 months x 31% (proximal)[a]</td>
<td>6 months</td>
<td>Published guidelines</td>
<td>£0.04 per day</td>
<td>British National Formulary July 2008 313</td>
</tr>
<tr>
<td>Extended hospital stay</td>
<td>10% x 4 days</td>
<td>90% x 6 days</td>
<td>VERITY database (c) for % / NHS reference costs 2005 for LOS 160</td>
<td>£192 per day(b)</td>
<td>NHS reference costs 2006/07 161</td>
</tr>
<tr>
<td>Instruction on self-administration of LMWH (nurse time)</td>
<td>90% x 30 minutes</td>
<td>10% x 30 minutes</td>
<td>Expert opinion</td>
<td>£22 per hour</td>
<td>Unit Costs of Health and Social Care 2007 139</td>
</tr>
</tbody>
</table>
### Table 4-11: Other treatment unit costs

<table>
<thead>
<tr>
<th>Event</th>
<th>Unit cost</th>
<th>Source</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke (first year)</strong></td>
<td>£8397</td>
<td>Grieve et al (2000)237</td>
<td>328 NHS patients followed prospectively for 12 months after stroke (inflated to 2006/7 prices)</td>
</tr>
<tr>
<td><strong>Stroke (subsequent years)</strong></td>
<td>£4826 per year</td>
<td>NICE Stroke guideline, 2008477</td>
<td>Assuming that 38% dependent stroke and 62% independent stroke.</td>
</tr>
<tr>
<td><strong>Post-thrombotic syndrome</strong></td>
<td>£653 per year</td>
<td>Average of: 1) Bergqvist et al (1997)55</td>
<td>1) Retrospective cohort study of 250 Swedish patients followed for 15 years after first symptomatic DVT (converted to UK£ and inflated to 2006/7 prices)</td>
</tr>
<tr>
<td><strong>Chronic thromboembolic pulmonary hypertension</strong></td>
<td>£1219 per month</td>
<td>NICE technology appraisal on Pulmonary arterial hypertension (adults) - drugs due for publication in 2009 478</td>
<td>Overall total cost for New York Heart Association class II functional status per 4 weeks</td>
</tr>
<tr>
<td><strong>Major bleeding without re-operation</strong></td>
<td>£722</td>
<td>NHS reference costs 2006/07161</td>
<td>Mean cost of a gastro-intestinal bleeding treatment episode (HRG codes: FC08A, FC08B, FC08C (non-elective and elective)</td>
</tr>
<tr>
<td><strong>Re-operation (General Surgery)</strong></td>
<td>£1224</td>
<td>NHS reference costs 2006/07161</td>
<td>Mean cost of an episode of gastro-intestinal bleeding with major procedure (HRG codes: FA16Z,</td>
</tr>
</tbody>
</table>
In the case of post-thrombotic syndrome (PTS) we did not find a suitable cohort based in the UK but we found:

1) A retrospective cohort study of 250 Swedish patients followed for 15 years after first symptomatic DVT55 (converted to UK£ using purchasing power parities[www.oecd.org/std/ppp November 2008] and inflated to 2006/7 prices using the hospital pay and prices index139). Using only post-thrombotic syndrome (PTS) costs (and not recurrent VTE) it was £244 per patient-year. This figure was per patient having a DVT. Assuming an incidence of PTS of 25% in this DVT group (section 4.3.1), this makes £977 per PTS patient per year.

2) An annual protocol derived for an NHS Health Technology Assessment228 cost-effectiveness analysis consisting of one new vascular surgery outpatient visit, two follow-up vascular surgery outpatient visits and two GP visits. Using current UK costs139 we recalculated this to be £329 per year.

Both have advantages and disadvantages: the Swedish study was a well-conducted empirical study but may not be applicable to a UK setting. The Health Technology Assessment is highly relevant but based only on expert opinion. Hence we used a simple average of these two estimates, which came to £653 per year.

For chronic thromboembolic pulmonary hypertension (CTEPH) we derived a monthly cost that is based on an ongoing NICE technology appraisal of pulmonary arterial hypertension in adults478. We have estimated the cost of CTEPH by adding together the cost of active and supportive therapy as well as the cost associated with primary and secondary care resource use. We took the average cost of bosentan, sitaxentan and sildenafil. We included in the supportive therapy package the cost of oxygen requirement associated with patients in New York Heart Association class II functional status. We also considered this functional status while estimating the cost associated with the use of primary and secondary care resources. We estimated £1,219 as the overall cost of CTEPH per four weeks. This included £1143, the average cost of bosentan, sitaxentan and sildenafil only. In a one-way sensitivity analysis, the cost of active therapies was the average cost of bosentan, sitaxentan, sildenafil, iloprost and epoprostenol. This was £2097, the average cost of the five active therapies. There are different unit costs for the use of epoprostenol in the first and second year. The four weekly cost of epoprostenol used in the sensitivity analysis was the cost to be incurred in the first year, which was £4283. In a one-way sensitivity analysis, we therefore estimated £2173 as the overall cost of CTEPH per four weeks.

4.4.4 Bleeding & stroke

The cost of treating major bleeding was assumed to vary primarily according to whether there was a decision to re-operate (Table 4-11).
We have been advised that although the cost of a hip revision after infection can be substantial, such cases are rare. Hence we used the cost of a minor hip operation for the cost of a re-operation due to major bleeding (Table 4-11).

For patients with stroke, we used a cost of £8397 first year and £4826 for subsequent years (NICE acute stroke guideline)\textsuperscript{477} (Table 4-11).

We hypothesised that the cost of treating major bleeding might vary by prophylaxis strategy due to substantial differences in the cost of antidotes. But in the end we decided that this would be difficult to substantiate, especially given that the prophylaxis is unlikely to be identified as the main cause of the major bleeding. So antidote costs were not explicitly incorporated.

4.4.5 Heparin induced thrombocytopenia (HIT)

The thromboembolic events associated with heparin induced thrombocytopenia (HIT) should be at least partially included within the trial data going into the model, hence it is not specifically included in the base case analysis.

However, as a sensitivity analysis we assumed the pathway presented in Figure 4-3. The cost of danaparoid was £507 for a prophylactic dose of 750 units twice daily for an average 8.5 days\textsuperscript{313}. The costs associated with death, major bleeding, and no event are the same as for the main model. A new or recurrent VTE was costed the same as a pulmonary embolism in the main model. The cost of amputation was from a US study of the cost-effectiveness of different heparin induced thrombocytopenia (HIT) treatment strategies\textsuperscript{513} converted to UK prices using purchasing power parities (www.oecd.org/std/ppp November 2008).

4.5 Life expectancy

4.5.1 Fatal events

Naturally for patients dying during hospitalisation, their expected life-years in the model is zero.

- Fatal pulmonary embolism
- Fatal bleeding event

4.5.2 Patients surviving without long-term complications

For patients surviving surgery we estimated life expectancy using a combination of population subgroup-specific data (Table 4-3) and general population data.

- For hip fracture surgery, general surgery and medical patients, from 12 months we had to assume age/sex-specific life expectancy for England & Wales (Source: Government Actuary Department 2007)
- For these patients, for the first 12 months we applied standardised mortality ratios to the relevant England and Wales mortality rate, so that for the first year after surgery we are using disease-specific mortality. Another adjustment was then made to subtract
from this mortality the mortality already captured in the model, so that we don’t double count deaths.

• For total hip replacement we were able to apply standardised mortality ratios for 10 years.

4.5.3 Patients surviving with long-term complications

In the absence of specific evidence, it was assumed that the life expectancy of patients with preventable post-thrombotic syndrome was the same as for other patients in their population subgroup who do not experience post-thrombotic syndrome.

For patients with chronic thromboembolic pulmonary hypertension, we assumed a life expectancy of 5 years (treated)\(^7,133\).

For patients with stroke, we assumed a life expectancy of 4.5 years (NICE acute stroke guideline).

<table>
<thead>
<tr>
<th>Health state</th>
<th>Utility</th>
<th>Source</th>
<th>Duration of health state after initial event</th>
</tr>
</thead>
<tbody>
<tr>
<td>No long term event (general population average)</td>
<td>0.82</td>
<td>EQ5D instrument completed by 3395 people resident in the UK(^{47})</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Asymptomatic DVT/pulmonary embolism</td>
<td>0.82</td>
<td>Assumed to be the same as the UK average</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Warfarin treatment after symptomatic VTE</td>
<td>0.82 x 0.99 = 0.81</td>
<td>Time trade-off, 70 patients with atrial fibrillation(^{203})</td>
<td>3 months distal 6 months proximal 6 months pulmonary embolism (then return to usual quality of life)</td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td>0.82 x 0.982 = 0.805</td>
<td>O’Meara et al 1994 (severe)(^{497})</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Pulmonary embolism (symptomatic)</td>
<td>0.82 x 0.94 = 0.771</td>
<td>Goodacre et al 2006 (^{228})</td>
<td>1 month then treatment with vitamin k antagonists(a)</td>
</tr>
<tr>
<td>Chronic thromboembolic pulmonary hypertension (CTEPH)</td>
<td>0.765</td>
<td>NICE guideline on pulmonary arterial hypertension (^{205,348})</td>
<td>Life expectancy: 5 years</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.50</td>
<td>Sarasin et al 2000(^{584}) (temporary disability following major gastrointestinal hemorrhage) (based on expert opinion)</td>
<td>1 month then return to usual quality of life*</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.52</td>
<td>The FOOD Trial Collaboration, Lancet 2005 EQ5D, 3086 stroke patients in an RCT</td>
<td>Life expectancy: 4¼ years</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Amputation after heparin induced thrombocytopenia (HIT) – sensitivity analysis only</td>
<td>0.73</td>
<td>A review in a cost-utility analysis of strategies for the management of heparin induced thrombocytopenia (HIT)</td>
<td>Life time</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal Pulmonary Embolism</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(a) These are assumed since the utility data relate to an acute event.

### 4.6 Quality of life weightings

We have sought to find quality of life weightings in the published literature, firstly by looking at source data for cost-utility studies included in our review and also by searching the Cost-effectiveness Analysis Registry’s Catalog of preference scores. The scores in Table 4-12 were combined with the life expectancy data to estimate QALYs.

For patients with no event, we used the population average quality of life for England and Wales measured using the EQ5D, a widely used and validated measure of overall health-related quality of life.

For other long-term states we took scores from well-conducted studies in the published literature.

### 4.7 Post-discharge / extended duration prophylaxis

![Figure 4-4: Post-discharge and Extended prophylaxis RCTs](image)

<table>
<thead>
<tr>
<th>Admission</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-14 days</td>
<td>21-28 days</td>
</tr>
<tr>
<td>Standard duration Prophylaxis RCTs</td>
<td>Post-discharge Prophylaxis RCTs</td>
</tr>
<tr>
<td>Network meta-analysis</td>
<td>GS: LMWH vs Nil</td>
</tr>
<tr>
<td>THR: LMWH vs Nil</td>
<td>HFS: Fondaparinux vs Nil</td>
</tr>
<tr>
<td>35 days</td>
<td>THR: Dabigatran vs LMWH</td>
</tr>
<tr>
<td></td>
<td>THR: Rivaroxaban vs LMWH</td>
</tr>
</tbody>
</table>

Extended duration prophylaxis RCTs
We did not include trials that administered prophylaxis for longer than 20 days in our network meta-analyses – typically they were 7-10 days duration. Our main model, which we describe as the standard duration prophylaxis model was based on these trials. Other trials considered longer durations, these were distinguished into two categories: post-discharge prophylaxis (which start at discharge) and extended duration prophylaxis (which start at admission and continue well beyond discharge) – see Figure 4-4.

There were trial data available on bleeding, pulmonary embolism and major bleeding for the following population subgroups:

- Hip fracture surgery (LMWH vs Nil post-discharge)
- Total hip replacement (LMWH vs Nil post-discharge)
- Total hip replacement (Dabigatran vs LMWH extended duration; Rivaroxaban vs LMWH extended duration)
- General surgery (LMWH vs Nil post-discharge) – most of the patients in these trials were cancer patients.

We modelled the cost-effectiveness of each of these comparisons using the same methods and data as for standard duration prophylaxis. The few differences are outlined as follows.
Table 4-13: Data for post-discharge / extended prophylaxis models

<table>
<thead>
<tr>
<th>Prophylaxis Type</th>
<th>Relative Risks</th>
<th>Duration of prophylaxis (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture surgery: post-discharge</td>
<td>Fondaparinux vs Nil</td>
<td>176</td>
</tr>
<tr>
<td>Total hip replacement: post-discharge</td>
<td>LMWH vs Nil</td>
<td>47,132,142,272,378,52</td>
</tr>
<tr>
<td>Total hip replacement: extended duration</td>
<td>Dabigatran vs LMWH; Rivaroxaban vs LMWH</td>
<td>6</td>
</tr>
<tr>
<td>General surgery: post-discharge</td>
<td>LMWH vs Nil</td>
<td>476,479</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risks</th>
<th>Duration of prophylaxis (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>0.04 (0.01, 0.13)</td>
<td>176</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>4.02 (0.86, 18.81)</td>
<td>24</td>
</tr>
</tbody>
</table>

**Baseline risks**

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>33.9%</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.9%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.6%</td>
</tr>
<tr>
<td>Other</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

**Relative risks**

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk</th>
<th>Duration of prophylaxis (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>0.41 (0.31, 0.54)</td>
<td>176</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.32 (0.01, 7.80)</td>
<td>24</td>
</tr>
</tbody>
</table>

**Major bleeding**

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk</th>
<th>Duration of prophylaxis (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>1.29 (0.70, 2.37)</td>
<td>35</td>
</tr>
<tr>
<td>Other</td>
<td>0.83 (0.22, 3.12)</td>
<td>21</td>
</tr>
</tbody>
</table>

(a) The GDG considered it implausible that these were less than 1 and so they were set to 1 in the deterministic analyses.

### 4.7.1 Risks

For post-discharge and extended duration prophylaxis we simply used the relative risks compared with no post-discharge from our direct comparison meta-analyses – summarised in Chapter 6. Baseline risks were also from the trials.

### 4.7.2 Resource use and cost

The duration of prophylaxis was determined by the RCTs – Table 4-8. This was used to calculate the cost of each prophylactic intervention.

We also assumed that 8% of patients would require daily visits from the district nurse to give the injection. This is on the basis of two surveys, which both found that 8% of patients could not comply with administering their own LMWH prophylaxis. The patients in these studies were not particularly frail, and therefore in older populations compliance with self-injection might be less. However, we have anecdotal evidence from within our Guideline Development Group and a stakeholder, that self-injection rates (including injection by family members/carers) of greater than 90% are achievable even in hip fracture patients. There maybe some monitoring costs involved but these are difficult to quantify and have not been included in the model.
4.8 Sensitivity analyses

4.8.1 Probabilistic sensitivity analysis

The deterministic analysis gives us a point estimate of additional cost, QALYs gained and incremental net benefit (INB) by using only the point estimates of each model parameter. In the probabilistic analysis we assign a probability distribution to each parameter (including the relative risk estimates). These probability distributions reflect the standard error of each parameter estimate. For the probabilistic analysis we randomly select from each parameter distribution simultaneously and calculate the cost, QALYs and INB. We then repeat this 5000 times such that we have a set of 5000 estimates of INB reflecting the uncertainty in our parameters. This process is known as Monte Carlo simulation. The analysis can take into account the covariance between different model parameters. However often we are unsure of the magnitude of the covariance and in these circumstances the analysis treats the model parameters as if they were independent of each other.

The best strategy is then the one that has the highest mean INB, averaged across all the 5000 simulations. This strategy may or may not be the one which was cost-effective in more simulations than any other simulation.

The estimates of relative risk in our deterministic analysis were taken from the network meta-analysis — this method is simulation based and therefore the output gives not just a point estimate for each relative risk (RR) but also an entire distribution of 60,000 RR estimates. In each of our 5000 simulations in our probabilistic analysis we randomly sampled from the 60,000 estimates of RR from our network meta-analysis. Each time, for the different strategies (e.g. LMWH vs Nil, LMWH vs fondaparinux and fondaparinux vs nil) we selected from the same network meta-analysis iteration to preserve the covariance between the different relative risk estimates.

For other model parameters we had to define the distribution. The distributions used reflect the nature of the data, so for example probabilities were given a beta distribution, which is bounded by zero and one — see Table 4-14. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 4-15 and Table 4-16.

For simplicity the following variables, were left deterministic (i.e. were not varied in the probabilistic analysis: Age, % male, standardised mortality ratio (since these were deemed to be fixed by the scenario) drug prices (which were subject to a deterministic sensitivity analysis — see below), and the discount rate and cost-effectiveness threshold (which were deemed to be fixed by NICE).
Table 4-14: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type of distribution</th>
<th>Properties of distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion</td>
<td>Beta</td>
<td>Bounded on 0 – 1 interval. Derived from sample size, number of patients experiencing events</td>
</tr>
<tr>
<td>Cost</td>
<td>Gamma</td>
<td>Bounded at 0, positively skewed. Derived from mean and standard error</td>
</tr>
<tr>
<td>Length of stay / duration of prophylaxis</td>
<td>Lognormal</td>
<td>Bounded at 0. Derived from log(mean) and standard error</td>
</tr>
<tr>
<td>Utility</td>
<td>Beta</td>
<td>Bounded on 0 – 1 interval. Derived from mean and standard error</td>
</tr>
<tr>
<td>Relative risk</td>
<td>Lognormal</td>
<td>Bounded at 0. Derived from log (mean) and standard error</td>
</tr>
</tbody>
</table>

Table 4-15: Baseline risk parameters used in the probabilistic sensitivity analysis (a)

<table>
<thead>
<tr>
<th>Parameter description</th>
<th>Point estimate</th>
<th>Distribution parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>20.9%</td>
<td>α = 860, β = 3255</td>
</tr>
<tr>
<td>Symptomatic pulmonary embolism</td>
<td>1.3%</td>
<td>α = 99, β = 7315</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.4%</td>
<td>α = 104, β = 7517</td>
</tr>
<tr>
<td>Symptomatic DVT / All DVT</td>
<td>6.2%</td>
<td>α = 40, β = 604</td>
</tr>
<tr>
<td>Pulmonary embolism fatality rate</td>
<td>6.0%</td>
<td>α = 11, β = 173</td>
</tr>
<tr>
<td>Major bleeding fatality rate</td>
<td>0.8%</td>
<td>α = 5, β = 627</td>
</tr>
<tr>
<td>General Medical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>13.4%</td>
<td>α = 106, β = 685</td>
</tr>
<tr>
<td>Symptomatic pulmonary embolism</td>
<td>0.9%</td>
<td>α = 24, β = 2661</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.4%</td>
<td>α = 11, β = 2864</td>
</tr>
<tr>
<td>Symptomatic DVT / All DVT</td>
<td>6.2%</td>
<td>α = 40, β = 604</td>
</tr>
<tr>
<td>Pulmonary embolism fatality rate</td>
<td>44.7%</td>
<td>α = 17, β = 21</td>
</tr>
<tr>
<td>Major bleeding fatality rate</td>
<td>14.3%</td>
<td>α = 8, β = 48</td>
</tr>
<tr>
<td>Hip fracture surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>39.8%</td>
<td>α = 471, β = 712</td>
</tr>
<tr>
<td>Symptomatic pulmonary embolism</td>
<td>7.9%</td>
<td>α = 63, β = 734</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.2%</td>
<td>α = 29, β = 877</td>
</tr>
<tr>
<td>Symptomatic DVT / All DVT</td>
<td>21.0%</td>
<td>α = 223, β = 840</td>
</tr>
<tr>
<td>Pulmonary embolism fatality rate</td>
<td>31.0%</td>
<td>α = 9, β = 20</td>
</tr>
<tr>
<td>Major bleeding fatality rate</td>
<td>0.8%</td>
<td>α = 5, β = 627</td>
</tr>
<tr>
<td>Total hip replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>45.0%</td>
<td>α = 530, β = 648</td>
</tr>
<tr>
<td>Symptomatic pulmonary embolism</td>
<td>3.4%</td>
<td>α = 32, β = 909</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.6%</td>
<td>α = 25, β = 1538</td>
</tr>
<tr>
<td>Symptomatic DVT / All DVT</td>
<td>21.0%</td>
<td>α = 223, β = 840</td>
</tr>
<tr>
<td>Pulmonary embolism fatality rate</td>
<td>6.0%</td>
<td>α = 11, β = 173</td>
</tr>
<tr>
<td>Major bleeding fatality rate</td>
<td>0.8%</td>
<td>α = 5, β = 627</td>
</tr>
<tr>
<td>Total knee replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>60.0%</td>
<td>α = 65, β = 43</td>
</tr>
<tr>
<td>Symptomatic pulmonary embolism</td>
<td>1.0%</td>
<td>[kept deterministic]</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.9%</td>
<td>α = 4, β = 270</td>
</tr>
<tr>
<td>Symptomatic DVT / All DVT</td>
<td>5.0%</td>
<td>α = 17, β = 320</td>
</tr>
<tr>
<td>Pulmonary embolism fatality rate</td>
<td>0.8%</td>
<td>α = 5, β = 627</td>
</tr>
<tr>
<td>General surgery (post-discharge)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>10.5%</td>
<td>α = 53, β = 454</td>
</tr>
</tbody>
</table>
## Development of Cost-Effectiveness Model

<table>
<thead>
<tr>
<th>Parameter description</th>
<th>Point estimate</th>
<th>Distribution parameters</th>
<th>Probability distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic pulmonary embolism</td>
<td>0.8%</td>
<td>α = 4, β = 490</td>
<td>Beta</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.9%</td>
<td>α = 5, β = 570</td>
<td>Beta</td>
</tr>
<tr>
<td>Symptomatic DVT / All DVT</td>
<td>6.2%</td>
<td>α = 40, β = 604</td>
<td>Beta</td>
</tr>
<tr>
<td>Pulmonary embolism fatality rate</td>
<td>6.0%</td>
<td>α = 11, β = 173</td>
<td>Beta</td>
</tr>
<tr>
<td>Major bleeding fatality rate</td>
<td>0.8%</td>
<td>α = 5, β = 627</td>
<td>Beta</td>
</tr>
<tr>
<td><strong>Total hip replacement (post-discharge)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>25.5%</td>
<td>α = 136, β = 397</td>
<td>Beta</td>
</tr>
<tr>
<td>Symptomatic pulmonary embolism</td>
<td>0.6%</td>
<td>α = 5, β = 889</td>
<td>Beta</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.2%</td>
<td>α = 1, β = 531</td>
<td>Beta</td>
</tr>
<tr>
<td>Symptomatic DVT / All DVT</td>
<td>21.0%</td>
<td>α = 223, β = 840</td>
<td>Beta</td>
</tr>
<tr>
<td>Pulmonary embolism fatality rate</td>
<td>6.0%</td>
<td>α = 11, β = 173</td>
<td>Beta</td>
</tr>
<tr>
<td>Major bleeding fatality rate</td>
<td>0.8%</td>
<td>α = 5, β = 627</td>
<td>Beta</td>
</tr>
<tr>
<td><strong>Hip fracture surgery (post-discharge)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>33.9%</td>
<td>α = 74, β = 144</td>
<td>Beta</td>
</tr>
<tr>
<td>Symptomatic pulmonary embolism</td>
<td>0.9%</td>
<td>α = 3, β = 327</td>
<td>Beta</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.6%</td>
<td>α = 2, β = 327</td>
<td>Beta</td>
</tr>
<tr>
<td>Symptomatic DVT / All DVT</td>
<td>21.0%</td>
<td>α = 223, β = 840</td>
<td>Beta</td>
</tr>
<tr>
<td>Pulmonary embolism fatality rate</td>
<td>31.0%</td>
<td>α = 9, β = 20</td>
<td>Beta</td>
</tr>
<tr>
<td>Major bleeding fatality rate</td>
<td>0.8%</td>
<td>α = 5, β = 627</td>
<td>Beta</td>
</tr>
<tr>
<td><strong>Total hip replacement (extended)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>4.4%</td>
<td>α = 110, β = 2398</td>
<td>Beta</td>
</tr>
<tr>
<td>Symptomatic pulmonary embolism</td>
<td>0.2%</td>
<td>α = 5, β = 2452</td>
<td>Beta</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.4%</td>
<td>α = 20, β = 3360</td>
<td>Beta</td>
</tr>
<tr>
<td>Symptomatic DVT / All DVT</td>
<td>21.0%</td>
<td>α = 223, β = 840</td>
<td>Beta</td>
</tr>
<tr>
<td>Pulmonary embolism fatality rate</td>
<td>6.0%</td>
<td>α = 11, β = 173</td>
<td>Beta</td>
</tr>
<tr>
<td>Major bleeding fatality rate</td>
<td>0.8%</td>
<td>α = 5, β = 627</td>
<td>Beta</td>
</tr>
</tbody>
</table>

(a) The type of distribution used was beta distribution and the sources of the parameters are given in Table 4-3

### Table 4-16: Parameters and parameter distributions used in the probabilistic sensitivity analysis that are common to each population subgroup

<table>
<thead>
<tr>
<th>Parameter description</th>
<th>Point estimate</th>
<th>Probability distribution</th>
<th>Distribution parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-thrombotic syndrome after symptomatic DVT</td>
<td>25.5%</td>
<td>Beta</td>
<td>α = 132, β = 396</td>
</tr>
<tr>
<td>Post-thrombotic syndrome after asymptomatic DVT</td>
<td>15.5%</td>
<td>Beta</td>
<td>α = 77, β = 436</td>
</tr>
<tr>
<td><strong>Cost (£)</strong></td>
<td></td>
<td>Gamma</td>
<td>Mean = 575.72, se = 73.43</td>
</tr>
<tr>
<td>DVT</td>
<td>575.72</td>
<td>Gamma</td>
<td>Mean = 575.72, se = 73.43</td>
</tr>
<tr>
<td>Symptomatic (non-fatal) pulmonary embolism</td>
<td>2521.19</td>
<td>Gamma</td>
<td>Mean = 2521.19, se = 321.58</td>
</tr>
<tr>
<td>Medical management of major bleeding</td>
<td>721.92</td>
<td>Gamma</td>
<td>Mean = 721.92, se = 92.08</td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td>7551.31</td>
<td>Gamma</td>
<td>Mean = 7551.31, se = 963.12</td>
</tr>
<tr>
<td>Chronic thromboembolic pulmonary hypertension</td>
<td>69,122.53</td>
<td>Gamma</td>
<td>Mean = 69,122.53, se = 8816.65</td>
</tr>
<tr>
<td>Stroke</td>
<td>22,969.10</td>
<td>Gamma</td>
<td>Mean = 22,969.10, se = 2929.73</td>
</tr>
<tr>
<td>Anti-embolism stockings (prophylaxis)</td>
<td>6.36</td>
<td>Gamma</td>
<td>Mean = 6.36, se = 0.81</td>
</tr>
<tr>
<td>Anti-embolism stockings (treatment)</td>
<td>13.11</td>
<td>Gamma</td>
<td>Mean = 13.11, se = 1.67</td>
</tr>
<tr>
<td>FID (equipment)</td>
<td>2228.00</td>
<td>Gamma</td>
<td>Mean = 2228.00, se = 284.18</td>
</tr>
<tr>
<td>IPCD (equipment)</td>
<td>471.80</td>
<td>Gamma</td>
<td>Mean = 471.80, se = 60.18</td>
</tr>
<tr>
<td>Parameter description</td>
<td>Point estimate</td>
<td>Probability distribution</td>
<td>Distribution parameters</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>--------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>IPCD (consumable)</td>
<td>2.61</td>
<td>Gamma</td>
<td>Mean = 2.61, se = 3.33</td>
</tr>
<tr>
<td>Tests (Full blood count, international normalized ratio)</td>
<td>2.92</td>
<td>Gamma</td>
<td>Mean = 2.92, se = 0.37</td>
</tr>
<tr>
<td>Cost of nursing time (staff nurse) (£)</td>
<td>22.00</td>
<td>Gamma</td>
<td>Mean = 22.00, se = 2.81</td>
</tr>
<tr>
<td>Cost of nursing time (district nurse) (£)</td>
<td>20.00</td>
<td>Gamma</td>
<td>Mean = 20.00, se = 2.55</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of major bleeding requiring reoperation (for all orthopaedic surgery subgroups)</td>
<td>13%</td>
<td>Beta</td>
<td>α = 32, β = 214</td>
</tr>
<tr>
<td>Proportion of major bleeding requiring reoperation (general surgery)</td>
<td>21%</td>
<td>Beta</td>
<td>α = 25, β = 93</td>
</tr>
<tr>
<td>Nursing time (injection) (minutes)</td>
<td>2.5</td>
<td>Lognormal</td>
<td>Log (mean) = 0.92, se = 0.10</td>
</tr>
<tr>
<td>Nursing time (mechanical prophylaxis) (minutes)</td>
<td>7.5</td>
<td>Lognormal</td>
<td>Log (mean) = 2.01, se = 0.18</td>
</tr>
<tr>
<td>Nursing time (warfarin) (minutes)</td>
<td>15</td>
<td>Lognormal</td>
<td>Log (mean) = 2.71, se = 0.18</td>
</tr>
<tr>
<td>Nursing time (aspirin) (minutes)</td>
<td>2.5</td>
<td>Lognormal</td>
<td>Log (mean) = 0.92, se = 0.10</td>
</tr>
<tr>
<td>Length of stay / Duration of health state</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT (years)</td>
<td>0.32</td>
<td>Lognormal</td>
<td>Log (mean) = -1.13, se = 0.13</td>
</tr>
<tr>
<td>Pulmonary embolism (years)</td>
<td>0.08</td>
<td>Lognormal</td>
<td>Log (mean) = -2.48, se = 0.13</td>
</tr>
<tr>
<td>Major bleeding (years)</td>
<td>0.08</td>
<td>Lognormal</td>
<td>Log (mean) = -2.48, se = 0.13</td>
</tr>
<tr>
<td>Stroke after major bleeding (years)</td>
<td>3.02</td>
<td>Lognormal</td>
<td>Log (mean) = 1.11, se = 0.13</td>
</tr>
<tr>
<td>Mean duration of prophylaxis (Hip fracture surgery, total hip replacement, total knee replacement and medical only) (days)</td>
<td>10</td>
<td>Lognormal</td>
<td>Log (mean) = 2.30, se = 0.13</td>
</tr>
<tr>
<td>Mean duration of prophylaxis (General surgery only) (days)</td>
<td>7</td>
<td>Lognormal</td>
<td>Log (mean) = 1.94, se = 0.13</td>
</tr>
<tr>
<td><strong>Prophylaxis relative risks (DVT) – extended duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran vs LMWH</td>
<td>0.80</td>
<td>Lognormal</td>
<td>Log (mean) = -0.22, se = 0.19</td>
</tr>
<tr>
<td>Rivaroxaban vs LMWH</td>
<td>0.22</td>
<td>Lognormal</td>
<td>Log (mean) = -1.51, se = 0.31</td>
</tr>
<tr>
<td><strong>Prophylaxis relative risks (DVT) – post-discharge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH (total hip replacement)</td>
<td>0.41</td>
<td>Lognormal</td>
<td>Log (mean) = -0.89, se = 0.14</td>
</tr>
<tr>
<td>Fondaparinux (Hip fracture surgery)</td>
<td>0.04</td>
<td>Lognormal</td>
<td>Log (mean) = -3.22, se = 0.65</td>
</tr>
<tr>
<td>LMWH (General surgery)</td>
<td>0.46</td>
<td>Lognormal</td>
<td>Log (mean) = -0.78, se = 0.24</td>
</tr>
<tr>
<td><strong>Prophylaxis relative risks (major bleeding) – extended duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran vs LMWH (total hip replacement)</td>
<td>1.29</td>
<td>Lognormal</td>
<td>Log (mean) = 0.25, se = 0.31</td>
</tr>
<tr>
<td>Rivaroxaban vs LMWH (total hip replacement)</td>
<td>3.02</td>
<td>Lognormal</td>
<td>Log (mean) = 1.11, se = 0.82</td>
</tr>
<tr>
<td><strong>Prophylaxis relative risks (major bleeding) – post-discharge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH (total hip replacement)</td>
<td>0.32</td>
<td>Lognormal</td>
<td>Log (mean) = -1.14, se = 1.70</td>
</tr>
</tbody>
</table>
### 4.8.2 Deterministic sensitivity analysis

In addition to the probabilistic sensitivity analysis, we varied a number of individual key parameters to see if the results were sensitive, as follows.

In particular we looked at the assumptions around the long-term consequences. We investigated the results under the following assumptions:

- 0% preventable chronic thromboembolic pulmonary hypertension after pulmonary embolism
- 0% chronic thromboembolic pulmonary hypertension and 0% post-thrombotic syndrome
- Low post-thrombotic syndrome (e.g. 15% after symptomatic DVT and 8% after asymptomatic DVT) – section 4.3.1.
- High post-thrombotic syndrome rate (e.g. 30% after symptomatic DVT and 21% after asymptomatic DVT) – section 4.3.1.
- High and low estimates of chronic thromboembolic pulmonary hypertension rate (section 4.3.1).
- High and low estimates of the cost of post-thrombotic syndrome (section 4.4.3).
- Higher estimate of the cost of treating chronic thromboembolic pulmonary hypertension (section 4.4.3).

Other assumptions that were tested were:

- For those drugs that we understand are substantially discounted to hospitals (LMWH, dabigatran and rivaroxaban), we used a price of £1 per injection/tablet, instead of the British National Formulary list price.
- We assumed a major bleeding fatality rate of 5% (instead of 1% for other types of surgery).
- Explicitly included the costs and health consequences of Heparin Induced Thrombocytopenia in the LMWH and UFH arms (section 4.3.2).

- We used population subgroup-specific major bleeding relative risks instead of relative risks pooled across the whole population.

- We assumed a pulmonary embolism fatality rate of 10% (instead of 6% for elective surgery, 31% for hip fracture surgery and 45% for general medical admissions).

- We varied the high-dose aspirin major bleeding relative risk vs Nil from 1 to
  - Low: Network Meta-analysis estimate of (RR = 0.5)
  - High: From direct meta-analysis (RR = 1.3)

- We increased the dabigatran major bleeding relative risk from 1.001 to be the same as LMWH

- We increased NICE threshold (£30,000/ QALY)

- Zero cost for foot impulse device equipment and £40 for foot impulse device consumable (section 4.4.1).

- We added district nurse visit costs.

As patients are discharged from hospital increasingly early, duration of prophylaxis carried out in-hospital is likely to be considerably shorter than observed in many of the clinical trials. It is possible that these interventions will be conducted post-discharge and if this is the case, additional costs would be incurred for those patients unable to inject themselves. We have conducted a threshold sensitivity analysis on the proportion of patients requiring a district nurse visit – a threshold sensitivity analysis is one where we keep changing the parameter until the optimal strategy switches to a different intervention. This was conducted for the post-discharge prophylaxis models and also for medical patients.

4.8.3 Stratification of results by baseline risk

It was recognised that within any surgical/medical population subgroup the risk of individuals may vary considerably and hence within a population subgroup the most cost-effective strategy will vary. Therefore, for each population subgroup we conducted a two-way sensitivity analysis, to show how the optimal strategy varied by baseline risk of pulmonary embolism and by baseline risk of major bleeding.

4.9 From evidence to recommendations

For each population subgroup, the strategy with the highest mean incremental net benefit (INB) based on the probabilistic analysis, was considered optimal. All INB estimates presented are in comparison with nil (no prophylaxis) with the exception of Total hip replacement extended duration where nil wasn't an option and so INB is measured compared with LMWH.
In some cases one may want to recommend a choice of strategies if the INB is similar for different strategies. Just how similar they have to be was a matter of judgement for the guideline development group. The Guideline Development Group also considered how sensitive the results are to specific key parameters or assumptions – section 4.8.2 and 4.8.3.
5 Risk, risk reduction and harm

5.1 Introduction

In making a judgement on the use of an intervention to reduce the risk of VTE, it is important to consider:

i. the reason for admission to hospital (e.g. a surgical procedure or a medical problem) and factors individual to the patient concerned (e.g. age, gender, pre-existing medical conditions and medication use) that influence the likelihood of VTE

ii. the likely treatment benefit from the specific prophylactic intervention

iii. the possible harmful effect of the intervention (e.g. bleeding from the use of pharmacological VTE prophylaxis).

While clinicians are used to evaluating these factors in a qualitative sense, the Guideline Development Group sought to obtain quantitative information where possible. The risk of VTE, risk reduction with a prophylactic intervention and risk of harm can all be expressed in absolute or relative terms. In some guidelines, patient related risk factors are expressed in relative terms. For example, patients with a prior history of VTE undergoing a surgical procedure were estimated to have an approximately 5-fold higher relative risk of DVT than patients with no such history (section 5.7.3). The current CMO risk assessment tool\textsuperscript{163} does not try to quantify the risks.

However, in balancing benefit and harms in an individual patient, it can be more helpful to consider risk in absolute terms. For example, if the absolute risk of VTE during hospitalisation is 10\% (i.e. a there is a 1 in 10 chance of VTE), and pharmacological prophylaxis reduces this risk by one half (i.e. a relative risk reduction of 50\%), the absolute reduction risk from the intervention would be 5\%. In simple terms, this means that there would be 5 fewer VTE events during hospitalisation in every 100 such patients treated, or 1 fewer event for every 20 treated (number needed to treat [NNT]=20). In a lower risk group of patients where the absolute risk of VTE is 1\% (i.e. a 1 in 100 chance of VTE during hospitalisation) but the same intervention continues to reduce VTE risk by one half (i.e. the same relative risk reduction), the reduction in absolute risk of VTE would be only 0.5\% (NNT=200). If the intervention doubles the risk of major bleeding from 0.5\% to 1\% in both situations (number needed to harm [NNH]=200), it might be considered to be helpful in the first group of patients but not the second.
5.2 Sources of information on risks, risk reduction and harm

Estimates of effect of treatment are obtained from randomised controlled trials (RCTs). Absolute risk reductions are readily calculated from data in individual RCTs, but meta-analysis of trial data, conducted to encompass the totality of evidence, conventionally generates a pooled estimate of the relative (rather than absolute) risk reduction. This is to overcome the problem that patients studied in different trials of the same intervention can have differing baseline absolute risk of VTE. A clinician may estimate the absolute risk reduction expected from an intervention by simply multiplying the pooled estimate of the relative risk reduction by the absolute risk of VTE in the patient group being considered. This requires reliable information on the absolute risk of VTE in different settings. However, the Guideline Development Group noted that information on the absolute risk of VTE in various clinical situations was limited. Three sources of information were considered:

(i) randomised controlled trials themselves
(ii) registries of routinely collected clinical data (e.g. Hospital Episode Statistics and the General Practice Research Database)
(iii) prospective cohort (incidence) studies

Because both the risk of VTE and the harms from treatment (particularly major bleeding) could differ substantially, information on absolute risks and harms in medical and surgical admission settings were considered separately.

5.3 Absolute risk of VTE during surgical admission

To assess absolute risk of VTE during a surgical admission or soon after, we have extracted data from three sources:

a) randomised controlled trials
b) registries of routinely collected clinical data
c) prospective cohort studies.

5.3.1 Evidence from randomised controlled trials

For these analyses, RCTs were grouped according to types of surgery using categories agreed by consensus within the guideline development group responsible for the development of the surgical guideline. Within each category, the total number of DVT events, the total number of symptomatic PE events and the total number of patients in the control (no prophylaxis arms) of RCTs were recorded. Studies were excluded if they reported any form of background prophylaxis other than early mobilisation. However, some patients may have had off-protocol prophylaxis at the discretion of their physicians. Studies were only included if they scanned all patients to find DVT (including asymptomatic DVT). This will result in the incidence figures reported being higher than the figures generally identified in practice which are usually only symptomatic events.

A pooled estimate of the absolute risk of any (including asymptomatic) DVT, and symptomatic pulmonary embolism (PE) was estimated by a fixed effects meta-analysis,
which used a Freeman-Tukey arcsine transformation to stabilise the variances of the individual study proportions \(446\) (Table 5-17). The types of surgery with the highest risk of DVT and symptomatic PE were (major) orthopaedic surgery followed by (major) general surgery and then neurosurgery.

The strengths of this source of information is that the patients are being carefully followed, ensuring that disease endpoints are unlikely to have been missed. In addition it is known in the control arms of the RCTs, no intervention was used, providing an estimate of absolute risk in the absence of any treatment. Finally it is known that the diagnosis of VTE was confirmed by appropriate imaging tests. However, the limitation is that patients studied in RCTs may not adequately represent the full spectrum of patients encountered in clinical practice which may limit the ability to generalise the findings. Furthermore, for some categories of surgery the available sample size was small.
### Table 5-17: Risk of DVT and pulmonary embolism by type of surgery, from the no prophylaxis arm of RCTs

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Number of patients with an event</th>
<th>Sample Size</th>
<th>Incidence</th>
<th>Incidence Lower 95% CL</th>
<th>Incidence Upper 95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DVT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>10</td>
<td>65</td>
<td>14%</td>
<td>7%</td>
<td>24%</td>
</tr>
<tr>
<td>General</td>
<td>569</td>
<td>2286</td>
<td>24%</td>
<td>23%</td>
<td>26%</td>
</tr>
<tr>
<td>Gynaecology</td>
<td>113</td>
<td>691</td>
<td>16%</td>
<td>13%</td>
<td>19%</td>
</tr>
<tr>
<td>Neurological</td>
<td>91</td>
<td>446</td>
<td>20%</td>
<td>17%</td>
<td>24%</td>
</tr>
<tr>
<td>Orthopaedic (Elective Hip)</td>
<td>530</td>
<td>1172</td>
<td>45%</td>
<td>42%</td>
<td>48%</td>
</tr>
<tr>
<td>Orthopaedic (Hip fracture)</td>
<td>471</td>
<td>1139</td>
<td>40%</td>
<td>37%</td>
<td>43%</td>
</tr>
<tr>
<td>Orthopaedic (Elective Knee)</td>
<td>65</td>
<td>108</td>
<td>60%</td>
<td>51%</td>
<td>69%</td>
</tr>
<tr>
<td>Orthopaedic Mixed</td>
<td>66</td>
<td>140</td>
<td>47%</td>
<td>39%</td>
<td>55%</td>
</tr>
<tr>
<td>Urological</td>
<td>18</td>
<td>144</td>
<td>10%</td>
<td>6%</td>
<td>15%</td>
</tr>
<tr>
<td>Vascular</td>
<td>2</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>286</td>
<td>1303</td>
<td>22%</td>
<td>19%</td>
<td>24%</td>
</tr>
<tr>
<td>Not known</td>
<td>102</td>
<td>276</td>
<td>36%</td>
<td>31%</td>
<td>42%</td>
</tr>
<tr>
<td>All</td>
<td>2353</td>
<td>8089</td>
<td>29%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Symptomatic Pulmonary Embolism

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Number of patients with an event</th>
<th>Sample Size</th>
<th>Incidence</th>
<th>Incidence Lower 95% CL</th>
<th>Incidence Upper 95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>0</td>
<td>0</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>72</td>
<td>3044</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Gynaecology</td>
<td>2</td>
<td>250</td>
<td>1%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Neurological</td>
<td>0</td>
<td>129</td>
<td>3%</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Orthopaedic (Elective Hip)</td>
<td>32</td>
<td>760</td>
<td>3%</td>
<td>2%</td>
<td>5%</td>
</tr>
</tbody>
</table>
### 5.3.2 Evidence from clinical registry data

**Hospital Episode Statistics**

The NHS Hospital Episode Statistics database holds data on every patient admitted to an NHS hospital in England. We extracted data from the year 2003/4. This section has been incorporated from the previous surgical guideline and has not been updated as part of the development of this guideline.

We identified all patients with a secondary diagnosis of symptomatic DVT or pulmonary embolism (ICD10=I26.0, I26.9, I80.2, I80.3, I80.8, I80.9, I82.1, I82.2, I82.8, I82.9) but excluded those that had not been admitted for surgery. We generated categories of surgical treatment by consensus. We then calculated the incidence of VTE for each surgical procedure using the total number of procedures performed over the same period as the denominator.

Table 5-18 shows the different surgical categories in order of the incidence of symptomatic VTE. The types of surgery with the highest risk of VTE are cardiothoracic, major orthopaedic and vascular surgery followed by major abdominal general surgery.

The advantage of this type of data is that they better reflect the spectrum of patients encountered in everyday practice. The disadvantages include the possibility that the diagnosis of VTE may have been inaccurate in some cases, the recording and coding of VTE may have been incomplete, and the absolute risks may not be directly comparable across categories because of the varying lengths of stay involved with different surgical interventions. Moreover, the estimates of absolute risk reflect may not be directly comparable with estimates made using data from the control arm of clinical trials because many patients in the HES registry will have received some form of thromboprophylaxis. Table 5-18 shows this incidence of symptomatic VTE by type of surgery, as recorded in HES.
Table 5-18: Incidence of symptomatic VTE estimated from HES 2003/4

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of patients with an event</th>
<th>Sample Size</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral head</td>
<td>237</td>
<td>23538</td>
<td>1.01%</td>
</tr>
<tr>
<td>Knee replacement</td>
<td>493</td>
<td>52535</td>
<td>0.94%</td>
</tr>
<tr>
<td>Vascular</td>
<td>1186</td>
<td>169218</td>
<td>0.70%</td>
</tr>
<tr>
<td>Adult cardiac</td>
<td>208</td>
<td>40180</td>
<td>0.52%</td>
</tr>
<tr>
<td>Hip replacement</td>
<td>293</td>
<td>57899</td>
<td>0.51%</td>
</tr>
<tr>
<td>Transplantation</td>
<td>11</td>
<td>2375</td>
<td>0.46%</td>
</tr>
<tr>
<td>Thoracic</td>
<td>117</td>
<td>26002</td>
<td>0.45%</td>
</tr>
<tr>
<td>Lower gastrointestinal (GI)</td>
<td>428</td>
<td>95968</td>
<td>0.43%</td>
</tr>
<tr>
<td>Renal replacement</td>
<td>140</td>
<td>39733</td>
<td>0.35%</td>
</tr>
<tr>
<td>Upper gastrointestinal (GI)</td>
<td>356</td>
<td>110562</td>
<td>0.32%</td>
</tr>
<tr>
<td>Fractures</td>
<td>555</td>
<td>181346</td>
<td>0.31%</td>
</tr>
<tr>
<td>Intensive Therapy Unit (ITU)</td>
<td>1215</td>
<td>448253</td>
<td>0.27%</td>
</tr>
<tr>
<td>Oncology</td>
<td>1311</td>
<td>529069</td>
<td>0.25%</td>
</tr>
<tr>
<td>Radiology cardiovascular</td>
<td>404</td>
<td>221317</td>
<td>0.18%</td>
</tr>
<tr>
<td>Endoscopic and percutaneous</td>
<td>2383</td>
<td>1376236</td>
<td>0.17%</td>
</tr>
<tr>
<td>Joints other</td>
<td>29</td>
<td>17553</td>
<td>0.17%</td>
</tr>
<tr>
<td>Spine</td>
<td>76</td>
<td>56559</td>
<td>0.13%</td>
</tr>
<tr>
<td>Orthopaedic (other)</td>
<td>254</td>
<td>219116</td>
<td>0.12%</td>
</tr>
<tr>
<td>Neurosurgery not spine</td>
<td>229</td>
<td>215533</td>
<td>0.11%</td>
</tr>
<tr>
<td>Plastic</td>
<td>259</td>
<td>314817</td>
<td>0.08%</td>
</tr>
<tr>
<td>Urology</td>
<td>121</td>
<td>164362</td>
<td>0.07%</td>
</tr>
<tr>
<td>Hernia</td>
<td>72</td>
<td>115703</td>
<td>0.06%</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>179</td>
<td>443529</td>
<td>0.04%</td>
</tr>
<tr>
<td>Arthroscopy</td>
<td>34</td>
<td>112123</td>
<td>0.03%</td>
</tr>
<tr>
<td>Anus and piles</td>
<td>26</td>
<td>86671</td>
<td>0.03%</td>
</tr>
<tr>
<td>Breast</td>
<td>22</td>
<td>78547</td>
<td>0.03%</td>
</tr>
<tr>
<td>Ear, Nose and Throat (ENT)</td>
<td>51</td>
<td>209680</td>
<td>0.02%</td>
</tr>
<tr>
<td>Head and neck</td>
<td>16</td>
<td>80258</td>
<td>0.02%</td>
</tr>
<tr>
<td>Max facial dental</td>
<td>34</td>
<td>184784</td>
<td>0.02%</td>
</tr>
<tr>
<td>Eyes</td>
<td>69</td>
<td>457382</td>
<td>0.02%</td>
</tr>
</tbody>
</table>

US clinical registry data

White et al. (2003) evaluated the incidence of symptomatic VTEs in a database of 1.7 million patients in 76 surgical categories in the USA. They included cases of symptomatic VTE occurring during either the initial hospitalisation or a subsequent hospitalisation within 91 days of the surgery. Procedures in patients without a diagnosis of cancer where the risk of VTE was greater than 2% were:

- Embolectomy or endarterectomy of lower limb artery 2.8%
- Total hip arthroplasty 2.4%
- Neurosurgery involving excision/destruction or biopsy of brain tissue 2.3%
- Partial hip arthroplasty 2.0%

Among patients with cancer, surgical procedures where the absolute risk of symptomatic VTE was greater than 2% were:

- Permanent colostomy 2.6%
Radical cystectomy 3.7%
- Percutaneous nephrostomy 3.6%
- Exploratory laparotomy 2.4%
- Internal fixation of femur 3.0%

In patients without a malignancy, gynaecological and head and neck, and laparoscopic abdominal surgery conveyed the lowest risk of VTE.

5.3.3 Prospective cohort studies

This section has been incorporated from the previous surgical guideline and has not been updated as part of the development of this guideline.

The sixteen other studies found were difficult to summarise, because of their heterogeneity, but if we compare the incidence rates with those in Table 2, it would seem that there is a relatively high risk of VTE associated with prostatectomy, gynaecological surgery and neurosurgery and a low risk associated with surgery for breast cancer or head and neck/ENT surgery (Evidence Table 1, Appendix D).

The data reported in this section are limited because of the heterogeneity of the methods used by the different studies and because it is difficult to control for the use of VTE prophylaxis or anaesthesia.

5.3.4 Discussion of data on surgical risk

We used different sources to estimate the risk of VTE for different categories of surgery compared with other surgery types. The incidence figures for VTE estimated using HES data were much lower than other estimates, implying under-reporting and/or treatment in the community. This was true even when compared to a similar database in the USA. The figures for DVT from the ‘no prophylaxis’ arms of the RCTs appears higher than other estimates due to the identification of asymptomatic DVT events by screening the legs, as well as symptomatic events.

Hip surgery (elective and hip fracture) had higher rates of VTE by all three approaches. Some categories of cardiothoracic, vascular, urological, neurological and general surgery were also at increased risk compared with other surgery types, although, the rankings were not necessarily the same for the different approaches. Except for cancer-related surgery, gynaecological surgery had some of the lowest rates of VTE by all three approaches – this could in part be due to these patients being younger on average than some of the other patient groups.

Comparisons between different categories of surgery are likely to be confounded by age and differences in prophylaxis and anaesthesia usage. Length of stay is likely to be a contributory factor since immobility is a causal mechanism. However it might also be a confounder since the longer people stay in hospital the more likely that their VTE will be recorded.

The differences in incidence within the broad surgical categories are probably much greater than the differences between categories.
The strategy that the Guideline Development Group adopted from this evidence was to consider major orthopaedic surgery as higher risk for VTE than cardiac, thoracic, urological, vascular, gynaecological, neurological and general surgery. Within orthopaedic surgery, hip fracture was considered to be highest risk followed by elective orthopaedic procedures and then other types of major orthopaedic surgery.

The surgical guideline development group decided that the no-prophylaxis arms of the RCTs was the best source for the baseline risk of VTE and major bleeding, and this was used in our cost-effectiveness analysis (Chapter 4). The advantage of these risk estimates is that they control for prophylaxis use. However, the Guideline Development Group acknowledged also the weaknesses in these data. Firstly trial populations might not be representative of surgical patients in general. Second, it has been postulated that the incidence of VTE has fallen over time due to prophylaxis use but also due to other factors. If this is true then the RCT evidence, which goes back to the 1970s may over-estimate the risk of DVT and PE. Conversely, since RCT protocols usually involve surveillance for asymptomatic DVT, they might under-estimate the incidence of PE if DVTs are being diagnosed and actively before the time when they would have become symptomatic in a non-trial setting.

5.4 Absolute risk of VTE during medical admissions

We obtained information on the absolute risk of VTE during a medical admission from:

a) randomised controlled trials

b) incidence studies

5.4.1 Evidence from randomised controlled trials

The incidence of all (including asymptomatic) DVT and symptomatic PE was estimated from the RCTs in our clinical review were extracted and analysed as per the methodology as detailed in Section 5.3. These data are presented in Table 5-19.
Table 5-19: Risk of DVT and symptomatic PE, by medical condition, from the nil arm of RCTs

<table>
<thead>
<tr>
<th></th>
<th>Number of patients with an event</th>
<th>Sample Size</th>
<th>Incidence</th>
<th>Incidence Lower 95% CL</th>
<th>Incidence Upper 95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DVT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Medical Patients</td>
<td>106</td>
<td>827</td>
<td>13%</td>
<td>11%</td>
<td>15%</td>
</tr>
<tr>
<td>Stroke</td>
<td>195</td>
<td>384</td>
<td>50%</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>Acute Coronary Syndromes</td>
<td>76</td>
<td>372</td>
<td>21%</td>
<td>17%</td>
<td>25%</td>
</tr>
<tr>
<td>All</td>
<td>377</td>
<td>1583</td>
<td>24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Symptomatic Pulmonary Embolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Medical Patients</td>
<td>24</td>
<td>2400</td>
<td>0.9%</td>
<td>0.6%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>54</td>
<td>3%</td>
<td>0%</td>
<td>9%</td>
</tr>
<tr>
<td>Acute Coronary Syndromes</td>
<td>5</td>
<td>156</td>
<td>4%</td>
<td>2%</td>
<td>8%</td>
</tr>
<tr>
<td>All</td>
<td>17</td>
<td>2638</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Alongside the limitations of using RCT data to determine the incidence of DVT as detailed in section 5.3.1 the studies reporting on ‘general medical patients’ included a range of different medical conditions. Therefore some studies included in this population will have ischaemic stroke or acute coronary syndromes, but it was not possible to identify these separately.

### 5.4.2 Incidence studies

A search was conducted to identify primary studies reporting the incidence of VTE in medical patients. The Guideline Development Group were concerned that the incidence of VTE may have changed over time due to advances in medical practice and so a time limit was put on the search to only find papers published from 1998 – 2008. After the review and data extraction of some of these studies (Evidence Table 2, Appendix D) it became apparent that similar problems as those detailed in section 5.3.2 were being encountered and the information provided was not as useful as had been hoped. The studies reviewed differed in the methods used, populations included, outcomes measured and confounding factors considered, particularly the use of VTE prophylaxis. These factors meant that the comparison of the results between studies was not possible. Once this had been identified as a problem, no further papers were reviewed and the results as presented below are used to demonstrate the inconsistency of these data.

Eighteen (18) studies were reviewed, 6 of these studies were database reviews 67,68,241,606,623,624 whereas 12 were cohort studies 77,134,144,149,173,320,349,453,469,501,512,567 (Evidence Table 2, Appendix D).

The larger studies looking across all hospital admissions used database coding in order to identify VTE which may not capture all events, particularly those occurring after discharge. In addition, most database reviews do not provide details on any VTE
prophylaxis, which is likely to be because the prophylaxis strategy was not recorded in the database and may have differed across departments and/or hospitals.

**Data from registries**

One database review found that the incidence of symptomatic PE in stroke patients (0.51% for ischaemic stroke and 0.68% for haemorrhagic stroke) and in patients admitted with cancer patients (0.6%) were greater than the symptomatic PE rate across all patients admitted to hospital (0.23% (95% CI: 0.21 – 0.25%)) which included medical, surgical and trauma patients.

**Cohort studies**

Cohort studies specifically for critical care patients (usually including surgical patients), acute exacerbation of COPD, ischaemic stroke, congestive heart failure and rehabilitation units were reviewed (Evidence Table 2, Appendix D).

**5.5 Absolute risk of major bleeding after surgery**

The relative risk increases for major bleeding from pharmacological prophylaxis after surgery are outlined in chapters 9-18. The current section summarises evidence on the absolute risk of bleeding after different surgery.

The absolute risk of bleeding after surgery is even more difficult to find than the absolute risk of VTE. The main source of information that was used to establish the baseline risks of major bleeding in this population were the nil prophylaxis arms of RCTs. These data from individual trials were combined using a meta-analysis technique as described in section 5.3.1.

Use of evidence for major bleeding incidence from RCTs has limitations as although many of the newer studies may use a fairly standard definition of major bleeding. A major bleeding event is defined as a bleeding event that results in one or more of the following: death; a decrease in haemoglobin concentration of 2g/dl or more; transfusion of at least 2 units of blood; bleeding from a retroperitoneal; intracranial; or intraocular site; a serious or life-threatening clinical event; a surgical or medical intervention. Some studies have modified this definition and others use their own trial specific definition. The Guideline Development Group agreed to use the definition of major bleeding as reported in the trials.

Another major limitation of using the absolute bleeding risk from RCTs is that they are likely to have excluded patients at increased risk of bleeding and so the incidence reported may be an underestimate of the total population.

We are not aware of any prospective cohort studies that investigate the absolute risk of bleeding after surgery in the absence of prophylaxis. Many of the definitions may not include the ‘minor’ bleeding which can cause serious wound complications which can be associated with a considerable loss of quality of life and cost.
Table 5-20: Risk of major bleeding, by type of surgery, from the nil arm of RCTs

<table>
<thead>
<tr>
<th>Major Bleeding</th>
<th>Number of patients with an event</th>
<th>Sample Size</th>
<th>Incidence</th>
<th>Incidence Lower 95% CL</th>
<th>Incidence Upper 95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>1</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>83</td>
<td>3980</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Gynaecology</td>
<td>13</td>
<td>306</td>
<td>4%</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Neurological</td>
<td>1</td>
<td>113</td>
<td>2%</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>25</td>
<td>117</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>29</td>
<td>772</td>
<td>3%</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>4</td>
<td>274</td>
<td>2%</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>0</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urological</td>
<td>2</td>
<td>170</td>
<td>2%</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Vascular</td>
<td>0</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>2</td>
<td>1153</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Not known</td>
<td>2</td>
<td>254</td>
<td>1%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>All</td>
<td>167</td>
<td>7241</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The absolute risk of major bleeding rate for most surgery was between 1-2% as reported in the trials, although the Guideline Development Group noted that gynaecological surgery had a higher risk of major bleeding at 4%.

5.6 Absolute risk of major bleeding after medical admissions

The relative risk increases for major bleeding from pharmacological prophylaxis are outlined in chapters 23 to 25. The current section summarises evidence on the absolute risk of bleeding in different settings.

The same method as in section 5.5 was used to identify the absolute risk of bleeding in patients admitted for medical conditions. The incidence of bleeding in the general medical population appeared to be lower than the risk of bleeding after stroke.
Table 5-21: Risk of major bleeding, by medical condition, from the nil arm of RCTs

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Number of patients with an event</th>
<th>Sample Size</th>
<th>Incidence</th>
<th>Incidence Lower 95% CL</th>
<th>Incidence Upper 95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Medical Patients</td>
<td>11</td>
<td>2629</td>
<td>0.4%</td>
<td>0.2%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Stroke</td>
<td>4</td>
<td>107</td>
<td>4%</td>
<td>1%</td>
<td>9%</td>
</tr>
<tr>
<td>Acute Coronary Syndromes</td>
<td>0</td>
<td>14</td>
<td>Not Estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>15</td>
<td>2750</td>
<td>0.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.7 Individual patient risk factors and relative risks of VTE

Published risk assessment tools

No existing, published risk assessment tools have been recommended because the literature search did not identify any that have been validated in a broad range of patients and been shown to improve patient outcomes. The Department of Health published a risk assessment tool in September 2008 and it is intended that this tool will be updated at the time of publication of the NICE guideline to ensure that the wording is consistent.

Search for individual patient risk factors

Because risk factors specific to the patient may modify absolute risk in any setting we searched for systematic reviews on patient related risk factors for DVT or PE. For the previous guideline, the search was confined to patients admitted for surgical procedures. We identified one study that included several systematic reviews encompassing various risk factors in surgical patients. The search was extended to any patient group exposed to a risk factor when insufficient information was found in surgical populations. Several reviews were identified for non-surgical populations.

Some reviews only included studies that used an objective test for diagnosing venous thromboembolism such as a fibrinogen uptake or ultrasound, whereas others did not report the method of diagnosis for studies included. The number of cases and controls was not always reported. Details for each systematic review are reported below. We also referred to previous guidelines for their included risk factors. The search for individual patient risk factors for VTE in surgical patients was not updated as part of the development of this guideline. Results have been incorporated from the previous surgical guideline.

For each risk factor, information is reported in relative rather than absolute terms (using relative risks or odds ratios). One way in which clinicians might use this information is to...
scale up absolute risk derived from the sources listed above in a patient with one of the risk factors listed below. For example a patient with a prior history of DVT undergoing a surgical procedure where the absolute risk of DVT is 1% on average might be expected to have personal absolute risk of 5%. However, in patients with more than one risk factor, risks are unlikely to simply be multiplicative because many individual risk factors are unlikely to be independent. For this reason, the Guideline Development Group recommends new prospective cohort studies of hospitalised patients be conducted for the development and validation of a multivariable risk models for the estimation of absolute risk of DVT in individual patients, that could be applied in the clinical setting (section 5.10).

5.7.1 Age

Edmonds et al \cite{169} identified six studies investigating the association between age and postoperative DVT (evidence level 2+). There was a general trend of increased age being associated with an increased risk of DVT in all studies. Two of the studies showed the incidence of DVT to be higher in those over 60 than those under; two studies showed the mean age of patients with DVT to be higher than those without DVT; and two studies showed an incremental increase associated with increasing age, one of them finding the risk to be constant at below 45 years of age. A pooled risk estimate was not possible because of the different ways of investigating across the studies (Evidence Table 3, Appendix D).

Rocha et al \cite{556} identified a further 5 studies, 3 of which were conducted in the general population and the remaining 2 in medical inpatients (evidence level 2+). All studies confirmed a significant increase in VTE risk with increasing age although cut offs were different for each study (cut offs ranged from 50 to 85 years) (Evidence Table 3, Appendix D).

Although the increased risk of DVT with increasing age has been demonstrated by many studies and is relatively uncontroversial, it is difficult to provide useful guidance without providing a cut-off at which a person should be considered at ‘increased risk’. There is no universally agreed figure for this cut off. Some guidelines have put an age threshold of 40 although White et al \cite{688} found that the relationship between age, type of surgery and risk is complex, in particular there is no evident step up in risk at 40. Anderson & Spencer \cite{17} noted stratification of risk by the simple dichotomy of age below or above 40 years fails to account for the significantly higher risk among the elderly patients undergoing high risk surgical procedures.

The guideline development group agreed that an age cut off of 60 years should be used. In addition to the evidence detailed above, the decision was also made based on the patients included in the trials. The patients included in the studies for general surgery patients (and therefore included in our cost effectiveness model) had average age of 60 years (chapter 9). It was the decision of the guideline development group that setting an age cut off lower than age 60 may lead to the provision of VTE prophylaxis unnecessarily where no other risk factors were present which could lead to greater harm than benefit.

Although the average age of patients included in VTE prophylaxis trials of medical patients (74 years) was greater than for general surgery trials it was noted that in the recommendation for medical patients both reduced mobility and an age over 60 years was required in order for prophylaxis to be offered.
5.7.2 Obesity

Edmonds et al. \(^{169}\) identified seven studies investigating the association between obesity and postoperative DVT (evidence level 2+). Five out of the seven studies found a significant association between an increase in obesity and risk of DVT and two found no significant difference. A pooled estimate was not possible because of different definitions for obesity used across the studies (Evidence Table 4, Appendix D).

Rocha et al.\(^{556}\) identified a further nine studies, although the definitions of VTE and of obesity used were unclear within the review (evidence level 2+). Three studies reported that they found no evidence of a correlation between obesity and VTE whereas five studies reported a significant increase in VTE risk (between 2.0 and 3.92). The remaining study found a large VTE relative risk increase (RR rose from 2 to 10) for obese patients using hormonal contraceptives (Evidence Table 4, Appendix D).

We used the definition of obesity as being patients with a body mass index greater than or equal to 30 kg/m\(^2\) which is the definition used in the current NICE guidelines\(^{474}\).

5.7.3 Personal or family history of VTE

Edmonds et al.\(^{169}\) identified four studies investigating the association between a history of venous thrombosis and postoperative DVT (evidence level 2+). When three of the studies were pooled, they indicated a significant association between past history of venous thrombosis and risk of DVT (OR=5.18, 95% CI: 3.16 to 8.49). The other study suggested no difference but did not provide any data (Evidence Table 5, Appendix D).

Rocha et al.\(^{556}\) identified six studies in medical patients and the general population (evidence level 2+); four of which were case control reports and the remaining two were cohort studies. All of these studies identified a significant association between a history or previous VTE and a risk of future VTE events. No pooling of events was completed (Evidence Table 5, Appendix D).

In addition to a personal history of VTE, the GDG felt it was important to ask about any family history of previous VTE events in first degree relatives during the risk assessment. In this way it may be possible to identify patients who are at risk of inherited thrombophilias that may remain undiagnosed at the time of admission.

5.7.4 Known thrombophilias

Thrombophilias are the genetic or acquired prothrombotic states that increase the tendency to venous thromboembolism (Evidence Table 6, Appendix D).

Edmonds et al.\(^{169}\) identified two studies investigating the association between activated protein C (APC) resistance or Factor V Leiden (FVL) mutation and postoperative DVT (evidence level 2+). One study reported low sensitivity to APC was shown to be significantly associated with postoperative DVT (RR=4.9, 95% CI: 1.1 to 22.2) with 95% of the cases being attributable to the FVL mutation. The second study reported that a low sensitivity of FVL to APC (OR=2.97, 95% CI: 1.27 to 6.92) and FVL mutation (OR=3.18, 95% CI: 0.99 to 10.2) were associated with postoperative DVT.

Rocha et al.\(^{556}\) identified nine studies investigating the impact of FVL mutation and VTE (evidence level 2+). The increase in relative risk reported ranged from 2.2 to 6.6 although no pooling was attempted. Five studies reported the impact of protein C
deficiency on VTE and the increase in relative risk ranged from 3.4 to 7.3. (Evidence Table 6, Appendix D). These results support the findings in surgical patients.

Two of the studies included in the review by Edmonds et al. examined antithrombin deficiency (evidence level 2+). One found patients who developed postoperative DVT had a lower level of antithrombin, the other did not find any association. We also identified one systematic review that looked at deficiency in antithrombin, protein C or protein S. All three were associated with an increased risk of postoperative venous thromboembolism with relative risks of 5, 6.5 and 1.7 respectively. No information was given as to how venous thrombosis was diagnosed. Edmonds et al. found no surgical studies investigating other thrombophilias.

Rocha et al. identified 3 studies investigating anti-thrombin III deficiency (evidence level 2+). These studies all found an increased risk of VTE with the deficiency with the odds ratio varying between 1.7 and 12.6 in the studies (Evidence Table 6, Appendix D).

One additional thrombophilia investigated in the systematic review by Rocha et al. was protein S deficiency. Four papers investigating the risk of VTE with protein S deficiency found that it increased the odds ratio for VTE between 0.7 and 14.4.

We identified one systematic review with 25 studies that looked at the association for lupus anticoagulants and/or anticardiolipin with thrombosis (venous or arterial) in medical populations (evidence level 2+). Results were grouped according to type of event: first event, recurrent event or any event (distinction between first and recurrent events not possible). Lupus anticoagulants were found to be significantly associated with DVT. Five studies investigating lupus anticoagulants and anticardiolipin antibodies gave pooled odds ratios of 5.71 for any event and 9.4 for a first event. None of the studies showed a significant association with anticardiolipin antibodies. Four studies investigating lupus anticoagulants alone gave pooled odds ratios of 16.2 for any event and 4.01 for a recurrent event.

We identified one systematic review with 24 studies that looked at the association between raised homocysteine levels and venous thrombosis (evidence level 2+). No information was given as to how venous thrombosis was diagnosed. The review showed that a 5μmol/L increase in measured plasma total homocysteine is associated with an increased risk of venous thrombosis (OR=1.27, 95% CI: 1.01 to 1.59 from three prospective studies, OR=1.60, 95% CI: 1.10 to 2.34 from 24 retrospective studies). The same review also looked at the association of MTHFR (Methylenetetrahydrofolate reductase) with venous thrombosis. The 677TT genotype was associated with a 20% higher risk of venous thrombosis compared to the 677CC genotype (OR=1.20, 95% CI: 1.08 to 1.32).

We identified one systematic review that looked at the association between prothrombin gene mutation and venous thromboembolism (evidence level 2+). In one study G20210a prothrombin was associated with a three fold increase in risk of venous thromboembolism (OR=2.8, 95% CI: 1.4 to 5.6). Similar results were found in a pooled analysis of eight case-control studies (OR=3.8, 95% CI: 3.0 to 4.9).

Rocha et al. reported eight studies investigating the links between VTE and prothrombin gene mutation (evidence level 2+). These concluded that there was an increase in VTE with the mutation with odds ratios reported between 2.0 and 11.5.
Samama et al also looked at the association between elevated plasma levels of coagulation factors and venous thromboembolism. Elevated factor VII, VIII, IX and XI were all found to be significantly associated with venous thromboembolism while elevated factor X or high plasma levels of fibrinogen were not.

Two externally produced guidelines, not specifically in surgical patients, considered risk factors for venous thromboembolism and highlighted the following thrombophilic conditions that increased the risk of VTE: myeloproliferative disease; paraproteinaemia; paroxysmal nocturnal haemoglobinuria and Behcet’s Disease. Although these conditions were specifically mentioned within the risk factor list within the NICE guideline for reducing the risk of VTE in surgical in-patients, for simplicity it is intended that these conditions are included within the ‘known thrombophilia’ risk factor in the current guideline.

5.7.5 Varicose veins

Edmonds et al. identified seven studies investigating the association between varicose veins and postoperative DVT (evidence level 2+). A pooled estimate of the six studies with data showed an increase risk (OR 2.39, 95% CI: 1.69 to 3.37). One study did not provide any data (Evidence Table 7, Appendix D).

Rocha et al. investigated varicose veins, venous insufficiency and peripheral arterial disease as risk factors for VTE. Eight studies were found (evidence level 2+). Four studies reported significant increases in risk of VTE in medical patients with varicose veins (OR ≥ 2.5) although an additional two studies did not find an association. One study reported that the risk of VTE associated with varicose veins decreases with age. There was an increase in VTE risk found associated with venous insufficiency (OR ≥ 1.7) and peripheral arterial disease (OR = 1.9) (Evidence Table 7, Appendix D).

5.7.6 Cardiovascular factors

Edmonds et al. identified two studies looking at the association between cardiovascular factors and postoperative DVT (evidence level 2+). Three potential risk factors were identified: recent myocardial infarction, hypertension and congestive cardiac failure. None were shown to be significantly associated with postoperative DVT. Congestive cardiac failure was shown to be significantly associated with DVT in univariate analysis but not in multivariate analysis in two studies, suggesting that the association was potentially explicable by confounding. Another non-surgical study reported by Edmonds showed similar results (Evidence Table 8, Appendix D).

The systematic review by Rocha et al. looked at two cardiovascular factors as risk factors for VTE, acute myocardial infarction and congestive heart failure (CHF) (evidence level 2+). The two studies included for the section on acute myocardial infarction were both RCTs and reported on the populations that did not receive prophylaxis, where they found a high incidence of DVT and PE (62.5% and 12.2% respectively). Five studies were found investigating CHF for VTE. They all reported an increase in VTE in medical patients who had CHF, with the risk increasing with decreasing ejection fraction and increasing functional compromise (Evidence Table 8, Appendix D).

5.7.7 Oral contraceptives

Edmonds et al. identified five cohort studies and two case control studies in surgical patients (evidence level 2+). A pooled risk estimate was only possible for three of the studies due to deficiencies in reported data. This showed oral contraceptive pills were
significantly associated with an increased risk of postoperative DVT (OR=2.48, 95% CI: 1.53 to 4.02). Edmonds et al. reported some weaknesses with the data available: the studies were somewhat dated and may not apply to the recent third generation of oral contraceptive pills; and only three out of the five cohort studies screened everyone for DVT. Another systematic review compared third generation with second generation users in non-surgical populations (evidence level 2+). Third generation contraceptives were associated with an increased risk of venous thrombosis compared to second generation contraceptives (unadjusted OR=1.6, 95% CI: 1.3 to 1.9; adjusted odds ratio OR=1.7, 95% CI: 1.4 to 2.0) (Evidence Table 9, Appendix D).

The Royal College of Obstetricians and Gynaecologists offers guidance on venous thromboembolism and hormonal contraceptives. In addition, The BNF states that:

“oestrogen-containing contraceptives should preferably be discontinued (and alternative contraceptive arrangements made) 4 weeks before major elective surgery and all surgery to the legs or surgery which involves prolonged immobilisation of a lower limb.”

The BNF recommends that progestogen only methods need not be discontinued prior to surgery even when immobilisation is expected.

If the decision to stop oral contraceptives is taken it is important that women are provided with advice on the use on contraceptives in the interim period. Further information is contained within the BNF.

**5.7.8 Hormone replacement therapy**

Edmonds et al. found no studies investigating hormone replacement therapy in a surgical population. We identified two recent systematic reviews that identified studies from a non-surgical population. The Royal College of Obstetricians and Gynaecologists identified nine studies but did not pool the relative risks, these varied from 2.1 to 6.9 (evidence level 2+). Miller et al. calculated a pooled relative risk of 2.14 (credible interval 1.64 to 2.81) from 12 studies (evidence level 2+). Six of these studies also compared the risk of hormone replacement use in the first year compared to subsequent years of use. Use in the first year had a higher risk estimate (relative risk in first year of use: 3.49, credible intervals: 2.33 to 5.59; relative risk in subsequent years of use: 1.91, credible intervals: 1.18 to 3.52) (Evidence Table 10, Appendix D).

Rocha et al. identified two additional studies (evidence level 2+) published since the publication of Miller et al. One was the Women’s Health Initiative RCT which supported a higher rate of VTE in the group receiving HRT compared to the placebo group (relative risk = 2.1; 95% CI = 1.6-2.8). The second study was a case control study which reported a higher VTE rate with oral hormone replacement therapy compared with transdermic administration (odds ratio: 4.0; 95% CI 1.9-8.3) (Evidence Table 10, Appendix D).

The Royal College of Obstetricians and Gynaecologists offers guidance on hormonal replacement therapy and venous thromboembolism. In addition, the BNF also provides guidance indicating that HRT should be considered a risk factor for VTE but it may be prudent to consider stopping treatment 4-6 weeks before major surgery under general anaesthesia.

Both BNF and RCOG documents highlights that stopping this may not necessary to stop prior to surgery provided that appropriate thromboprophylaxis is used.
5.7.9 Cancer

Edmonds et al\textsuperscript{169} identified nine studies investigating the association between cancer and postoperative DVT (evidence level 2+). An assumption in the review is that an effect of cancer on thrombosis following general surgery is the same as the effect when surgery is for the treatment of that cancer. All nine studies found an increased risk associated with cancer giving a pooled odds ratio of 2.94 (95% CI: 2.01 to 4.29). Around a third of the total number of patients also received thromboprophylaxis (Evidence Table 11, Appendix D).

Rocha et al\textsuperscript{556} identified 5 studies investigating the risk of VTE with various cancers (evidence level 2+). These studies indicated that although some cancers were associated with an increased risk of VTE (e.g. leukaemia, brain and uterus), others cancers had a lower relative risk of VTE compared to patients with no cancer (e.g. head and neck, bladder cancer, breast cancer). However, very little details are provided about these studies and the additional risk factors that the patient may have (e.g. surgery). A full list of the risk associated with 18 cancer types is presented in the evidence table (Evidence Table 11, Appendix D).

5.7.10 Chemotherapy

No surgical studies were found investigating the association between chemotherapy and postoperative DVT. We identified one systematic review of 32 studies that investigated vascular and neoplastic events associated with tamoxifen in non-surgical patient groups \textsuperscript{79} (evidence level 1+). Eleven of the included studies reported pulmonary embolisms and demonstrated overall a significantly increased risk of pulmonary embolism (RR=1.88, 95% CI: 1.17 to 3.01) and 15 of the included studies reported DVT also demonstrating an increased risk (RR=1.87, 95% CI: 1.33 to 2.64). Seven of the 11 pulmonary embolism studies and 11 of the 15 DVT studies investigated the use of tamoxifen in patients with malignancy. The other four studies were for the prevention of cancer (Evidence Table 12, Appendix D).

Rocha et al\textsuperscript{556} reported an additional 5 studies (evidence level 2+). These studies reported significant increases in VTE when patients were ‘on chemotherapy’ compared with ‘off chemotherapy’ in breast cancer patients. In addition tamoxifen was highlighted as an additional factor increasing VTE risk for breast cancer patients in three studies. The use of thalidomide was observed to increase DVT in patients with multiple myeloma in another study (Evidence Table 12, Appendix D).

5.7.11 Smoking

Edmonds et al\textsuperscript{169} identified four studies investigating the association between smoking and postoperative DVT (evidence level 2+). Two studies showed smokers to have significantly less DVTs than non-smokers; one study showed smoking to be protective in a univariate analysis but not in a multivariate analysis and the fourth study showed no difference. Overall, the studies suggest a non-significant association of fewer postoperative DVTs for smokers despite studies indicating it to be a risk factor for DVT in the general population. However, smoking is associated with other postoperative adverse events such as wound related or cardiopulmonary complications.

Rocha et al\textsuperscript{556} did not find any evidence for smoking and venous thromboembolism.
5.7.12  Prolonged travel

Immobility associated with prolonged and continuous travel immediately before or after surgery may increase a patient's risk of developing postoperative VTE. We found no studies that specifically addressed this patient group. We identified one systematic review that investigated venous thromboembolism risk in long distance travel\(^24\) (evidence level 2+). Long haul travel was shown to significantly increase risk (OR=1.59, 95% CI: 1.04 to 2.43) in three case control studies, (RR=2.93, 95% CI: 1.58 to 5.58 from two cohort studies). Two of the studies provided a risk estimate for any form of long distance travel, these also showed an increase risk of venous thrombosis (OR=2.6, 95% CI: 1.79 to 3.79). All the studies related to travel were in journeys over three hours. In three, travel related to the previous four weeks and in the fourth, travel related to the previous three weeks. Meaningful comparison between patients travelling for surgery and data from people on long haul flight is difficult. Long haul flight travellers are often healthier than the general population and, therefore, not a true sample\(^24\) (Evidence Table 13, Appendix D).

Rocha et al\(^556\) did not look for evidence on the any association between prolonged travel and venous thromboembolism.

5.7.13  Admission to critical care

Rocha et al\(^556\),\(^556\) identified admission to a critical care unit as an independent risk factor for VTE (Relative risk 1.8 to 2.9) (evidence level 2+). The review reports the incidence of DVT for patients within critical care as between 25-30% in the absence of prophylaxis. (Evidence Table 14, Appendix D)

5.7.14  Severe medical illness

The systematic review by Rocha et al\(^556\) identified an increase in risk due to medical illnesses such as acute rheumatologic diseases and inflammatory bowel disease, infections, nephrotic syndrome, respiratory diseases and stroke (evidence level 2+) (Evidence Table 15-18, Appendix D). These acute medical illnesses were also identified in other guidelines as risk factors for VTE\(^219,591\).

5.7.15  Reduced mobility

Rocha et al, 2007\(^556\) identified three studies which investigated acute hemiplegia as a risk factor for VTE. One cohort study identified the incidence of VTE as 26% (no confidence intervals provided) and two case control studies identified paralysis as a significant risk factor for VTE compared with no paralysis (Evidence Table 19, Appendix D).The systematic review by Rocha et al\(^556\) also reviewed the evidence for reduced mobility (as opposed to paresis or paralysis of lower extremities) as a risk factor. Again, a significant association between VTE risk and mobility was identified, although the authors commented that the definition of mobility used in each of the studies was different which made it difficult to interpret these data (Evidence Table 21, Appendix D).

Within the recommendations in the guideline we have referred to ‘significantly reduced mobility’ as a risk factor. This was defined by the GDG as bed bound, unable to walk unaided or likely to spend a proportion of the day in bed or in a chair.
5.7.16 Duration of surgery

Both the work to determine the baseline risk of VTE (section 5.3) and the systematic review of risk in surgical patients\(^1\)\(^6\)\(^9\) identified that VTE risk differed by surgery type. The GDG discussed this in conjunction with the evidence that reduced mobility increased the risk of VTE (section 5.7.15). They agreed that procedures involving general anaesthetic which would involve complete, prolonged immobilisation for the duration of the surgery would increase VTE risk. They agreed that patients undergoing surgery where the total anaesthetic time of 90 minutes should be considered for VTE prophylaxis. In addition, they noted that surgery of the pelvis and lower limbs had an increased risk of VTE (Table 5-17: Risk of DVT and pulmonary embolism by type of surgery, from the no prophylaxis arm of RCTsTable 5-17) and so for any operation in these regions an increased risk should be considered if the surgery time was 60 minutes or more.

5.7.17 Pregnancy and ≤6 weeks postpartum

Rocha et al\(^5\)\(^5\)\(^6\) identified one retrospective case-reference study identifying the incidence of VTE in pregnant patients as 103:100,000 (95% CI: 55 – 177), which was higher than all women where the VTE incidence was 36:100,000 (95% CI: 29– 44) . The authors of the study noted that this incidence was higher than for those patients receiving combined oral contraceptives (Evidence Table 20, Appendix D).

The risk of VTE and prophylaxis for this population is discussed in more detail in chapter 30.

5.7.18 Discussion of data on patient risk

The identified systematic reviews of patient related risk factors varied in the quality of their evidence: the diagnosis of venous thromboembolism was not always achieved using an objective test (for example fibrinogen uptake test, ultrasound); only some of the studies provided the number of cases and controls on which the data were based; some studies gave pooled risk ratios for their results while others only provided the risk ratios for individual studies.

The evidence for risk factors is heterogenous in several ways:

- only some of our evidence comes from surgical populations and some from medical patients,
- the way risk is measured differed between studies, some use odds ratios while others use relative risk,
- the amount and quality of the evidence differed considerably between risk factors.

We acknowledge that risk factor information is difficult to use and the risk factors may be additive or interacting. Because of the uncertainty of how to use the risk factor evidence, and the different levels of risk within our included patients we have opted for a simplified approach to the recommendations. We have identified one list of risk factors that can be used in conjunction with accompanying recommendations for medical patients and surgical and trauma patients.

Some operations (e.g. elective hip replacement, elective knee replacement, surgery for fracture of the proximal femur) were felt to constitute a sufficiently high risk alone to
warrant prophylaxis (chapters 10 to 12). For other surgery any patients with any of the risk factors in this list were felt to be at increased risk of VTE should be considered for prophylaxis.

5.8 Individual patient risk factors and relative risk of bleeding

Although many different studies have been completed on risk factors for VTE (section 5.7), the risk of bleeding in patients at risk of VTE does not appear to have studied as rigorously. A full search for bleeding risk factors in patients admitted to hospital was not completed.

During the process of developing recommendations for VTE prophylaxis the GDG identified that assessing the bleeding risk was key and that it needed to be considered prior to offering pharmacological prophylaxis in order to reduce the risk of harm.

The risk factors included in the risk factor list were identified from a number of different sources including exclusion criteria from the randomised controlled trials included in our systematic review, from cautions included in the summary of product characteristics for pharmacological VTE prophylactic agents and the clinical expertise of the GDG. As such, no quantitative assessment of the relative risk of bleeding for each of the factors included in the list was possible.

5.9 Recommendations and link to evidence

The Guideline Development Group felt that while the available quantitative information on relating to absolute risk of VTE and major bleeding had important shortcomings, it was important to collate and report these data. The Guideline Development Group opted to utilise the available data in a semi-quantitative manner as outlined in the following recommendations.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Assess all patients on admission to identify those who are at increased risk of venous thromboembolism (VTE).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade off between clinical benefit and harms</td>
<td>The risks of VTE must be identified to determine whether the patients are at increased risk of the condition in order for a decision about whether prophylactic measures are appropriate. In order for this decision to be made the risk of VTE must be assessed.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>No cost-effectiveness model was completed to answer whether risk assessment was cost effective. There will be some cost associated with the resources required to complete the risk assessment. However, the benefits of identifying patients at an increased risk of VTE were felt to outweigh the costs of administering the risk assessment tool.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>The Guideline Development Group agreed that the best way to ensure that all patients were risk assessed for VTE was to complete the assessment at the initial admission to hospital. This should allow the high risk patients to be identified early and should allow appropriate prophylaxis to be administered without delay.</td>
</tr>
</tbody>
</table>
Regard medical patients as being at increased risk of VTE if they:

- have had or are expected to have significantly reduced mobility for 3 days or more, or
- are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.

**Box 1 – Risk factors for VTE**

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

Relative values of different outcomes

The main venous thromboembolic outcomes when considering risk factors were asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism.

Trade off between clinical benefit and harms

The decision of whether to provide prophylaxis will be a balance between the increased risk of VTE for the individual patient balanced against their risk of bleeding. The only way that this balance can be determined is by identifying which risk factors for VTE that each patient has.

Economic considerations

No cost-effectiveness model was completed to answer whether risk assessment was cost effective. However, the benefits of identifying patients at an increased risk of VTE were felt to outweigh the costs of administering the risk assessment tool. Many of the individual risk factors that were identified as establishing a person as ‘increased risk’ for VTE (e.g. reduced mobility with severe medical illness, critical care admission) were criteria for inclusion in the randomised trials on which the cost effectiveness of treatments were based (Chapter 23). Other factors were patients who were groups who were generally excluded from the trial evidence (e.g. known thrombophilias) but are likely to have a risk of VTE at least as high as those.
patients included in the trials and are discussed in section 5.7.

Quality of evidence

All of the risk factors in the list in the recommendation and in box 1 were established from the evidence from systematic reviews on individual patient risk factors as presented in section 5.7 except for dehydration which is presented in section 7.3. The limitations of the evidence were that the risk factors within the systematic reviews were from many small studies which had different populations and for medical patients no attempts were made to statistically pool these data. No information about the interaction or additive effect of risk factors was identified within the literature.

Other considerations

The GDG discussed the term ‘ongoing reduced mobility relative to their normal state’ and felt that this should include any time at home with reduce mobility. They concluded that it was not possible to include precise time for this reduced mobility and that this factor would need clinical judgement according to the individual affected.

Recommendation

Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more risk factors shown in Box 1.
**Box 1 – Risk factors for VTE**

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

**Relative values of different outcomes**

The main venous thromboembolic outcomes considered were asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism.

**Trade off between clinical benefit and harms**

The decision of whether to provide prophylaxis will be a balance between the increased VTE risk for the individual patient balanced against their risk of bleeding. The only way that this balance can be determined is by identifying which factors the patient has which increase the risk of VTE.

**Economic considerations**

No cost-effectiveness model was completed to answer whether risk assessment was cost effective. However, the benefits of identifying patients at an increased risk of VTE were felt to outweigh the costs of administering the risk assessment tool. Many of the individual risk factors that were identified as establishing a person as ‘increased risk’ for VTE.

**Quality of evidence**

All of the risk factors in the recommendation and in box 1 were established from the evidence from systematic reviews on individual patient risk factors as presented in chapter 5.7 except for dehydration which is detailed in section 7.3. The limitations of the evidence were that the risk factors within the systematic reviews were from many small studies which had different populations and which were sometimes difficult to draw accurate conclusions from. No information about the interaction or additive effect of risk factors was identified within the literature.

**Other considerations**

The risk factor list is different to that presented in the previous surgical guideline⁷³. The changes were made in order to clarify and simplify the list of risk factors and to allow one list for all patients admitted to hospital which aims to improve the ease of use in hospital. Five of the risk factors in the previous guideline (active heart or respiratory failure, acute medical
illness, nephrotic syndrome, recent myocardial infarction or stroke and severe infection) were included under the heading 'one or more significant medical comorbidity'.

Five of the more specific conditions listed as risk factors in the surgical guideline (antiphospholipid syndrome, behcet's disease, myeloproliferative diseases, paraproteinaemia and paroxysmal nocturnal haemoglobinuria) are included within the 'known thrombophilias' risk factor in this guideline. This decision was taken in order to make the list simpler to use in practice. The GDG felt that junior doctors who might be completing the risk assessment should have an understanding on the conditions constituting 'known thrombophilias'.

Continuous travel was removed from the list as it was felt that the evidence for this was not strong and the risk factor was really immobility rather than travel and hence captured elsewhere.

The inclusion criteria for the previous surgical guideline were all patients undergoing surgery with an overnight stay. As the current guideline extends the inclusion criterion to all patients admitted to hospital the timing of surgical procedure was felt to be a helpful guideline to identify people at risk.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Reassess patients’ risk of bleeding and VTE within 24 hours of admission, and whenever the clinical situation changes, to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• ensure that the methods of VTE prophylaxis used are suitable</td>
</tr>
<tr>
<td></td>
<td>• ensure that VTE prophylaxis is being used correctly</td>
</tr>
<tr>
<td></td>
<td>• identify adverse events resulting from VTE prophylaxis.</td>
</tr>
</tbody>
</table>

| Trade off between clinical benefit and harms | The complete picture of the VTE risk for the individual patient may not be entirely clear when first assessed upon admission. In order to ensure that patients are treated appropriately, the Guideline Development Group felt it was important that the patient is reassessed. |

| Economic considerations | No cost-effectiveness model was completed to answer whether reassessment of risk was cost effective. There will be a cost associated with the resources required to complete the reassessment of VTE risk. However, the benefits of identifying patients at an increased risk of VTE (or of identifying those whose risk is lower than had been previously assessed) were felt to outweigh the cost of completing the assessment. |

It is clear that the cost-effectiveness of prophylaxis is dependent on maintaining adherence and preventing
complications. In our cost-effectiveness analyses comparing different types of prophylaxis (Chapter 4) we included the cost of clinician time for the administration of prophylaxis.

Other considerations

All of the Guideline Development Group agreed that reassessment of VTE was important, however the timing of the second assessment was more controversial than the first assessment on admission to hospital. There is no evidence for reassessing VTE risk 24 hours after the first assessment, but the Guideline Development Group felt that at this time diagnostic tests required for each patient would have been completed and the bleeding risks were likely to be better established. Some Guideline Development Group members were concerned about the resources available for this recommendation but felt that by providing a timeframe it was more likely to occur.

In addition the Guideline Development Group felt that when the clinical situation changed there was need to reassess the VTE risk of patients to ensure the appropriate prophylaxis is established or continued.
**Recommendation**  
Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.  

*The summary of product characteristics for the pharmacological thromboprophylaxis being used or planned should be consulted for further details.*

**Box 2. Risk assessment - Bleeding**  
Regard hospitalised patients as being at risk of bleeding if they have any of the following risk factors:

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal analgesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than $75 \times 10^9/l$)
- Uncontrolled systolic hypertension ($230/120$ mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease).

**Trade off between clinical benefit and harms**  
For each of the recommendations about providing prophylaxis the potential benefits of reducing the risk of VTE events (symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism) needs to be balanced against the potential harms of bleeding events (major bleeding, fatal bleeding and stroke). In some patients the risk of bleeding is not cost effective.

**Economic considerations**  
Where cost effectiveness models have been developed and run for different sub-populations within the guideline (Chapters 9-12, 23) the bleeding risk used has been the average bleeding risk of patients within the individual trials. It is known that most of the trials will have excluded patients with a high risk of bleeding and so the recommendations as made in the chapters may not be appropriate to the high bleeding risk population.

**Other considerations**  
The Guideline Development Group developed a list of clinical indications where the risks of bleeding should be carefully considered before providing pharmacological prophylaxis. This list of factors in box 2 was based on the exclusion criteria used in the trials of pharmacological VTE agents in our
systematic review, information from the summary of product characteristics and the experience of the clinicians within the guideline development group. No quantitative assessment of the relative risk of bleeding for each of the factors included in the list was possible.

The GDG felt it was important to reference to the summary of product characteristics as the timing of provision of pharmacological VTE may differ according to the half life of the different agents being used, or planned and needs to be within licensed indication. For example, fondaparinux has a half life of 17-21 hours which is longer than low molecular weight heparins.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Advise patients to consider stopping oestrogen-containing oral contraceptives or hormone replacement therapy 4 weeks before elective surgery. If stopped, provide advice on alternative contraceptive methods.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative values of different outcomes</td>
<td>The main outcomes considered were venous thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).</td>
</tr>
<tr>
<td>Trade off between clinical benefit and harms</td>
<td>The increased risk of VTE through use of oestrogen containing oral contraceptives and hormone replacement therapy was considered.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>No cost effectiveness model was completed to identify the cost effectiveness of stopping these treatments before surgery. The guideline development group felt that the benefits in terms of reducing the risk of VTE after surgery may, in some patients, outweigh the benefits of maintaining therapy, and so felt that it should be considered for all relevant patients.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>The systematic reviews of risk factors for VTE identified oestrogen containing oral contraceptives and hormone replacement therapy as factors which significantly increased the risk of VTE (section 5.7.7 and 5.7.8). These treatments although improve the quality of the patient’s life are unlikely to be life threatening if stopped. Therefore consideration should be given to their continued use.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>This recommendation is based on the recommendation from the previous surgical guideline. The Guideline Development Group used both the evidence from systematic reviews and advice provided in the BNF313, which included the advice of when to stop these hormone treatments before elective surgery (4-6 weeks). Additional guidance can be found in the RCOG guidelines on guidance on venous thromboembolism and hormonal contraceptives564 and hormonal replacement therapy and</td>
</tr>
</tbody>
</table>
venous thromboembolism\textsuperscript{562}, and the BNF\textsuperscript{313}.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Assess the risks and benefits of stopping pre-existing established antiplatelet therapy 1 week before surgery. Consider involving the multidisciplinary team in the assessment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade off between clinical benefit and harms</td>
<td>The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. The group of patients who are receiving antiplatelet or anticoagulation therapy before surgery are at an increased risk of bleeding.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>No cost effectiveness model was completed to identify the cost effectiveness of stopping these treatments before surgery. The guideline development group felt that the benefits in terms of reducing the risk of bleeding after surgery may, in some patients, outweigh the benefits of maintaining therapy, and therefore felt that it should be considered for all relevant patients.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>This recommendation is based on the recommendation from the previous surgical guideline. This recommendation needs to be carefully considered in the context of the individual patient and should take into consideration all of their existing or potential comorbidities that may occur from stopping treatment. In order to balance these factors, advice from different disciplines may be needed. The BNF should be consulted for appropriate timing for stopping and restarting antiplatelet therapies around surgery. Current advice suggests that antiplatelets should be stopped 1 week before surgery.</td>
</tr>
</tbody>
</table>

5.10 Recommendations for research

5.10.1 Research question 1

- What is the absolute risk of VTE among different groups of hospital patients and can the risk be reliably estimated on admission to hospital to ensure that appropriate patients are offered VTE prophylaxis?

Why this is important

One of the most difficult areas the Guideline Development Group faced when developing the guideline was to identify the absolute risk of VTE among specific patient groups in relation to the reason for admission. A new, large pragmatic cohort study and/or record linkage study using Hospital Episode Statistics and the General Practice Research Database is proposed. This would allow all people admitted to hospital to be
studied to identify those who develop VTE, including people who are diagnosed with VTE in primary care after discharge from hospital. Information on baseline patient-related factors, procedures and duration of stay, complications, prophylactic therapies and concomitant drug use should be collected and analysed. It should allow the identification of independent risk factors for VTE and the development and subsequent validation of a risk model to estimate the absolute risk of VTE in individual patients. This research would allow clearer identification of those patients at risk of VTE and those in whom the risk is so low that the bleeding risk of pharmacological VTE prophylaxis would add overall hazard.

**Recommended study design:** Cohort/ record linkage study.

**5.10.2 Research question 2**

- What is the incidence, loss of quality of life and cost associated with post-thrombotic syndrome after potentially preventable deep vein thrombosis?

**Why this is important**

During development of the guideline it became apparent that the incidence of post-thrombotic syndrome, particularly after asymptomatic deep vein thrombosis, was not well reported. This study should use standard, validated definitions to identify the incidence of post-thrombotic syndrome both when a deep vein thrombosis has occurred as a result of a hospital admission and in the absence of hospital-acquired deep vein thrombosis. The study also should aim to identify the costs to the NHS of treating post-thrombotic syndrome.

**Recommended study design:** Cohort

**5.11 Summary of recommendations**

- Assess all patients on admission to identify those who are at increased risk of venous thromboembolism (VTE).

- Regard medical patients as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more or
  - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.

- Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
  - acute surgical admission with inflammatory or intra-abdominal condition
  - expected significant reduction in mobility
  - have one or more risk factors shown in Box 1.
Box 1 Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

- Reassess patients’ risk of bleeding and VTE within 24 hours of admission, regularly thereafter and whenever the clinical situation changes, to:
  - ensure that the methods of VTE prophylaxis used are suitable
  - ensure that VTE prophylaxis is being used correctly
  - identify adverse events resulting from VTE prophylaxis.

- Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.

* The summary of product characteristics for the pharmacological thromboprophylaxis being used or planned should be consulted for further details.
Advise patients to consider stopping oestrogen-containing oral contraceptives or hormone replacement therapy 4 weeks before elective surgery. If stopped, provide advice on alternative contraceptive methods.

Assess the risks and benefits of stopping pre-existing established antiplatelet therapy 1 week before surgery. Consider involving the multidisciplinary team in the assessment.

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**Box 2. Risk factors for bleeding**

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10⁹/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand’s disease)
6 Summary of the effectiveness of mechanical and pharmacological prophylaxis

6.1 Introduction

The purpose of this chapter is to provide an overview of all the evidence comparing different prophylaxis methods across all populations (medical, surgical and trauma patients). This chapter also presents some general comparisons that are relevant to many of the patient groups in the guideline.

The chapter is structured in the following way:

- A description of the different types of mechanical and pharmacological prophylaxis,
- A matrix showing for which comparisons evidence was found,
- A summary of the pooled results of these studies by comparison,
- Specific comparisons that are relevant across patient groups,
- Patient views for mechanical and pharmacological prophylaxis,
- Recommendations for the general use of prophylaxis methods.

Data comparing different types of mechanical and pharmacological prophylaxis for each specific population are presented in the chapters relevant to those populations (chapters 9 to 30).

As we are comparing prophylaxis methods across all populations we have not recorded the statistical heterogeneity for each prophylaxis comparison within this chapter. Details on the heterogeneity can be found in the forest plots (Appendix E) and in the discussions for each specific population.
6.2 Description of mechanical and pharmacological prophylaxis

6.2.1 Mechanical methods of prophylaxis

Venous stasis in the deep leg veins causes a decrease in the mean flow and pulsatility of the venous flow trace. Mechanical methods of DVT prophylaxis work to combat venous stasis and include:

- Anti-embolism stockings/ Graduated compression stockings (GCS)
- Intermittent pneumatic compression devices (IPCD)
- Foot impulse devices, also known as foot pumps (FID)

In the previous guideline for surgical patients\textsuperscript{473} these three methods were combined into one ‘mechanical’ category as the evidence did not indicate that there was a difference in effectiveness between the devices. For this guideline, anti-embolism stockings have been separated out from the other methods on the basis that they used a passive mechanism for reducing the risk of VTE whereas the other two methods used ‘active’ methods. Additionally, the distinction between IPCD and FID is not always clear and therefore in this guideline, intermittent pneumatic compression devices and foot impulse devices have been combined and are treated as equally effective.

Unlike pharmacological prophylaxis, none of the mechanical methods are associated with an increased risk of bleeding.

Anti-embolism stockings / graduated compression stockings (GCS)

The term compression hosiery refers to two different products; anti-embolism stockings (AES) and graduated compression stockings (GCS). Although the terms AES and GCS are often used interchangeably and both offer graduated compression, they have different indications, different British and European Standards and different levels of compression. AES are designed for the prevention of VTE in the immobile patient and GCS are designed for management and treatment of conditions such as venous leg ulcers and lymphoedema in the ambulant patient. This guideline covers VTE prophylaxis only and therefore any recommendations regarding compression hosiery refer to AES only. Within this guideline we have used the abbreviation “GCS” to cover both antiembolism stockings and graduated compression stockings.

Anti-embolism stockings exert graded circumferential pressure from distal to proximal regions of the leg. They have two potential actions in preventing DVT in the immobile patient exerting graduated compression increases blood flow velocity and promotes venous return, and preventing passive venous distension is thought to prevent sub-endothelial tears and the activation of clotting factors. Application of AES is not without risk, it is important that patients are fully assessed and their legs carefully measured before stockings are fitted and that stocking use is closely monitored.

The Sigel profile which equates to a graduated compression pressure profile of 18mmHg at the ankle, 14mmHg at the mid calf, 8mmHg at the Knee (popliteal break), 10mmHg at the lower thigh and 8mmHg at the upper thigh was found to increase deep venous flow velocity by 75\%\textsuperscript{400}. The current British and European Standards for AES [BS7672 (1); ENV 12719(70)] do not replicate the Sigel profile and the British Standard only requires pressure to be measured at three points rather than the five specified by Sigel.
Healthcare professionals must consider the clinical evidence available for each individual product when purchasing and prescribing AES.

Anti-embolism stockings are contraindicated in patients with peripheral arterial disease, arteriosclerosis, severe peripheral neuropathy, massive leg oedema or pulmonary oedema, oedema secondary to congestive cardiac failure, local skin/soft tissue diseases such as recent skin graft or dermatitis, extreme deformity of the leg, gangrenous limb and doppler pressure index < 0.8, or cellulitis.

The length of stockings is a controversial issue and there is no clear randomised evidence that one length of stocking is more effective than another. Thigh length stockings can be more difficult to fit and often roll down creating a tourniquet effect. Clinical judgement, patient preference, concordance and surgical site are all important issues when deciding on stocking length.

**Intermittent pneumatic compression (IPCD) devices**

IPCD involves the use of inflatable garments wrapped around the legs, which are inflated by a pneumatic pump. The pump provides intermittent cycles of compressed air which alternately inflate and deflate the chamber garments, enhancing venous return. It combats VTE through its haemodynamic effect on reducing venous stasis and by stimulating fibrinolytic activity. This fibrinolytic mechanism is involved in the dissolution of clot and prevention of thrombus formation.

**Foot impulse devices (FID)**

Foot impulse devices (or foot pumps) increase venous outflow and reduce stasis in immobilized patients. The haemodynamic effect of the pumping mechanism in the sole of the foot is activated by weight bearing. On weight bearing the venous plexus in the sole is rapidly emptied into the deep veins of the legs. The pulsatile flow produced by walking reduces the risk of thrombus formation. It is within this physiological mechanism that the foot impulse device is designed to stimulate the venous pump artificially by compressing the venous plexus and mimicking normal walking and reducing stasis in immobilised patients.

### 6.2.2 Pharmacological prophylaxis

**Fondaparinux**

Fondaparinux is a synthetic pentasaccharide, which is based on the antithrombin binding region of heparin in the body. It acts by potentiating the antithrombin (ATIII) inhibition of factor Xa. However, it does not directly inhibit thrombin, because this requires a minimum of 13 additional saccharide units which is present in unfractionated heparin and low molecular weight heparin. It is therefore a specific, indirect inhibitor of activated factor Xa through its potentiation of antithrombin. It is given subcutaneously postoperatively and administered once daily.

**Heparins**

Natural heparin is a mixture of mucopolysaccharides of differing chain lengths and hence molecular sizes. Such ‘unfractionated’ pharmaceutical heparin (UFH) consists of
chains of molecular weights from 5000 to over 40,000 Da (average 20,000 Da). Heparin acts as an anticoagulant by binding and accelerating the action of antithrombin, a naturally occurring inhibitor of thrombin and other coagulation enzymes (X, IX, XI and XII).

By distinctly different processes of fractionating or depolymerisation of natural heparin, several preparations of low molecular weight heparins (LMWH) are produced. Thus, although they are dissimilar in physical, chemical and biological properties, they consist of short chains of polysaccharides with an average molecular weight 3000 Da. They bind less avidly to other heparin binding proteins in the blood and are therefore more biologically available at lower doses and have more predictable levels. Both unfractionated and low molecular weight heparins can be administered intravenously (boluses and continuous) or by subcutaneous injections (twice to three times for UFH, once to twice daily for LMWH).

In addition to the outcomes for venous thromboembolism and major bleeding, we also considered heparin-induced thrombocytopenia (HIT). Few trials reported this outcome, we have reported it when available.

Vitamin K antagonists

Warfarin is a coumarin derivative and acts as a vitamin K antagonist.

The synthesis of active clotting factors II, VII, IX and X (as well as the anticoagulant proteins C and S) requires carboxylation of glutamic acid residues which is dependent on the presence of vitamin K. Antagonism of vitamin K therefore reduces the amount of these factors, thereby producing a state of anticoagulation.

Warfarin is usually given at an adjusted, variable doses to achieve a therapeutic level, as estimated by attaining an INR (International Normalised Ratio) of 2.5. This requires frequent monitoring and takes approximately 5 days for a stable antithrombotic effect to be achieved. There is much variability in responses to warfarin, which is determined by several factors including age, genetic status, medications, diet and medical conditions. The most important complication of anticoagulation is bleeding but, if required, the effect of warfarin can be reversed with vitamin K, prothrombin concentrates and replenishment of clotting factors by the use of fresh frozen plasma.

Aspirin

Aspirin inhibits platelet function through its irreversible inhibition of the enzyme cyclooxygenase-1 (COX-1) and thereby blocking thromboxane A2 production. Thromboxane induces platelet aggregation (and vessel wall vasoconstriction) which are required for the clotting cascade and thrombus formation. This effect lasts for the duration of the platelet lifespan. However, although it may take 10 days for the entire platelet population to be renewed, haemostasis has been shown to be normal if 20% of them have normal COX activity. The Guideline Development Group separated studies of aspirin into two categories; those using ‘high dose’ aspirin (classified as 300mg per day or more) or ‘low dose’ aspirin (classified as less than 300mg per day).

Dabigatran

Dabigatran etexilate is a new oral anticoagulant that has been licensed during the development of the guideline. It is direct inhibitor of the enzyme thrombin. Thrombin is a key enzyme in blood clot (thrombus) formation because it enables the conversion of
fibrinogen to fibrin during the coagulation cascade. Dabigatran was reviewed and approved for use for the prevention of venous thromboembolism after hip or knee replacement surgery in adults in a NICE technology appraisal published in September 2008476.

Rivaroxaban

Rivaroxaban is a new oral anticoagulant that has been licensed during the development of the guideline. It directly inhibits activated factor X (factor Xa). Inhibiting factor Xa interrupts the pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban was reviewed and approved for use for the prevention of venous thromboembolism after total hip or total knee replacement in a NICE technology appraisal published in April 2009479.

6.3 Summary of evidence for mechanical and pharmacological prophylaxis

6.3.1 Matrix of comparisons

The following matrix provides an overview of the RCT comparisons we identified that reported at least one of the three outcomes under investigation, DVT (both asymptomatic and symptomatic), Pulmonary Embolism (PE) or major bleeding. All cause mortality was not included in this comparison as these data could not be collected for all of the studies included in the original surgical guideline. Where a systematic review of all cause mortality has been completed for the population, this is presented in the relevant individual population chapter (chapters 9 to 30).
The number in each cell relates to the number of studies that we found investigating that comparison for all populations.

<table>
<thead>
<tr>
<th>Method</th>
<th>Cell</th>
<th>Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>IPCD/FID</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LMWH</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>65</td>
<td>1</td>
</tr>
<tr>
<td>VKA</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>High dose aspirin</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Low dose aspirin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>GCS + IPCD/FID</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mech + pharm</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Other comparisons</td>
<td>1</td>
<td>(b)</td>
</tr>
</tbody>
</table>

**Figure 6-5: Number of studies which compared various types of prophylaxis methods.**

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicate areas where no studies were identified.

GCS – anti-embolism/graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg); Asp (LD) – low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

(a) 1 study was Dabigatran vs. LMWH used for an extended period (28-35 days)
(b) 1 study of LMWH vs VKA post discharge
(c) One of these studies compared extended duration prophylaxis from surgery to 28-35 days, another other study investigated extended duration rivaroxaban (28-35 days) compared with standard duration LMWH (14 days)

### 6.3.2 Summary of most effective interventions

Table 6-22 shows a summary of all the effectiveness data for all hospitalised patients for all the main outcomes (DVT, PE and major bleeding (MB)). Results are shown by comparison. Where there were no studies the comparison is not shown. Where one method was significantly more effective than the other, the most effective method is shown in bold for the relevant outcome. Where the result was not significant ‘not sig’ is shown. Where there were no data ‘-’ is shown.

The full data for these comparisons can be found later in the guideline and in the evidence tables and forest plots.
Table 6-22: Summary of evidence on the effectiveness of prophylaxis for DVT, symptomatic pulmonary embolism and major bleeding (MB) outcomes.

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
<th>Forest plots (FPs)</th>
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<td></td>
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<td>PE</td>
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<td>GCS</td>
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</tr>
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<td>not sig</td>
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<td>not sig</td>
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<td>-</td>
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<td>-</td>
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<td></td>
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<td>GCS knee-length</td>
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<td>LMWH</td>
<td>LMWH</td>
<td>not sig</td>
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<tr>
<td>VKA</td>
<td>Aspirin</td>
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<td>UFH</td>
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<tr>
<td>Aspirin (low dose)</td>
<td>UFH</td>
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<td>-</td>
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<td>VKA (adjusted dose)</td>
<td>VKA (fixed dose)</td>
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<td>not sig</td>
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<td>Fondaparinux (day 2 postop start)</td>
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<td>LMWH (preop start)</td>
<td>LMWH (postop start)</td>
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<td>not sig</td>
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<td>Aspirin (high dose)</td>
<td>Aspirin (low dose)</td>
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<td>not sig</td>
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<tr>
<td>Mechanical vs pharmacological prophylaxis</td>
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## Summary of the effectiveness of mechanical and pharmacological prophylaxis

### Intervention(s) vs. Comparison(s) vs. Intervention favoured

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<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
<th>Forest plots (FPs) Appendix E</th>
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<td>LMWH</td>
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<tr>
<td>IPCD/FID</td>
<td>UFH</td>
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<td>not sig</td>
</tr>
<tr>
<td>IPCD/FID</td>
<td>UFH then Asp (HD)</td>
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<td>not sig</td>
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<td>IPCD/FID</td>
<td>VKA</td>
<td>not sig</td>
<td>not sig</td>
</tr>
<tr>
<td>IPCD/FID</td>
<td>Asp (HD)</td>
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<tr>
<td>(IPCD + GCS) or FID</td>
<td>LMWH</td>
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<td>not sig</td>
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<td>IPCD/FID + GCS</td>
<td>LMWH</td>
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<td>-</td>
</tr>
<tr>
<td>IPCD/FID + GCS</td>
<td>UFH</td>
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### Adjuvant studies (mechanical)

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<th>Forest plots (FPs) Appendix E</th>
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<td>-</td>
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<td>GCS + LMWH</td>
<td>LMWH</td>
<td>not sig</td>
<td>not sig</td>
</tr>
<tr>
<td>GCS + UFH</td>
<td>UFH</td>
<td>GCS + UFH</td>
<td>not sig</td>
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<td>GCS + Fondaparinux</td>
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<td>not sig</td>
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<td>GCS + Asp (LD)</td>
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<td>not sig</td>
</tr>
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<td>IPCD/FID + GCS</td>
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<td>IPCD/FID + UFH</td>
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<td>IPCD/FID + Asp (HD)</td>
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<td>IPCD/FID + (UFH then Asp(HD))</td>
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### Adjuvant studies (pharmacological)

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<th>Forest plots (FPs) Appendix E</th>
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<td>IPCD</td>
<td>Fon + IPCD</td>
<td>-</td>
</tr>
<tr>
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</tr>
<tr>
<td>LMWH + IPCD + GCS</td>
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<td>not sig</td>
</tr>
<tr>
<td>UFH + GCS</td>
<td>GCS</td>
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<td>UFH + IPCD</td>
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<td>-</td>
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<td>UFH + VKA</td>
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<td>not sig</td>
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<tr>
<td>UFH + aspirin</td>
<td>aspirin</td>
<td>UFH + aspirin</td>
<td>not sig</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Comparison(s)</td>
<td>Intervention favoured</td>
<td>Forest plots (FPs)</td>
</tr>
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<td>---------------</td>
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<td>-------------------</td>
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<td>-</td>
</tr>
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<td>VKA + IPCD + GCS</td>
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<td>-</td>
</tr>
<tr>
<td>VKA + UFH</td>
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<tr>
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<td>-</td>
<td>not sig</td>
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<tr>
<td>Aspirin + UFH</td>
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<td>-</td>
<td>Aspirin</td>
</tr>
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<td>GCS + LMWH</td>
<td>IPC/FID + LMWH</td>
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<td>IPC/FID + Aspirin</td>
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<td>LMWH + GCS</td>
<td>UFH + GCS</td>
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<td>not sig</td>
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<td>UFH + IPCD+ GCS</td>
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<td>LMWH + Aspirin</td>
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<td>VKA + GCS</td>
<td>UFH + GCS</td>
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<td>-</td>
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<tr>
<td>VKA + GCS</td>
<td>Aspirin + GCS</td>
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<td>not sig</td>
</tr>
<tr>
<td>VKA + IPCD+ GCS</td>
<td>Aspirin + IPCD+ GCS</td>
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<tr>
<td>IPCD+ GCS</td>
<td>UFH + GCS</td>
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<td>-</td>
</tr>
<tr>
<td>IPCD+ GCS</td>
<td>LMWH + GCS</td>
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<td>not sig</td>
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<tr>
<td>IPCD+ GCS</td>
<td>VKA + GCS</td>
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<td>not sig</td>
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<td>IPCD then LMWH</td>
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</tr>
<tr>
<td>UFH + IPCD</td>
<td>LMWH</td>
<td>-</td>
<td>-</td>
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</table>

**Post discharge**

| Fondaparinux Post Discharge | No Fondaparinux | Fondaparinux | not sig | not sig | FPs. 221 – 223 |
Summary of the Effectiveness of Mechanical and Pharmacological Prophylaxis

Overall, there is evidence that mechanical prophylaxis and many of the pharmacological methods are effective at reducing the risk of DVT and there is evidence that some methods effectively reduce the risk of PE. It is more difficult to draw conclusions on the relative effectiveness between the different prophylaxis methods. There are significant differences with some of the comparisons but there are many areas where there is no significant difference. In some cases this may be due to the included studies having small sample sizes meaning that the trial may not be able to identify a significant difference between treatments if there was one. In chapters 9 to 12 and 23 we describe the network meta-analyses that have been performed for specific patient populations. In these analyses, we have used these data to rank the VTE prophylaxis methods in order of effectiveness. The methodology used for the network meta-analysis is detailed in section 3.10.

6.4 Specific mechanical comparisons not presented elsewhere

The following sections report on studies comparing aspects of mechanical prophylaxis that were not compared within the specific population chapters. They are presented here as comparisons across any population.

6.4.1 Thigh vs knee-length GCS

Table 6-23: Summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention (a)</th>
<th>Control (b)</th>
<th>Relative risk</th>
<th>Forest plots &amp; Evidence Tables</th>
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</thead>
<tbody>
<tr>
<td>DVT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS - thigh vs knee-lengths[313,694] (a)</td>
<td>2</td>
<td>9/100</td>
<td>9/102</td>
<td>1.06 (0.32, 3.55)</td>
<td>ET: 30 FP:36</td>
</tr>
<tr>
<td>GCS thigh-length + LMWH vs GCS knee-length + LMWH[397] (b)</td>
<td>1</td>
<td>8/195</td>
<td>11/99</td>
<td>0.37 (0.15, 0.89)</td>
<td>ET: 30 FP:36</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis
(a) General surgery patients
(b) Mixed surgical patients
Overall, there is little RCT evidence directly comparing the length of anti-embolism / graduated compression stockings in patients. There is no statistically significant difference between thigh and knee-length stockings alone in reducing the risk of DVT. However, the sample size was small and confidence intervals were wide. No studies reported pulmonary embolism. Thigh-length stockings plus LMWH are more effective than knee-length stockings plus LMWH in reducing the risk of DVT in mixed surgical patients. The analyses of studies using anti-embolism stockings in specific populations have combined all data for knee and thigh-length stockings together rather than analysing separately by length. Most the RCTS comparing stockings with other prophylaxis used thigh-length stockings and where the length of stocking is reported in the paper we have included this information in the evidence table.

### 6.4.2 Thigh vs knee-length IPCD

#### Table 6-24: Summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Forest plots &amp; Evidence Tables*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD – thigh vs knee-length&lt;sup&gt;611&lt;/sup&gt; (a)</td>
<td>1</td>
<td>0/47</td>
<td>1/43</td>
<td>0.31 (0.01, 7.31)</td>
<td>ET: 30 FP: 37</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD – thigh vs knee-length&lt;sup&gt;611&lt;/sup&gt; (a)</td>
<td>1</td>
<td>1/47</td>
<td>0/43</td>
<td>2.75 (0.12, 65.76)</td>
<td>ET: 30 FP: 38</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis
(a) Urological surgery patients

There is no statistically significant difference between thigh and knee-length IPCD in reducing DVT or pulmonary embolism. Overall, there is little RCT evidence directly comparing the length of intermittent pneumatic compression devices in patients. The analyses of studies using IPCD in specific populations have combined all data for knee and thigh-length devices together. Where the length of IPCD was reported within a study it has been reported in the evidence tables.

### 6.4.3 Intermittent pneumatic compression devices vs foot impulse devices

#### Table 6-25: Summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Forest plots &amp; Evidence Tables*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD vs foot impulse devices&lt;sup&gt;20,170&lt;/sup&gt; (a)</td>
<td>2</td>
<td>4/111</td>
<td>16/130</td>
<td>0.29 (0.11, 0.79)</td>
<td>ET: 30 FP: 255</td>
</tr>
<tr>
<td>IPCD+GCS vs FID+GCS&lt;sup&gt;701&lt;/sup&gt; (b)</td>
<td>1</td>
<td>0/59</td>
<td>1/75</td>
<td>0.42 (0.02, 10.18)</td>
<td>ET: 30 FP: 259</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD vs foot impulse devices&lt;sup&gt;20&lt;/sup&gt; (c)</td>
<td>1</td>
<td>0/49</td>
<td>1/69</td>
<td>0.47 (0.02, 11.22)</td>
<td>ET: 30 FP: 256</td>
</tr>
<tr>
<td>IPCD+GCS vs FID+GCS&lt;sup&gt;701&lt;/sup&gt; (b)</td>
<td>1</td>
<td>0/59</td>
<td>1/75</td>
<td>0.42 (0.02, 10.18)</td>
<td>ET: 30 FP: 259</td>
</tr>
<tr>
<td>Major bleeding</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IPCD vs FID&lt;sup&gt;170&lt;/sup&gt; (d)</td>
<td>1</td>
<td>1/74</td>
<td>0/75</td>
<td>3.04 (0.13, 73.44)</td>
<td>ET: 30 FP: 260</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D
There is evidence that intermittent pneumatic compression devices are significantly more effective than foot impulse devices at reducing DVT from a study in head injury patients. There is no statistically significant difference between IPCD and foot impulse devices in reducing pulmonary embolism. The distinction between IPCD and FID is not always clear and therefore in this guideline, intermittent pneumatic compression devices and foot impulse devices have been combined and are treated as equally effective. The GDG therefore decided to analyse the devices together for the rest of the guideline.

6.5 Specific pharmacological comparisons not presented elsewhere

The following section reports on studies comparing aspects of pharmacological prophylaxis that were not compared within the specific population chapters. They are presented here as comparisons across any population.

6.5.1 Pre vs post op initiation of LMWH

Table 6-26: Summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Interventions</th>
<th>Control</th>
<th>Relative risk</th>
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<td>DVT</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop LMWH vs postop LMWH&lt;sup&gt;508&lt;/sup&gt;</td>
<td>1</td>
<td>27/65</td>
<td>24/66</td>
<td>1.14 (0.74, 1.76)</td>
<td>ET: 53 FP: 75</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop LMWH vs postop LMWH&lt;sup&gt;508&lt;/sup&gt;</td>
<td>1</td>
<td>0/90</td>
<td>0/89</td>
<td>not estimable</td>
<td>ET: 53 FP: 76</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop LMWH vs postop LMWH&lt;sup&gt;508&lt;/sup&gt;</td>
<td>1</td>
<td>2/90</td>
<td>3/89</td>
<td>0.66 (0.11, 3.85)</td>
<td>ET: 53 FP: 77</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D
(Proph - prophylaxis)
(a) Elective hip replacement patients

There is no statistically significant difference in risk of DVT, PE or major bleeding between starting low molecular weight heparin preoperatively and postoperatively in the one RCT identified. Overall, there is little RCT evidence directly comparing the pre- or post-operative administration of pharmacological agents in patients. In the RCTs comparing LMWH with other prophylaxis methods, LMWH was initiated both preoperatively in some and postoperatively in others and these studies were analysed together.

6.5.2 Vitamin K antagonists – fixed vs adjusted dose

Table 6-27: Summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Interventions</th>
<th>Control</th>
<th>Relative risk</th>
<th>Forest plots &amp; Evidence Tables*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted vs fixed dose VKA&lt;sup&gt;48,184,530&lt;/sup&gt;</td>
<td>3</td>
<td>17/176</td>
<td>33/164</td>
<td>0.51 (0.30, 0.86)</td>
<td>ET: 55 FP: 69</td>
</tr>
</tbody>
</table>

There is no statistically significant difference in risk of DVT, PE or major bleeding between starting low molecular weight heparin preoperatively and postoperatively in the one RCT identified. Overall, there is little RCT evidence directly comparing the pre-or post-operative administration of pharmacological agents in patients. In the RCTs comparing LMWH with other prophylaxis methods, LMWH was initiated both preoperatively in some and postoperatively in others and these studies were analysed together.
Comparison | No. of studies | Intervention | Control | Relative risk | Forest plots & Evidence Tables*
--- | --- | --- | --- | --- | ---
Pulmonary embolism | | | | | |
Adjusted vs fixed dose VKA$^{58,184}$ (b) | 2 | 1/141 | 0/132 | 2.97 (0.12, 72.01) | ET: 55 FP: 70
Major bleeding | | | | | |
Adjusted vs fixed dose VKA$^{184,630}$ (c) | 1 | 8/135 | 6/132 | 0.95 (0.12, 7.17) | ET: 55 FP: 71

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis
(a) Two studies elective hip replacement patients, one study gynaecological surgery patients
(b) Two studies elective hip replacement patients
(c) One study elective hip replacement patients, one study gynaecological surgery patients

Adjusted dose vitamin K antagonists (VKA) are significantly more effective in reducing the risk of DVT than fixed dose VKA. There is no statistically significant difference between adjusted and fixed dose VKA in reducing pulmonary embolism or increasing major bleeding. As it is more usually given at adjusted dose and the adjusted dose is significantly more effective in reducing DVT, this guideline presents the evidence for just adjusted dose VKA in Chapters 9 to 26. In chapter 27: Patients with central venous catheters, the use of fixed dose VKA is still a topic of interest and the comparison between fixed and adjusted methods has been considered here.

6.6 Patient views

6.6.1 Patient views and adherence to mechanical devices

6.6.1.1 Anti-embolic stockings / graduated compression stockings

We identified one study of anti-embolic stockings in orthopaedic patients$^{43}$ and two in mixed surgical patients$^{33,430,510}$.

The first study was a RCT was conducted to investigate the effect of graduated compression stockings on venous haemodynamics$^{43}$. In total, 160 patients were randomised to thigh-length or knee-length stockings. After 1 hour of wear, significantly more patients in the thigh-length group had wrinkles in their stockings (17.5% vs 7.5%) and reported discomfort (21% vs 11%). About half of the patients in each group were unable to manage the stockings independently (Evidence table 61, Appendix D).

The second study was carried out in a London hospital with a policy of wearing thigh-length graduated compression stockings$^{33,510}$. A survey (observation) was carried out in 16 mixed-specialty surgical wards over one day. Ninety-nine (46%) of the 218 patients observed were wearing stockings. Of these, more patients wore knee-length stockings correctly (77 out of 85, 91%) compared with thigh-length stockings (9 out of 14, 64%). Overall, 39% (86 patients) wore a graduated compression stockings in a correct manner (Evidence table 61, Appendix D).

The third study was a telephone interview of 12 patients who had worn anti-embolic stockings for at least 48 hours to investigate what type of information should go into a patient information leaflet on stockings$^{430}$. The study found that patients did not receive enough information to support proper use of anti-embolic stockings$^{430}$(Evidence table...
6.6.1.2 Intermittent pneumatic compression devices (IPCD)

Four studies on patient adherence to IPCD were found (Evidence table 61, Appendix D). The adherence results of these studies are summarised in Table 6-29.

One study examined patient views on a new IPCD applied to either the calf or foot of 30 patients having elective joint replacement (Evidence table 61, Appendix D). Twenty three of the 27 patients who gave feedback found the device either ‘comfortable’ or ‘very comfortable’. Three patients who had reported discomfort or sleep disturbance had been allocated to the foot garment.

6.6.1.3 Foot impulse devices (FID)

Five studies reported the acceptability or adherence to FID with all studies conducted in hip and/or knee arthroscopy patients (Evidence table 61, Appendix D). The results of the study are summarised in Table 6-28.

Generally, the studies found patients were comfortable with the FIDs (Evidence table 61, Appendix D). Reasons for non-adherence were discomfort around the ankles and sleep disturbances (30% and 70% respectively among patients who discontinued use) in Pitto et al (687). Robertson et al (555) reported that pain, forceful pulsation, a tight fit and blisters were reasons for non-adherence. For more information about adherence, see Table 6-29.

Table 6-28: Summary of tables which reported patient views of foot impulse devices (FIDs)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Total knee or hip replacement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>800</td>
<td>30</td>
<td>43</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>Setting</td>
<td>NZ</td>
<td>Ireland</td>
<td>UK</td>
<td>US</td>
<td>US</td>
</tr>
<tr>
<td>Painful</td>
<td>0.4%</td>
<td>14.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affects sleep</td>
<td>8.8%</td>
<td>56.7%</td>
<td>27.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noise</td>
<td>-</td>
<td>26.7%</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Too hot</td>
<td>-</td>
<td>43.3%</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restrict mobility</td>
<td>-</td>
<td>-</td>
<td>65.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomfortable</td>
<td>2.5%</td>
<td>30.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comfortable</td>
<td>63.1% (a)</td>
<td>7.1% (b)</td>
<td>51.2% (a)/(7.3%) (b)</td>
<td>55% (a)</td>
<td>Foot wrap 7.4 (b) Pumping action 6.1 (b)</td>
</tr>
<tr>
<td>Soothing/Relaxing</td>
<td>26.5%</td>
<td>-</td>
<td>53.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(a) Percentage of patients who reported the devices as comfortable.
(b) Mean scores from questions on comfort. Higher values represent higher comfort. Visual analogues scales (VAS) or Likert items were used. The format and definitions of response choices differ between studies. One study used scales ranging from 1 to 10. Another used a scale ranging from 0 to 10, where a score of 0 was “most uncomfortable” and 10 was “most comfortable”. The third study had questions with response choices ranging from 1 to 9. (Evidence table 61, Appendix D)

6.6.1.4 Combination of mechanical prophylaxis methods

One observational study was found that investigated the adherence to IPCD and GCS (Evidence table 61, Appendix D). Patients were recruited based on GCS and IPCD orders from the pharmacy records. The paper does not indicate how many patients...
should receive both methods. The number of patients who used each of these methods correctly was reported but the total number of people who used both correctly was not reported. This paper, found no correlation between gender and adherence rates, but older patients were more likely to wear GCS or IPCD (Pearson r=0.25, p<0.01).

6.6.2 Patient views and adherence to pharmacological prophylaxis

Five studies which reported patient views or adherence were found and included\textsuperscript{106,128,317,492,614}. One is a qualitative study conducted to understand patient perception of LMWH prophylaxis\textsuperscript{492}. The other four studies looked at self-injection of LMWH in orthopaedic patients; including hip or knee replacement\textsuperscript{128}, knee replacement\textsuperscript{614}, spinal cord injury\textsuperscript{106} (Evidence Table 62, Appendix D. Information about adherence to self-injection in patients with lower limb plaster casts were also extracted from an RCT\textsuperscript{317} reviewed for effectiveness of intervention and presented in Table 6-29 (Evidence Table 62, Appendix D).

The qualitative study was conducted among 28 cancer patients receiving palliative care in the UK with all patients having received LMWH for at least 5 days\textsuperscript{492}. Recruitment continued until theme saturation was achieved. The study found that patients were aware of the purpose of subcutaneous LMWH thromboprophylaxis, and they understood that death could be a consequence of VTE. The potential benefit of reducing the risk of VTE was balanced against potential side effects (bruising was quoted) and patients found it acceptable to receive the LMWH injections\textsuperscript{492} (Evidence table 62, Appendix D).

Colwell et al\textsuperscript{128} evaluated postoperative self injection of subcutaneous LMWH injection for 21 days in 51 total hip or knee replacement patients. Patients were given routine instructions and a demonstration by the staff nurses. Written and video instructional materials were also given on discharge. Most patients (86%) performed self-injections with 14% being assisted by a family or friend. Follow up telephone interviews were conducted once per week and each patient was given a self-report diary to complete. Forty patients completed the trial, and their diaries showed that 55%, 37.5% and 7.5% had “full”, “partial” and “noncompliance” to the injection regimen respectively (Evidence table 62, Appendix D for definitions). Most patients (98%) understood the importance of self administering heparin and 68% (34/ 50) felt comfortable doing it. Generally, patients were happy with the level of information received regarding self-injection and felt that the syringe was relatively easy to use. Sixteen reported mild burning or stinging at the injection site and one reported mild bruising. The authors thought that adherence might be higher in this study than in a normal practice due to the weekly phone calls to check how patients were coping.

Spahn et al\textsuperscript{614} evaluated postoperative self-injection of LMWH for around 10 days in knee replacement patients. Patients were provided with training for self-injection and were free to choose between self-administration or a nursing service. Assessment was carried out by anonymous questionnaire. Fully completed questionnaires were received from 69% of patients (207/300). Sixteen percent (16%, 31/191) of patients who selected self-administration of injections required family or friends to help. Only 77.3% (160/207) performed self-injection independently while 7.7% (16/207) used the nursing service. Fewer patients who self-injected independently found it ‘very unpleasant’ compared to patients who engaged the help of family members or the nursing service. Overall, adherence was incomplete in 28.3% (54/191) of patients who self injected or required family or friends to help. Some injections were left out by 17.8% (34/191) of patients injections and 13.1 % (25/191) discontinued the injections early. All patients
under 20 years old had incomplete adherence (N=24) compared to 18% (30/167) (p<0.001, Chi square test) among patients aged 20 years and above. (Evidence table 61, Appendix D).

The study among patients with spinal cord injury was conducted as an RCT comparing two compounds which required once vs twice daily injections per day\textsuperscript{106}. There were no significant differences between the two groups in terms of adherence, pain and perception of hassle of injections. The two groups were combined in analysis. On average, the patients in this did not find the injections painful (mean1.5 (s.d. =0.61) and the range of scores chosen by patients were 1-4 (1=not painful at all, 10=extremely painful). When asked to compare the hassle of injections to taking pills three times a day, the mean score was 2.5 (s.d.= 2.16), and the range of scores chosen by patients was 1 to 10 (1=much less of a hassle, 10= very much of a hassle). The adherence data from this study are shown in Table 6-29.

6.6.3 Comparison of patient views and preferences of different types of interventions

6.6.3.1 Comparison of different types of mechanical devices

We identified two studies that compared mechanical interventions\textsuperscript{555,701} (Evidence table 61, Appendix D). In one study, IPCD plus anti-embolism / graduated compression stockings (GCS) (n=104) were compared with FiDS (n=120) in hip joint replacement patients\textsuperscript{555}. Significantly more patients were "comfortable" or had no complaints with the FiD (71% vs. 55% in IPCD plus GCS group). Thirty-five participants in the foot impulse device group were having revision surgery and had previously used an IPCD. Of these, 69% preferred the FiD, 20% preferred the IPCD and 11% had no preference (Evidence table 61, Appendix D).

The second study\textsuperscript{701} was an RCT that compared the use of pneumatic foot wraps (Plexi-Pulse) with IPCD in adults undergoing major spinal procedures. All participants also wore thigh-length GCS. The devices were started postoperatively and worn when in bed until discharge. There was a wide range of responses in both groups ranging from extremely comfortable to extremely uncomfortable. There was no difference in visual analogue scores for comfort between the two groups (Evidence table 61, Appendix D).

6.6.3.2 Comparison of different types of pharmacological prophylaxis

No studies comparing different types of pharmacological prophylaxis were found.

6.6.3.3 Comparison of different mechanical and pharmacological prophylaxis

We found two studies comparing patient views for mechanical interventions with those for pharmacological interventions\textsuperscript{16,429} (Evidence Table 63, Appendix D).

One study looked at the views of 207 women undergoing surgery for gynaecological malignancy who were randomised to LMWH or IPCD in an RCT\textsuperscript{429}. Fewer patients (4%) receiving LMWH reported discomfort or side effects compared to the IPCD group (26%) who experienced discomfort, inconvenience, problems and/or side effects. The most common side effect associated with the IPCD was excessive perspiration. Eleven percent indicated that they removed the IPCD when the nurse was out of the room. The IPCD was not optimally functional in 9.6% patients at some point of postoperative recovery period whereas the protocol for LMWH was not strictly adhered to in 6.8% patients. Overall, there were no significant differences in preference or adherence between the two groups.
using although IPCD appear to lead to more discomfort. (Evidence Table 63, Appendix D).

A UK study compared the acceptability of FID to subcutaneous LMWH injections among patients who had total hip or knee replacements and received both these prophylactic methods\textsuperscript{16}. Patient ratings for comfort and pain were slightly better (not significant) for the FID, (mean score of comfort level was 6.3 for LMWH and 7.3 for FID, 10 = most comfortable; 14% found LMWH painful vs. 11.6% for FID). However, significantly more patients answered that they “would rather not have these” for FID (37%) compared to LMWH (14.0%) and willingness to continue the prophylaxis method for 4 weeks was higher for LMWH (76.7% vs. 51.2% in FID) (Evidence Table 63, Appendix D).

**Discussion on Patient views**

Adherence rates obtained from studies using various thromboprophylaxis methods are tabulated in Table 6-29. Across the studies, there were no consistent definitions of adherence and methods of measurements used. The setting of the studies (e.g. RCTs vs observational studies, different types of wards) and methods of reporting adherence could have contributed to differences identified. In general, adherence for subcutaneous LMWH injection during hospitalisation reached more than 99%, both for once and twice daily injections\textsuperscript{106}. However, 12% dropped out from a post-discharge RCT due to discomfort or refusal to self-inject\textsuperscript{317}. Adherence to FIDs ranged from 30% to 95%, depending on the timing of observations and definition of adherence used. Similarly, adherence to GCS and IPCD varies depending on definition of adherence.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population &amp; setting</th>
<th>Methods and definition of measurement</th>
<th>Outcomes (Adherence)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Population &amp; setting</td>
<td>Methods and definition of measurement</td>
<td>Outcomes (Adherence)</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------</td>
<td>---------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Pharmacological</strong></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| **SC LMWH (in hospital)** | Spinal cord injury (United States) | Adherence with injections as recorded in hospital logs | - 99.2% for twice daily
- 99.5% for once daily regimen |
| **SC LMWH (self administered)** | Below knee plaster cast, N=148 RCT (Denmark) | Number of patients who stayed in trial (no discomfort with self injection) | - 88% continued with trial
- 60% reported no problems administering self-injection |
| **SC LMWH (self-administered)** | TKR N=191 self-injection patients from 300 recruited. (Germany) | Self-reported (questionnaire, interview). Incomplete adherence include early termination or missed doses | - 71.7% (137/191) overall
- 0% in subgroup of patients under 20 years |
| **SC LMWH (self-administered)** | THR/TKR N=51, 40 evaluable Observational (United States) | Self-completed diaries reporting adherence for 21 days. | - 55% full adherence, 37.5% partial adherence, 7.5% non-adherence |
| **Mechanical – foot impulse devices (FID)** | | | |
| **FID** | THR/TKR, N=104 Observational study (United States) | Total number of hours worn, as measured by the internal measurement device of the FID and hourly nursing observation (b) | - 72% (52/72 hours for 3 days post operatively |
| **FID** | TKR, N=100 Observational (United States) | As charted by around clock, hourly observations by clinical staff. | - 87.1% overall compliance |
| **FID** | THR/TKR, N=30 Observational study (Ireland) | Reported as % of adherent observations per day (3 random observations per day conducted). | - Day 3 post surgery: 80-90% |
| | | | - Day 5 post surgery: 30% |
| **FID[ANAND2007]** | THR/TKR, N=43 Observational study (UK) | Number of patients who discontinued foot pump due to pain | - 95.3% (41/43) |
| **FID+/- GCS** | THR/TKR, N=846 RCT study (New Zealand) | 1) Internal measurement device of the FID
2) Discontinuation Protocol requires patients to use 16 hours per day | - 66% (15.9/24 hours)
- 95% (800/846) discontinuation |
| **Mechanical – IPCD** | | | |
| **IPCD (thigh-length)** | THR, N pre/post intervention(a) = 49/30 Observational (Vancouver) | Monitoring device (external) % time used | - Pre-intervention: 78±17%
- Post-intervention: 80.6±14.0% |
| **IPCD (non portable vs portable devices)** | Trauma, N=33 Observational (US) | Monitoring device Overall % of time used | - 58.8% for non portable devices; 77.7% for portable devices |
| **IPCD (length not specified)** | Surg (including ICU) N unknown Observational (California) | Reported as % of correct usage observations (once in the morning & once in the evening). Pre and post education imitative | - Surgical ward: Pre: 62% (131/213) Post: 65% (93/142)
- Non-surgical ward: Pre & post: 48% (73/152) |
### Venous Thromboembolism Prophylaxis

<table>
<thead>
<tr>
<th>Study</th>
<th>Population &amp; setting</th>
<th>Methods and definition of measurement</th>
<th>Outcomes (Adherence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPCD (calf length)</td>
<td>Orthopaedic (trauma/THR/TKR) N=70</td>
<td>Surveys (Patients at Day 3/ discharge, staff at end of study) % time used</td>
<td>▪ 81-85% patient reported</td>
</tr>
<tr>
<td></td>
<td>Observational (Pennsylvania)</td>
<td></td>
<td>▪ 66-71% staff reported</td>
</tr>
<tr>
<td>Mechanical - GCS</td>
<td>Mixed surgery wards N=218</td>
<td>Number of patients observed to wear stockings and wearing it correctly. Observation carried out in 16 wards in 1 day.</td>
<td>▪ 9/14 thigh-length</td>
</tr>
<tr>
<td>GCS</td>
<td>Observational (UK)</td>
<td></td>
<td>▪ 77/85 knee-length</td>
</tr>
<tr>
<td>GCS + IPCD or FID</td>
<td>THR/TKR Observational N=120</td>
<td>Hourly nursing observation (b)</td>
<td>▪ Overall correct use: 86/218 (39%)</td>
</tr>
<tr>
<td>GCS + IPCD</td>
<td>Med &amp; surg, N=137 Observational</td>
<td>% wearing IPCD or GCS, and % of correct fitting observed at one time point (timing not stated)</td>
<td>▪ IPCD: 29.2% wearing, 19% wearing correctly</td>
</tr>
<tr>
<td></td>
<td>(California)</td>
<td></td>
<td>▪ GCS: 62.8% wearing, 25.5% wearing correctly</td>
</tr>
</tbody>
</table>

THR = Total hip replacement; TKR = Total knee replacement; N = number of participants, GCS = anti-embolism stockings/ graduated compression stockings; IPCD = Intermittent pneumatic compression devices; SC = subcutaneous

For details about the studies, see Evidence Tables 61-63, Appendix D.

(a) In this study, adherences were measured pre and post an awareness campaign among staff and provision of a small leaflet to patients to remind them about keeping the devices on. For details, see Chapter 32.
(b) The methods of adherence measurement in for the FID and IPCD+GCS arms for Robertson et al \(^555\) was different because the FID had an integral measurement meter. The IPCD+GCS combination had to be done only through hourly observations by nursing staff.

### 6.7 Recommendations and link to evidence – mechanical prophylaxis

The following recommendations cover the general use of mechanical methods of prophylaxis. Recommendations for specific patient groups are discussed in the later chapters.

| Recommendation | Base the choice of mechanical VTE prophylaxis on individual patient factors including clinical condition, surgical procedure and patient preference. Choose any one of:
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• anti-embolism stockings (thigh or knee length)</td>
</tr>
<tr>
<td></td>
<td>• foot impulse devices</td>
</tr>
<tr>
<td></td>
<td>• intermittent pneumatic compression devices (thigh or knee length)</td>
</tr>
</tbody>
</table>

| Trade off between clinical benefit and harms | There is a lack of strong evidence available to suggest one method of mechanical prophylaxis is better than any other other, or to suggest thigh length of stockings or intermittent pneumatic compression devices are better than knee length. |
| Economic considerations | None |
**Recommendation**

Do not offer anti-embolism stockings to patients who have:
- suspected or proven peripheral arterial disease
- peripheral arterial bypass grafting
- peripheral neuropathy or other causes of sensory impairment
- any local conditions in which stockings may cause damage for example fragile ‘tissue paper’ skin, dermatitis, gangrene or recent skin graft
- known allergy to material of manufacture
- cardiac failure
- severe leg oedema or pulmonary oedema from congestive heart failure
- unusual leg size or shape
- major limb deformity preventing correct fit.

Use caution and clinical judgement when applying anti-embolism stockings over venous ulcers or wounds.

**Trade off between clinical benefit and harms**

In cases where patients have a known contra-indication to anti-embolism stockings this outweighs the benefit of reducing the risk of VTE and the stockings should not be offered. The patient should be offered alternative methods of prophylaxis.

**Economic considerations**

None

**Other considerations**

None

**Recommendation**

Ensure that patients who need anti-embolism stockings have their legs measured and that the correct size of stocking is provided. Anti-embolism stockings should be fitted and patients shown how to use them by staff trained in their use.

**Recommendation**

Ensure that patients who develop oedema or postoperative swelling have their legs re-measured and stockings refitted.

**Trade off between clinical benefit and harms**

Stockings protect against venous thrombosis but if incorrectly fitted the harms may outweigh the benefits. Poorly fitted stockings or those of an incorrect shape and size have the potential to cause a tourniquet effect on the proximal part of the limb where the stocking is applied. This can result in ischaemia and an increased risk of thrombosis development.
### Economic considerations
Although there is a cost involved in the nursing time required to fit stockings clearly it would not be cost effective to provide stockings that were not effective at reducing the risk of VTE.

### Other considerations
Properly fitting stockings increase the effectiveness at reducing VTE. Poorly fitting stockings are unlikely to be worn by patients. Patients legs may swell during hospitalisation, particularly after surgery and so it is important that patients legs are re-measured in this situation.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>If arterial disease is suspected, seek expert opinion before fitting anti-embolism stockings.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade off between clinical benefit and harms</td>
<td>Although it takes staff time to measure pedal pulses the GDG considered that this was worthwhile in certain high risk patients as it is important to ensure the safety of patients wearing anti-embolism stockings.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>It is clear that the cost-effectiveness of stockings is dependent on patient selection, information and adherence. In our cost-effectiveness analyses comparing different types of prophylaxis (Chapter 4) we included the cost of clinician time for the administration of anti-embolism stockings.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Use anti-embolism stockings that provide graduated compression and produce a calf pressure of 14-15mmHg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade off between clinical benefit and harms</td>
<td>The effectiveness of these prophylactic methods in reducing the risk of pulmonary embolism and deep vein thrombosis was considered against the potential of causing bleeding problems. The correct pressure profile needs to be used to give the best balance between benefits and harms.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>None</td>
</tr>
<tr>
<td>Other considerations</td>
<td>The above pressure profile has been identified as the profile which is effective at reducing the risk of venous thromboembolism</td>
</tr>
<tr>
<td><strong>Recommendation</strong></td>
<td><strong>Encourage patients to wear their anti-embolism stockings day and night until they no longer have significantly reduced mobility.</strong></td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Recommendation</strong></td>
<td><strong>Remove anti-embolism stockings daily for hygiene purposes and to inspect skin condition. In patients with a significant reduction in mobility, poor skin integrity or any sensory loss, inspect the skin two or three times per day, particularly the heels and bony prominences.</strong></td>
</tr>
<tr>
<td><strong>Relative values of different outcomes</strong></td>
<td>The GDG considered that it was a priority to reduce the risk of death from PE and to prevent long term morbidity from DVT such as PTS. However the safety of the patient and adverse effects of the prophylaxis should be considered.</td>
</tr>
<tr>
<td><strong>Economic considerations</strong></td>
<td>The cost-effectiveness of stockings will continue as long as the patient is immobile. However, they may no longer be cost-effective when the patient has returned to the community because of the need to monitor use. There is no cost-effectiveness evidence for the prophylactic use of stockings beyond discharge.</td>
</tr>
<tr>
<td><strong>Other considerations</strong></td>
<td>None</td>
</tr>
</tbody>
</table>

| **Recommendation** | **Discontinue the use of anti-embolism stockings if there is marking, blistering or discoloration of the skin, particularly over the heels and bony prominences or the patient experiences pain or discomfort. If suitable offer a foot impulse device or intermittent pneumatic compression device as an alternative.** |
| **Trade off between clinical benefit and harms** | The effectiveness of these prophylactic methods in reducing the risk pulmonary embolism and deep vein thrombosis was considered against the potential of causing harm and patient comfort. |
| **Economic considerations** | Clearly, it would not be effective or cost-effective to provide stockings, if contra-indicated. Regular checking will reduce the risk of patients experiencing adverse events caused by the use of stockings which may add additional cost to the health service. |
| **Other considerations** | None |
**Recommendation**  Show patients how to use anti-embolism stockings correctly and ensure they understand that this will reduce their risk of developing VTE.

**Recommendation**  Monitor the use of anti-embolism stockings and offer assistance if they are not being worn correctly.

**Trade off between clinical benefit and harms**  Not wearing the stockings as instructed may mean the patient is not adequately protected against VTE. Poorly fitted stockings or those of an incorrect shape and size have the potential to cause a tourniquet effect on the proximal part of the limb where the stocking is applied. This can result in ischaemia and an increased risk of thrombosis development.

**Economic considerations**  Clearly, it would not be effective or cost-effective to provide stockings, if contra-indicated. Regular checking will reduce the risk of patients experiencing adverse events caused by the use of stockings which may add additional cost to the health service.

**Other considerations**  None

For patients who are discharged with antiembolism stockings, further guidance is provided in section 32.6

**Recommendation**  Do not offer foot impulse or intermittent pneumatic compression devices to patients with a known allergy to the material of manufacture.

**Trade off between clinical benefit and harms**  In cases where patients have a known contra-indication to intermittent pneumatic compression devices and foot impulse devices this outweighs the benefit of reducing the risk of VTE and these devices should not be offered. The patient should be offered alternative methods of prophylaxis.

**Economic considerations**  Clearly, it would not be effective or cost-effective to provide intermittent pneumatic compression devices or foot impulse devices, if contraindicated.

**Other considerations**  None
Summary of the effectiveness of mechanical and pharmacological prophylaxis

6.8 Recommendations and link to evidence – pharmacological prophylaxis

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Encourage patients on the ward who have foot impulse or intermittent pneumatic compression devices to use them for as much of the time as is possible and practical, both when in bed and when sitting in a chair.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade off between clinical benefit and harms</td>
<td>Not wearing the using the devices as instructed may mean the patient is not adequately protected against VTE.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>The cost-effectiveness of intermittent pneumatic compression or foot impulse devices will continue as long as the patient is immobile.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Base the choice of pharmacological agents on local policies and individual patient factors, including clinical condition (such as renal failure) and patient preferences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade off between clinical benefit and harms</td>
<td>Different prophylaxis methods have different levels of evidence of efficacy and safety in different populations. Ideally, the choice of agent should be based on the most evidence-based and cost-effective agent for a given population. However, in situations where there are strong patient concerns, these need to be discussed openly.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>Where a choice of agents is provided within a recommendation this is based either on the results of the cost-effectiveness model for that population, or on the extrapolation of cost-effectiveness results in other populations. In these circumstances the guideline development group were unable to conclusively state which of the strategies were the most cost-effective. Another of the reasons for local factors to influence choice of drug is that the contract prices (and therefore cost-effectiveness) of some of the drugs vary considerably between NHS Trusts.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>While it is important to offer patients alternatives if there are concerns about using animal based products, it is also important that patients are aware of the clinical benefits or disadvantages (if any) of using these alternative products. More information is available in section 32.5.</td>
</tr>
</tbody>
</table>
6.9 Summary of recommendations

Mechanical VTE prophylaxis

 Base the choice of mechanical prophylaxis on individual patient factors including clinical condition, surgical procedure and patient preference. Choose any one of:

  • anti-embolism stockings (thigh or knee length)
  • foot impulse devices
  • intermittent pneumatic compression devices (thigh or knee length)

 Do not offer anti-embolism stockings to patients who have:

  • suspected or proven peripheral arterial disease
  • peripheral arterial bypass grafting
  • peripheral neuropathy or other causes or sensory impairment
  • any local conditions in which stockings may cause damage e.g. fragile ‘tissue paper’ skin, dermatitis, gangrene or recent skin graft
  • known allergy to material of manufacture
  • cardiac failure
  • severe leg oedema or pulmonary oedema from congestive heart failure
  • unusual leg size or shape
  • major limb deformity preventing correct fit.

Use caution and clinical judgement when applying anti-embolism stockings over venous ulcers.

 Ensure that patients who need anti-embolism stockings have their legs measured and that the correct size of stocking is provided. Stockings should be fitted and patients shown how to use them by staff trained in their use.

 Ensure that patients who develop oedema or postoperative swelling have their legs re-measured and stockings refitted.

 If arterial disease is suspected, detect pedal pulses and seek expert opinion before fitting anti-embolism stockings.

 Use anti-embolism stockings should provide graduated compression and produce a calf pressure of 14-15mmHg.

 Encourage patients to wear their anti-embolism stockings day and night until they no longer have significantly reduced mobility.
SUMMARY OF THE EFFECTIVENESS OF MECHANICAL AND PHARMACOLOGICAL PROPHYLAXIS

 Remove anti-embolism stockings daily for hygiene purposes and to inspect skin condition. In patients with a significant reduction in mobility, poor skin integrity or any sensory loss, skin should be inspected two or three times per day, particularly the heels and bony prominences.

 Discontinue the use of anti-embolism stockings if there is marking, blistering or discoloration of the skin, particularly over the heels and bony prominences or the patient experiences pain or discomfort. If suitable offer a foot impulse device or intermittent pneumatic compression device as an alternative.

 Show patients how to use anti-embolism stockings correctly and ensure they understand that this will reduce their risk of developing VTE.

 Monitor the use of anti-embolism stockings and offer assistance if they are not being worn correctly.

 Do not offer foot impulse or intermittent pneumatic compression devices to patients with a known allergy to the material of manufacture.

 Encourage patients on the ward who have foot impulse or intermittent pneumatic compression devices to use them for as much of the time as is possible and practical, both when in bed and when sitting in a chair.

Pharmacological VTE prophylaxis

 Base the choice of pharmacological agents on local policies and individual patient factors, including clinical condition (such as renal failure) and patient preferences.
7 Nursing care: early mobilisation, physiotherapy and hydration

7.1 Early mobilisation and leg exercises

7.1.1 Introduction

Immobility and lack of exercise are widely accepted as risk factors for developing venous thromboembolism. When normal venous pump function is lost as a result of bed rest, venous stasis manifests itself in two ways. Firstly, there is a decrease in the linear velocity of blood, affecting venous return from the lower extremities. Secondly, this decrease in the mean flow and pulsatility of the venous flow is followed by dilatation of the vein delaying further venous return and leading to venous stasis.

It has long been suggested that early mobilisation prevents stasis and reduces subsequent risk of thrombi formation\textsuperscript{339,671}. Although there are no robust clinical data or RCTs, attesting to support the value of early mobilisation in combating venous stasis, experimental physiology has demonstrated that it promotes venous return and thus reduces the risk of VTE\textsuperscript{213,600}.

Leg exercises are a safe and effective method of increasing venous return to the heart. The contraction during leg exercises, particularly the calf muscle pump, compresses the deep leg veins and with the aid of the venous valves, moves blood flow toward the heart. Mechanical devices that perform continuous passive motion imitate these contractions and increase the volume and velocity of venous flow.

7.1.2 Clinical evidence

We identified no RCTs that looked at the effect of early mobilisation or leg exercises on venous thromboembolism outcomes measured using objective criteria.

7.1.3 Economic evidence

We did not find any relevant economic evidence.

7.1.4 Patient views

We did not identify any patient views evidence for leg exercises or early mobilisation.
7.2 Leg elevation

7.2.1 Introduction

Leg elevation has a dual physiological effect: it reduces limb swelling and promotes venous return by its gravitational effect. It is generally held that promoting venous return can contribute to the prevention of thrombi formation. In addition, postural changes in the supine position can have a haemodynamic effect and are associated with an increase in blood flow in deep veins and reduction in venous pressure.

7.2.2 Clinical evidence

We found one RCT that compared foot elevation with no intervention\textsuperscript{560} (Evidence Table 66, Appendix D). Twenty five mixed surgical patients (elective surgery excluding surgeries performed on the leg below groin) were randomised to either bilateral leg elevation at 15 degrees from pre-medication until one week post surgery, or no leg elevation. The study did not report whether patients received any other VTE prophylaxis. Pulmonary embolism and major bleeding events were not reported.

**Effect on DVT**: No significant difference was found between leg elevation and no leg elevation (RR=1.08, 95% CI 0.35 to 3.40, one study) (Figure 250, Appendix E).

7.2.3 Economic evidence

We did not find any relevant economic evidence.

7.2.4 Patient views

We did not identify any patient views evidence for foot elevation.

7.3 Hydration

7.3.1 Introduction

It is believed that dehydration predisposes to venous thromboembolism. Kelly et al found a strong association between dehydration after acute ischaemic stroke and VTE\textsuperscript{335}. Allowing a patient to become dehydrated during surgery may also be associated with VTE.

7.3.2 Clinical evidence

We found one RCT that looked at the effect of intravenous saline administration on post-operative deep vein thrombosis\textsuperscript{308} (Evidence Table 67, Appendix D). Sixty patients undergoing routine abdominal surgery were randomised. Thirty patients received 1 litre of Hartmann's solution per hour of surgery, and then 2-3 litres of dextrose-saline per 24 hours for 2 days. Patients in the second group were given no intravenous fluids either during or after the surgery, but small, increasing amounts of water were allowed by mouth from the first day onwards. The study did not report location of thrombosis, pulmonary embolism or major bleeding events.

**Effect on DVT**: Intravenous saline was associated with a significantly higher number of DVT events (RR=4.50, 95% CI 1.06-19.11, one study) (Figure 251, Appendix E).
7.3.3 Economic evidence

We did not find any relevant economic evidence.

7.3.4 Patient views

We did not identify any patient views evidence for hydration.

7.4 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Encourage patients to mobilise as soon as possible.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative values of different outcomes</td>
<td>The GDG considered that it was a priority to reduce the risk of death from PE and to prevent long term morbidity from DVT such as Post thrombotic syndrome. However the safety of the patient and adverse effects of the prophylaxis should be considered.</td>
</tr>
<tr>
<td>Trade off between clinical benefit and harms</td>
<td>Whilst encouraging patients to mobilise as soon as possible requires staff resources, the benefit of reducing the risk of VTE mean that it is good practice.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>There is no cost-effectiveness evidence for encouraging patients to mobilise early. The GDG believe that this represents a good use of resources.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>There is no RCT evidence to contradict the practices of encouraging patients to mobilise early or exercising their legs while immobile in bed.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Do not allow patients to become dehydrated unless clinically indicated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative values of different outcomes</td>
<td>The GDG considered that it was a priority to reduce the risk of death from PE and to prevent long term morbidity from DVT such as PTS.</td>
</tr>
<tr>
<td>Trade off between clinical benefit and harms</td>
<td>It was considered that unless clinically indicated for other reasons the potential to increase the risk of VTE whilst dehydrated meant that it was good practice to avoid this happening.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>It seems likely that this is cost-effective, since the cost of the intervention is minimal.</td>
</tr>
</tbody>
</table>
Quality of evidence  We found no RCTs that looked at the effect of oral hydration on venous thromboembolism. This recommendation was developed through GDG consensus.

Other considerations  None

7.4.1 Recommendations for research

Although the GDG did not rate research into nursing care for the prevention of VTE as one of their top 5 research recommendations (See section 2.3) they did acknowledge that there was a lack of research in this area and more research would be beneficial.

7.5 Summary of recommendations

- Encourage patients to mobilise as soon as possible.
- Do not allow patients to become dehydrated unless clinically indicated.
8 Vena caval filters

8.1 Introduction

Vena caval filters are placed in the inferior vena cava by radiologically controlled percutaneous techniques. Their purpose is to trap the thrombus which comes free from the veins of the lower limbs or pelvis and to prevent them reaching the pulmonary circulation. In the earlier designs, once placed they could not be removed, but retrievable and temporary filters are now available. They are usually used in patients who have a known DVT and who may have already had an embolism or for patients in whom anticoagulation is contraindicated.

Filter placement necessitates instrumentation of the veins, either via the groin (femoral vein) or the neck (jugular vein) and there are complications associated with placement. These can occur immediately following placement or develop or come to light months to years later. The complications include misplacement, pneumothorax, haematoma, air embolism, inadvertent carotid artery puncture and arteriovenous fistula.

8.2 Clinical evidence

We found no RCTs investigating vena caval filters, either permanent or retrievable, in surgical patients.

We identified one RCT that compared the use of permanent vena caval filters with no filters in 400 hospitalised patients with proximal DVT considered to be at high risk of pulmonary embolism (Evidence Table 69, Appendix D). All patients received vitamin K antagonists from the 4th day of the study and continued for at least 3 months. Patients were also randomised to receive either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for 8 to 12 days.

Significantly more patients had a pulmonary embolism in the first 12 days in patients without the filter than in those with the filter. More patients in the group allocated to receive no filters had symptomatic pulmonary embolism than those allocated to receive filters at 2 years and 8 years. The difference was significant at 8 years. There was no difference in the number of major bleeds. However, significantly more patients using filters had recurrent DVT at 2 years.
8.3 Economic evidence

We found no economic studies evaluating vena cava filters specifically in surgical patients. However, we did find six economic studies that evaluated vena cava filters in other contexts (Evidence Table 70, Appendix D).

Two decision models\textsuperscript{80,105} compared the surgical placement of vena cava filters with anticoagulation in high-risk trauma patients and in patients with malignant brain tumour. Both studies found that the filter was not cost-effective. A third decision model\textsuperscript{583} found that vena cava filter placement is cost-saving compared with either anticoagulation or observation for patients with advanced cancer. However, their assumption of a 90\% reduction in symptomatic VTE attributable to filters seems optimistic compared with the RCT results above.

Four studies, three cohort studies\textsuperscript{60,168,303} and one decision model\textsuperscript{80} found that bedside percutaneous placement of vena cava filters was less costly and safe compared with surgical placement.

8.4 Patient views

No studies of patient views were identified for vena caval filters.

8.5 Recommendations and link to evidence

\begin{tabular}{|l|p{14cm}|}
\hline
\textbf{Recommendation} & Consider offering temporary inferior vena caval filters to patients who are at very high risk of VTE (such as previous VTE event or an active malignancy) and for whom mechanical and pharmacological VTE prophylaxis are contraindicated. \\
\hline
\textbf{Relative values of different outcomes} & The GDG considered that it was a priority to reduce the risk of death from PE and to prevent long term morbidity from DVT such as PTS. However the safety of the patient and adverse effects of the prophylaxis should be considered. \\
\hline
\textbf{Trade off between clinical benefit and harms} & This is a more invasive method of prophylaxis and therefore the GDG considered this should only be offered to patients at high risk of VTE where all methods of pharmacological and mechanical prophylaxis are contraindicated. The recommendation is made on the basis that the filter is to remain in situ only for the period of increased risk, and should be removed within 3 months. Permanent insertion of vena caval filters may be associated with an increased long-term risk of lower limb VTE. \\
\hline
\textbf{Economic considerations} & The economic data showed that vena cava filters are unlikely to be cost-effective in patients that can be coagulated. Where filters are prescribed bedside placement may be more cost-effective than surgical placement. \\
\hline
\end{tabular}
Quality of evidence

There is no evidence on the use of vena cava filters in this patient group. There was a significant reduction in PE on treating hospitalised patients with existing proximal DVTs using vena cava filters and anticoagulation. This recommendation was developed through GDG consensus.

Other considerations

The British Committee for Standards in Haematology have produced guidelines on the use of vena cava filters. They reviewed the clinical studies mentioned above and came to a consensus on the recommendations.

8.6 Summary of recommendations

- Consider offering temporary inferior vena caval filters to patients who are at very high risk of VTE (such as patients with a previous VTE event or an active malignancy) and for whom mechanical and pharmacological VTE prophylaxis are contraindicated.
9 Gastrointestinal, gynaecological, laparoscopic, thoracic and urological surgery

9.1 Introduction

This section covers major abdominal and thoracic surgery. It includes both open and laparoscopic surgery. The introduction is presented in the following sections:

- Gastrointestinal surgery
- Bariatric surgery
- Gynaecological surgery
- Laparoscopic surgery
- Thoracic surgery
- Urological surgery

All data were analysed together when investigating the clinical and cost-effectiveness of VTE prophylaxis in these groups.

Gastrointestinal surgery

This section covers inpatients undergoing open gastrointestinal surgery. Gastrointestinal surgery of its nature is heterogeneous in the age of patients, the pathological conditions being dealt with and organs and systems operated upon. There remain a variety of procedures retained within this category that are specialisations in themselves. These include upper gastrointestinal surgery and lower intestinal surgery (or coloproctology).

We have no data specifically reported as gastrointestinal surgery. Most studies were classified as ‘general surgery’. We have estimated from the incidence of RCTs that the risk of developing DVT, pulmonary embolism and major bleeding in general surgery patients not receiving thromboprophylaxis is:

- DVT - 24% (95% confidence intervals: 23% to 26%)
- Symptomatic pulmonary embolism – 1% (95% confidence intervals: 1% to 2%)
Major bleeding - 2% (95% confidence intervals: 1% to 2%)

Factors that may alter the risk of VTE

- Patients having surgery for cancer will have an increased risk of developing a DVT or pulmonary embolism.
- Patients having emergency procedures are often elderly and will consequently be at higher risk of developing a DVT or pulmonary embolism.
- Some patients having emergency procedures may already be using anticoagulation or antiplatelet therapy. This needs to be considered when deciding on the method of VTE prophylaxis.

There are no specific factors that increase the risk of bleeding or the hazard associated with it in open gastrointestinal surgery.

There are no other special factors that would affect the choice of, and use of, specific methods of VTE prophylaxis in open gastrointestinal surgery.

Bariatric surgery

This section covers inpatients undergoing open gastrointestinal surgery. Although part of gastrointestinal surgery, all patients undergoing bariatric surgery would be considered at increased risk of VTE because they have a BMI of greater than 30 and are therefore classified as obese. Consequently, we have mentioned them separately. Most bariatric surgery is performed laparoscopically.

No data were available specifically investigating patients under bariatric surgery so no estimates are available for the risk of DVT, pulmonary embolism or major bleeding.

All patients are at high risk of developing VTE due to obesity. It is not known whether the presence of additional risk factors will add to this risk.

Factors that may increase the risk of bleeding or the hazard associated with it:

- Difficult access may result in poor views because of obesity
- There is a danger of converting from laparoscopic to open surgery if bleeding occurs

Other factors that may affect the choice of prophylaxis:

- There may be a higher number of patients who are contraindicated to anti-embolism stockings in this group because of an unusual leg size and shape.
- There is a higher incidence of diabetes which may mean a higher number of patients will contraindicated to anti-embolism stockings due to diabetic neuropathy.

Gynaecological surgery
This section covers inpatients undergoing open gynaecological surgery excluding caesarean section (see section 30). This includes abdominal and vaginal surgery.

We have estimated from the incidence of RCTs that the risk of developing DVT, pulmonary embolism and major bleeding in gynaecological surgery patients not receiving thromboprophylaxis is:

- DVT - 16% (95% confidence intervals: 13% to 19%)
- Symptomatic pulmonary embolism – 1% (95% confidence intervals: 0% to 3%)
- Major bleeding - 4% (95% confidence intervals: 2% to 7%)

Factors that may alter the risk of VTE:

- Patients may be using hormonal contraception and hormone replacement therapy, which will increase their risk of developing a DVT or pulmonary embolism.
- Patients having surgery for cancer will have increased risk of developing a DVT or pulmonary embolism.

There are no special factors that increase the risk of bleeding or the hazard associated with it in open gynaecological surgery.

There are no other special factors that would affect the choice of, and use of, specific methods of VTE prophylaxis in open gynaecological surgery.

**Urological surgery**

This section covers inpatients undergoing open urological surgery. The procedures can be divided into two major groups: pelvic cancer surgery and renal surgery. Patients undergoing these procedures are usually between the ages of 65 and 75.

We have estimated, from the incidence in the RCTs (Chapter 5), that the risk of developing DVT, pulmonary embolism and major bleeding in urological surgery patients not receiving VTE thromboprophylaxis is 10% (95%CI: 6% to 15%),

- DVT - 10% (95% confidence intervals: 6% to 15%).
  - Its ranking among other surgery in our HES data would suggest that the risk could be higher.
- Symptomatic pulmonary embolism – 1% (95% confidence intervals: 0% to 3%)
- Major bleeding - 4% (95% confidence intervals: 2% to 7%)

Factors that may alter the risk of VTE:

- Many urological surgery patients get spinal and epidural anaesthesia. This may reduce the risk of developing a deep vein thrombosis.
Renal surgery procedures may involve division of the renal vein where it drains into the inferior vena cava possibly. This could potentially increase the risk of VTE.

There are no other special factors that would affect the choice of, and use of, specific methods of VTE prophylaxis in open urological surgery.

Thoracic surgery

We did not find data from the placebo arms of RCTs (Section 5.3) that would allow us to estimate the risk of developing deep vein thrombosis in thoracic surgery patients not receiving thromboprophylaxis. However, according to our HES data, its ranking among other surgery would suggest that the risk is high.

Factors that may alter the risk of VTE

- After lung resection, pulmonary embolism to the remaining lung carries a commensurately higher risk of death.

- Most patients having video-assisted thorascopic surgery (VATS), particularly for pneumothorax, are young (less than 30 years) and are able to walk around the ward up to the time of surgery and soon after and have short lengths of stay.

There are no special factors that increase the risk of bleeding or the hazard associated with it in thoracic surgery.

There are no other special factors that would affect the choice of, and use of, specific methods of VTE prophylaxis in thoracic surgery.

Laparoscopic surgery

We did not find data from the placebo arms of RCTs (Section 5.3) that would allow us to estimate the risk of developing deep vein thrombosis in laparoscopic surgery patients not receiving thromboprophylaxis.

Laparoscopic surgery is used in gastrointestinal, gynaecological and urological surgery. The same considerations apply to it in all these specialities.

Factors that may alter the risk of VTE

- There is some concern that the increased pressure in the peritoneal cavity during laparoscopic surgery would cause venous stasis\(^{314,610,698}\).

- Laparoscopic procedures also tend to last longer than open urological procedures.

Factors that may alter the risk of bleeding

- Laparoscopic procedures may be associated with less bleeding than open surgery.
**Gastrointestinal, Gynaecological, Laparoscopic, Thoracic and Urological Surgery**

- Bleeding may make laparoscopic surgery difficult or impossible and result in the need for conversion to open surgery.

There are no other special factors that may affect the choice, and use of, specific methods of VTE prophylaxis in laparoscopic surgery.

### 9.2 Evidence of methods of prophylaxis

#### 9.2.1 Summary of comparisons identified for any outcome

One hundred and forty six (146) randomised controlled trials which reported at least one of the three main outcomes were identified: 1,5,9,10,13,14,29,30,32,37,40,46,48,50,52,54,57,65,72,73,76,82,89,92,100,104,111-117,119,138,140,171,172,179,182,199,207,209,210,224,227,230,238,246,254,262,264,266,267,269,279,280,282,283,308,319,321,324,328,329,358,359,361,363,366,368,371-373,384-386,393,403,406,407,414,416,423,424,429,439,440,486,487,496,498,499,503,504,511,516,517,528,530,532,546,547,550,552,560,568-570,575,585,586,588-590,592-594,599,611,629,633,639-641,643,645,653,656,657,670,682,685,691,693,694,703,711,713,716. Some of these investigated more than two methods of prophylaxis, and some studies reported results in more than one paper. Most the RCTs had their data extracted from systematic reviews. Where applicable the study is cited in the evidence table for that review. Six systematic reviews included RCTs with patients having general surgical procedures: 15,21,125,355,450,557.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).
9.2.2 Results from pairwise comparisons

Table 9-30: DVT – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
<th>Mech + pharm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS vs no prophylaxis</td>
<td>5</td>
<td>30/448</td>
<td>90/435</td>
<td>0.35</td>
<td>(-0.13, -0.04)</td>
<td>ET: 23</td>
<td></td>
</tr>
<tr>
<td>IPCD/FID vs no prophylaxis</td>
<td>8</td>
<td>37/402</td>
<td>82/389</td>
<td>0.44</td>
<td>(-0.12, -0.03)</td>
<td>ET: 24</td>
<td></td>
</tr>
<tr>
<td>LMWH vs no prophylaxis</td>
<td>4</td>
<td>6/219</td>
<td>28/214</td>
<td>0.22</td>
<td>(-0.10, -0.03)</td>
<td>ET: 26</td>
<td></td>
</tr>
<tr>
<td>UFH vs no prophylaxis</td>
<td>21</td>
<td>170/1729</td>
<td>342/1586</td>
<td>0.45</td>
<td>(-0.12, -0.09)</td>
<td>ET: 27</td>
<td></td>
</tr>
<tr>
<td>VKA (adj dose) vs no prophylaxis</td>
<td>2</td>
<td>4/83</td>
<td>22/85</td>
<td>0.21</td>
<td>(-0.21, -0.11)</td>
<td>ET: 28</td>
<td></td>
</tr>
</tbody>
</table>

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) – low dose aspirin (<300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis
<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (high dose) +/- other antplatelet vs no prophylaxis</td>
<td>12</td>
<td>196/836</td>
<td>195/647</td>
<td>0.65 (0.46, 0.92) (b)</td>
<td>-0.11 (-0.20, -0.03)</td>
<td>ET: 29 FP: 28</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS vs UFH</td>
<td>3</td>
<td>30/151</td>
<td>30/155</td>
<td>1.07 (0.69, 1.67)</td>
<td>0.01 (-0.06, 0.09)</td>
<td>ET: 37 FP: 84</td>
</tr>
<tr>
<td>IPCD vs UFH</td>
<td>4</td>
<td>8/222</td>
<td>15/228</td>
<td>0.61 (0.25, 1.49)</td>
<td>-0.02 (-0.08, 0.03)</td>
<td>ET: 37 FP: 90</td>
</tr>
<tr>
<td>IPCD vs VKA (adj dose)</td>
<td>1</td>
<td>4/47</td>
<td>0/53</td>
<td>10.13 (0.56, 183.23)</td>
<td>0.09 (0.00, 0.17)</td>
<td>ET: 37 FP: 95</td>
</tr>
<tr>
<td>LMWH vs UFH</td>
<td>35</td>
<td>338/7436</td>
<td>385/7152</td>
<td>0.89 (0.77, 1.03)</td>
<td>0.00 (-0.01, 0.00)</td>
<td>ET: 32 FP: 48</td>
</tr>
<tr>
<td>Fondaparinux vs LMWH</td>
<td>1</td>
<td>43/1024</td>
<td>59/1018</td>
<td>0.72 (0.49, 1.06)</td>
<td>-0.02 (-0.03, 0.00)</td>
<td>ET: 31 FP: 44</td>
</tr>
<tr>
<td>Aspirin (high dose) vs UFH</td>
<td>2</td>
<td>22/101</td>
<td>14/99</td>
<td>1.48 (0.81, 2.70)</td>
<td>0.05 (-0.06, 0.16)</td>
<td>ET: 36 FP: 64</td>
</tr>
<tr>
<td>VKA vs UFH</td>
<td>2</td>
<td>12/98</td>
<td>4/99</td>
<td>2.74 (0.30, 24.92) (c)</td>
<td>0.08 (-0.08, 0.24)</td>
<td>ET: 33 FP: 54</td>
</tr>
<tr>
<td>Double proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS + IPCD vs IPCD</td>
<td>2</td>
<td>8/132</td>
<td>13/132</td>
<td>0.49 (0.06, 4.02)</td>
<td>-0.04 (-0.14, 0.06)</td>
<td>ET: 38 FP: 106</td>
</tr>
<tr>
<td>GCS + UFH vs UFH</td>
<td>4</td>
<td>30/352</td>
<td>56/354</td>
<td>0.37 (0.14, 0.98)</td>
<td>-0.08 (-0.12, -0.04)</td>
<td>ET: 38 FP: 109</td>
</tr>
<tr>
<td>Fondaparinux + IPCD vs IPCD</td>
<td>1</td>
<td>7/424</td>
<td>22/418</td>
<td>0.31 (0.14, 0.73)</td>
<td>-0.04 (-0.06, -0.01)</td>
<td>ET: 40 FP: 131</td>
</tr>
<tr>
<td>Aspirin + UFH vs UFH</td>
<td>2</td>
<td>17/107</td>
<td>27/106</td>
<td>0.64 (0.37, 1.09)</td>
<td>-0.10 (-0.20, 0.00)</td>
<td>ET: 42 FP: 162</td>
</tr>
<tr>
<td>UFH + GCS vs GCS</td>
<td>3</td>
<td>5/159</td>
<td>46/168</td>
<td>0.18 (0.04, 0.82) (d)</td>
<td>-0.24 (-0.31, -0.16)</td>
<td>ET: 27 FP: 142</td>
</tr>
<tr>
<td>UFH + aspirin vs aspirin</td>
<td>1</td>
<td>5/57</td>
<td>19/63</td>
<td>0.29 (0.12, 0.73)</td>
<td>-0.21 (-0.35, -0.08)</td>
<td>ET: 27 FP: 150</td>
</tr>
<tr>
<td>GCS + IPCD vs UFH</td>
<td>1</td>
<td>3/50</td>
<td>7/50</td>
<td>0.43 (0.12, 1.56)</td>
<td>-0.08 (-0.20, 0.04)</td>
<td>ET: 37 FP: 105</td>
</tr>
<tr>
<td>Double proph vs double</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + GCS vs LMWH + GCS</td>
<td>1</td>
<td>1/106</td>
<td>2/105</td>
<td>0.50 (0.05, 5.38)</td>
<td>-0.01 (-0.04, 0.02)</td>
<td>ET: 49 FP: 202</td>
</tr>
<tr>
<td>IPCD + GCS vs UFH + GCS</td>
<td>1</td>
<td>10/54</td>
<td>2/52</td>
<td>4.81 (1.11, 20.93)</td>
<td>0.15 (0.03, 0.26)</td>
<td>ET: 50 FP: 120</td>
</tr>
<tr>
<td>LMWH + GCS vs UFH + GCS</td>
<td>2</td>
<td>6/184</td>
<td>3/139</td>
<td>1.29 (0.32, 5.16)</td>
<td>0.01 (-0.02, 0.05)</td>
<td>ET: 45 FP: 174</td>
</tr>
<tr>
<td>Post discharge prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs no prophylaxis</td>
<td>3</td>
<td>23/388</td>
<td>52/402</td>
<td>0.46 (0.29, 0.74)</td>
<td>-0.07 (-0.11, -0.03)</td>
<td>ET: 58 FP: 225</td>
</tr>
</tbody>
</table>

* FP = forest plot number in appendix E; ET = evidence table number in appendix D

(a) There was significant heterogeneity within the results (chi squared on 6 df = 13.52, p = 0.04, I² = 55.6%) which was largely attributable to the inclusion of one study of patients undergoing pelvic surgery for malignancy.14

(b) There was significant unexplained heterogeneity within the results (chi squared on 11 df = 34.99,52, p = 0.0002, I² = 68.6%). This does not appear to be due to speciality, year of publication or antiplatelet dose.
(c) There was significant heterogeneity between the two studies (chi squared on 1 df = 3.00, p = 0.08, I² = 66.7%). One study gave different durations of treatment with vitamin K antagonist given for 14 days and the UFH given for 7 days. This study showed no difference in DVT whereas the other significantly favoured UFH.

(d) There was significant heterogeneity within the results (chi squared on 2 df = 5.12, p = 0.08, I² = 60.9%). One study had a greater reduction in DVT compared to the other two.

Table 9-31: Pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID vs no prophylaxis</td>
<td>3</td>
<td>6/192</td>
<td>3/186</td>
<td>1.79</td>
<td>(0.43, 7.45)</td>
<td>0.02</td>
</tr>
<tr>
<td>LMWH vs no prophylaxis</td>
<td>5</td>
<td>2/2551</td>
<td>13/2583</td>
<td>0.22</td>
<td>(0.06, 0.78)</td>
<td>0.00</td>
</tr>
<tr>
<td>UFH vs no prophylaxis</td>
<td>10</td>
<td>26/645</td>
<td>48/630</td>
<td>0.52</td>
<td>(0.30, 0.90)</td>
<td>-0.03</td>
</tr>
<tr>
<td>Aspirin +/- other antiplatelet vs no prophylaxis</td>
<td>13</td>
<td>5/1820</td>
<td>23/1608</td>
<td>0.27</td>
<td>(0.11, 0.65)</td>
<td>-0.01</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS vs UFH</td>
<td>1</td>
<td>1/25</td>
<td>1/25</td>
<td>1.00</td>
<td>(0.07, 15.12)</td>
<td>0.00</td>
</tr>
<tr>
<td>IPCD vs UFH</td>
<td>3</td>
<td>3/121</td>
<td>3/121</td>
<td>1.00</td>
<td>(0.21, 4.84)</td>
<td>0.00</td>
</tr>
<tr>
<td>IPCD vs VKA (adj dose)</td>
<td>1</td>
<td>2/47</td>
<td>0/53</td>
<td>5.63</td>
<td>(0.28, 14.47)</td>
<td>0.04</td>
</tr>
<tr>
<td>LMWH vs UFH</td>
<td>18</td>
<td>18/4352</td>
<td>22/4343</td>
<td>0.95</td>
<td>(0.49, 1.84)</td>
<td>0.00</td>
</tr>
<tr>
<td>Fondaparinux vs LMWH</td>
<td>1</td>
<td>5/1465</td>
<td>3/1462</td>
<td>1.66</td>
<td>(0.40, 6.95)</td>
<td>0.00</td>
</tr>
<tr>
<td>Aspirin (high dose) vs UFH</td>
<td>1</td>
<td>0/63</td>
<td>2/57</td>
<td>0.18</td>
<td>(0.01, 3.70)</td>
<td>-0.04</td>
</tr>
<tr>
<td>Double proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS + UFH vs UFH</td>
<td>1</td>
<td>0/94</td>
<td>1/84</td>
<td>0.30</td>
<td>(0.01, 7.22)</td>
<td>-0.01</td>
</tr>
<tr>
<td>Fondaparinux + IPCD vs IPCD</td>
<td>1</td>
<td>1/650</td>
<td>1/659</td>
<td>1.01</td>
<td>(0.06, 16.17)</td>
<td>0.00</td>
</tr>
<tr>
<td>Aspirin + UFH vs UFH</td>
<td>2</td>
<td>0/107</td>
<td>3/106</td>
<td>0.25</td>
<td>(0.03, 2.25)</td>
<td>-0.03</td>
</tr>
<tr>
<td>UFH + GCS vs GCS</td>
<td>3</td>
<td>5/159</td>
<td>46/168</td>
<td>0.18</td>
<td>(0.04, 0.82)</td>
<td>-0.24</td>
</tr>
<tr>
<td>UFH + aspirin vs aspirin</td>
<td>1</td>
<td>0/57</td>
<td>0/63</td>
<td>not estimable</td>
<td>0.00</td>
<td>-0.03</td>
</tr>
<tr>
<td>Double proph vs double</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH + GCS vs UFH + GCS</td>
<td>1</td>
<td>0/103</td>
<td>0/100</td>
<td>not estimable</td>
<td>0.00</td>
<td>(-0.02, 0.02)</td>
</tr>
<tr>
<td>Post discharge prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs no prophylaxis</td>
<td>2</td>
<td>0/370</td>
<td>4/389</td>
<td>0.22</td>
<td>(0.03, 1.94)</td>
<td>-0.01</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D
### Table 9-32: Major bleeding – summary of results from RCTs

| Comparison | No. of studies | Intervention | Control | Relative risk | Absolute effect | Forest plots & Evidence tables *
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proph vs no proph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs no prophylaxis</td>
<td>7</td>
<td>75/2696</td>
<td>37/2730</td>
<td>2.01 (1.31, 3.07)</td>
<td>0.01 (0.01, 0.02)</td>
<td>ET: 26 FP: 15</td>
</tr>
<tr>
<td>UFH vs no prophylaxis</td>
<td>22</td>
<td>97/1878</td>
<td>58/1664</td>
<td>1.38 (0.98, 1.96)</td>
<td>0.01 (0.00, 0.02)</td>
<td>ET: 27 FP: 19</td>
</tr>
<tr>
<td>VKA (adj dose) vs no prophylaxis</td>
<td>2</td>
<td>11/83</td>
<td>5/85</td>
<td>1.97 (0.75, 5.15)</td>
<td>0.07 (0.00, 0.14)</td>
<td>ET: 28 FP: 23</td>
</tr>
<tr>
<td>Aspirin +/- other antiplatelet vs no prophylaxis</td>
<td>9</td>
<td>3/568</td>
<td>0/400</td>
<td>2.42 (0.13, 45.97)</td>
<td>-0.01 (0.00, 0.02)</td>
<td>ET: 29 FP: 30</td>
</tr>
<tr>
<td><strong>Single proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS vs UFH</td>
<td>1</td>
<td>0/52</td>
<td>0/45</td>
<td>not estimable</td>
<td>0.00 (-0.04, 0.04)</td>
<td>ET: 37 FP: 86</td>
</tr>
<tr>
<td>LMWH vs UFH</td>
<td>28</td>
<td>232/6716</td>
<td>239/6716</td>
<td>1.09 (0.85, 1.40)</td>
<td>0.00 (-0.01, 0.01)</td>
<td>ET: 32 FP: 50</td>
</tr>
<tr>
<td>Fondaparinux vs LMWH</td>
<td>1</td>
<td>49/143</td>
<td>34/142</td>
<td>1.43 (0.93, 2.21)</td>
<td>0.01 (0.00, 0.02)</td>
<td>ET: 31 FP: 46</td>
</tr>
<tr>
<td>Aspirin vs UFH</td>
<td>1</td>
<td>0/63</td>
<td>0/57</td>
<td>Not estimable</td>
<td>0.00 (-0.03, 0.03)</td>
<td>ET: 36 FP: 66</td>
</tr>
<tr>
<td>VKA vs UFH</td>
<td>1</td>
<td>3/48</td>
<td>5/49</td>
<td>0.61 (0.15, 2.42)</td>
<td>-0.04 (-0.15, 0.07)</td>
<td>ET: 33 FP: 56</td>
</tr>
<tr>
<td><strong>Double proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux + IPCD vs UFH</td>
<td>1</td>
<td>10/635</td>
<td>1/650</td>
<td>10.24 (1.31, 79.73)</td>
<td>0.01 (0.00, 0.02)</td>
<td>ET: 40 FP: 133</td>
</tr>
<tr>
<td>Aspirin + UFH vs UFH</td>
<td>2</td>
<td>4/107</td>
<td>1/106</td>
<td>3.92 (0.45, 33.84)</td>
<td>0.02 (-0.06, 0.10)</td>
<td>ET: 42 FP: 164</td>
</tr>
<tr>
<td>UFH + GCS vs GCS</td>
<td>3</td>
<td>5/165</td>
<td>1/168</td>
<td>3.08 (0.50, 18.95)</td>
<td>0.01 (-0.01, 0.03)</td>
<td>ET: 27 FP: 144</td>
</tr>
<tr>
<td>UFH + aspirin vs aspirin</td>
<td>1</td>
<td>0/57</td>
<td>0/63</td>
<td>Not estimable</td>
<td>0.00 (-0.03, 0.03)</td>
<td>ET: 27 FP: 152</td>
</tr>
<tr>
<td><strong>Double proph vs double</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH + GCS vs UFH + GCS</td>
<td>2</td>
<td>2/187</td>
<td>0/142</td>
<td>2.53 (0.12, 51.53)</td>
<td>0.00 (-0.02, 0.03)</td>
<td>ET: 45 FP: 176</td>
</tr>
<tr>
<td><strong>Post discharge prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs no prophylaxis</td>
<td>2</td>
<td>4/458</td>
<td>5/470</td>
<td>0.88 (0.08, 9.09)</td>
<td>0.00 (-0.02, 0.02)</td>
<td>ET: 58 FP: 227</td>
</tr>
</tbody>
</table>

* FP = forest plot number in appendix E; ET = evidence table number in appendix D

(a) There was significant unexplained heterogeneity within the results (chi squared on 1 df =2.22, p=0.14, I² =54.9%).

### 9.2.3 Additional information

#### 9.2.3.1 All cause mortality

All cause mortality was not identified as a key outcome during the development of the surgical guideline. Much of the data were identified from systematic reviews where all cause mortality was not reported. There was not time during the development of this guideline to review all cause mortality for this population.
9.2.3.2 Other outcomes

Chronic thromboembolic pulmonary hypertension, post thrombotic syndrome or heparin induced thrombocytopenia were not identified as key outcomes during the development of the surgical guideline. Much of the data were identified from systematic reviews where these outcomes were not reported. There was not time during the development of this guideline to check all RCTs for these outcomes.

9.2.3.3 Additional studies

An additional study compared post-discharge LMWH after video laparoscopic surgery\textsuperscript{637}. Patients were randomised after on average just under 4 days in hospital to 7 days LMWH or no prophylaxis. Although most of the procedures could be described as general or other internal procedures, this paper appeared to include a different population to the other post-discharge studies: patients were in hospital for a shorter period, the duration was shorter and all procedures were laparoscopic. Also, the study planned to recruit 760 patients but stopped at 200 when it became apparent that the DVT risk in this group was far lower than expected. Consequently, it was not included in the network meta-analysis or economic model for post-discharge prophylaxis. There was only 1 DVT occurring within the 28 day post-discharge follow up that occurred in the group not receiving prophylaxis.

9.3 Network meta-analysis results

9.3.1 Introduction

A network meta-analysis was completed for DVT, symptomatic pulmonary embolism and major bleeding. Details on the network meta-analysis methods can be found in section 3.10.

9.3.2 Results

DVT results

There were 95 studies included in the network meta-analysis for DVT\textsuperscript{1,5,9,10,13,14,30,32,37,50,52,54,57,72,82,89,92,104,111,117,119,254,406,528,546,633,641-645,653,667,670,682,685,691,693,703,713,716}. Six of these studies were trials comparing three prophylaxis methods within the same trial\textsuperscript{119,254,406,528,546,633}.
Figure 9-7: Network diagram for DVT. Numbers indicate the number of studies which contributed results for each comparison.

Table 9-33: DVT – network meta-analysis results

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH + GCS</td>
<td>0.09 (0.04, 0.17)</td>
</tr>
<tr>
<td>Fondaparinux + IPCD/FID</td>
<td>0.11 (0.03, 0.43)</td>
</tr>
<tr>
<td>LMWH + GCS</td>
<td>0.16 (0.03, 0.94)</td>
</tr>
<tr>
<td>UFH + Asp (high dose)</td>
<td>0.18 (0.07, 0.44)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>0.20 (0.06, 0.59)</td>
</tr>
<tr>
<td>LMWH</td>
<td>0.28 (0.19, 0.40)</td>
</tr>
<tr>
<td>VKA</td>
<td>0.29 (0.11, 0.66)</td>
</tr>
<tr>
<td>UFH</td>
<td>0.34 (0.25, 0.44)</td>
</tr>
<tr>
<td>GCS</td>
<td>0.35 (0.21, 0.56)</td>
</tr>
<tr>
<td>IPCD/FID</td>
<td>0.36 (0.22, 0.58)</td>
</tr>
<tr>
<td>Asp (high dose)</td>
<td>0.60 (0.42, 0.83)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals. The residual deviance was 209.1, which is quite close to the number of data points of 196, implying that the model fits the data well.
Pulmonary embolism results

There were 37 studies included in the network meta-analysis for PE. Of these, three studies compared three prophylaxis methods within the same trial. There were 37 studies included in the network meta-analysis for PE. Of these, three studies compared three prophylaxis methods within the same trial.

Figure 9-9: Network diagram for PE. Numbers indicate the number of studies which contributed results for each comparison.

Figure 9-10: PE — network meta-analysis results of interventions compared to no prophylaxis.

Table 9-34: Pulmonary embolism — network meta-analysis results.

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH + Aspirin (high dose)</td>
<td>0.02 (0.00, 0.87)</td>
</tr>
<tr>
<td>UFH + GCS</td>
<td>0.04 (0.00, 5.63)</td>
</tr>
<tr>
<td>VKA (adjusted-dose)</td>
<td>0.07 (0.00, 4.49)</td>
</tr>
<tr>
<td>Aspirin (high dose)</td>
<td>0.13 (0.03, 0.58)</td>
</tr>
<tr>
<td>LMWH</td>
<td>0.18 (0.05, 0.59)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>0.32 (0.02, 5.69)</td>
</tr>
<tr>
<td>UFH</td>
<td>0.48 (0.18, 1.26)</td>
</tr>
<tr>
<td>GCS</td>
<td>0.70 (0.02, 16.83)</td>
</tr>
<tr>
<td>IPCD/FID</td>
<td>1.27 (0.27, 5.80)</td>
</tr>
<tr>
<td>Fondaparinux + IPCD/FID</td>
<td>1.30 (0.02, 41.56)</td>
</tr>
</tbody>
</table>
Credible intervals are the Bayesian equivalent of confidence intervals.

The residual deviance was 79.3, which is quite close to the number of data points of 77, implying that the model fits the data well.

Major bleeding results

A network meta-analysis for major bleeding was conducted using studies across hip fracture surgery, hip replacement surgery, knee replacement surgery, general medical patients and general surgical patients.

One hundred and twenty eight (128) studies were included in the analysis of which:

- 10 studies were in medical patients\(^{45,121,191,256,257,350,387,390,394,579}\),
- 48 studies were in general surgery patients\(^{10,14,29,40,50,52,72,75,76,92,113,199,210,227,230,238,262,266,267,269,280,283,321,324,329,358,366,385,439,496,499,503,504,516,517,530,552,553,570,575,588,589,633,639,641,645,657,667,703,711,713}\),
- 28 studies were in elective hip replacement patients\(^{126,129,151,153,174,188,195,201,202,243,260,293,299,377,380,400,409,421,465,527,573,574,635,650,651,659,684}\),
- 9 studies were in patients undergoing hip fracture surgery\(^{175,178,204,248,463,533,609,704,715}\),
- 15 studies were in elective knee replacement patients\(^{36,66,130,186,201,202,274,388,399,436,476,479}\),
- 7 studies were in mixed orthopaedic surgery patients\(^{69,200,242,250,292,459,531}\),
- 11 studies were in mixed surgery patients\(^{54,166,270,271,340,344,396,416,486,568,569,575,585,655}\).

Seven of these studies included three comparison arms\(^{153,299,380,504,533,633,655}\).
Figure 9-11: Network diagram for major bleeding. Numbers indicate the number of studies which contributed results for each comparison.

Table 9-35: Major bleeding – network meta-analysis results (pooled across all population subgroups)

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (high dose)</td>
<td>0.83 (0.32, 1.98)</td>
</tr>
<tr>
<td>VKA</td>
<td>2.30 (1.54, 3.44)</td>
</tr>
<tr>
<td>LMWH</td>
<td>2.33 (1.74, 3.17)</td>
</tr>
<tr>
<td>UFH</td>
<td>2.66 (1.99, 3.56)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>4.14 (2.41, 7.30)</td>
</tr>
<tr>
<td>Aspirin (high dose) + UFH</td>
<td>5.03 (1.89, 13.27)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals.
The residual deviance was 291.5, which is quite close to the number of data points of 263, implying that the model fits the data well.

Figure 9-12: Major bleeding – network meta-analysis results of interventions compared to no prophylaxis (pooled across all population subgroups)
9.4 Cost-effectiveness evidence

9.4.1 Introduction

General assumptions and methods for model are described in chapter 4.

The results are driven by the network meta-analysis above. Other data used for the cost-effectiveness analysis which are specific to general surgical patients can be found in Table 9-36 and

Table 9-36: Baseline risk and other population specific parameters used in the economic model for general and other internal organ surgery patients

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Source</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>Systematic review of RCTs (b) (weighted mean)</td>
<td>60</td>
</tr>
<tr>
<td>% Male</td>
<td>Systematic review of RCTs (b)</td>
<td>50%</td>
</tr>
<tr>
<td>Standardised Mortality Ratio (a) (1 year)</td>
<td>Assumed</td>
<td>100%</td>
</tr>
<tr>
<td>Mean duration of prophylaxis (days)</td>
<td>Systematic review of RCTs (b)</td>
<td>7</td>
</tr>
<tr>
<td>Proportion of DVTs that are symptomatic (Ratio of symptomatic DVTs to all DVTs)</td>
<td>Systematic review of RCTs (b)</td>
<td>6.2% (40/644)</td>
</tr>
<tr>
<td>Major Bleed Fatality Rate (c)</td>
<td>Systematic review of RCTs</td>
<td>0.8% (5/632)</td>
</tr>
<tr>
<td>PE Fatality Rate (d)</td>
<td>Systematic review of RCTs</td>
<td>6.0% (11/184)</td>
</tr>
<tr>
<td>DVT risk</td>
<td>Systematic review of RCTs (b)</td>
<td>20.9%</td>
</tr>
<tr>
<td>Symptomatic PE risk</td>
<td>Systematic review of RCTs (b)</td>
<td>1.3%</td>
</tr>
<tr>
<td>Major bleeding risk</td>
<td>Systematic review of RCTs (b)</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

(a) Ratio of the death rate in the surgical group compared with the death rate in the general population, adjusting for age and sex

(b) This refers to the systematic review of RCTs for the current guideline

(c) Fatal major bleeds divided by all major bleeds

(d) Fatal PEs divided by all symptomatic PEs

Table 9-37: Weights used for events in the base case analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Cost (£)</th>
<th>QALYs lost</th>
<th>Net loss (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT Asymptomatic</td>
<td>0</td>
<td>0.0000</td>
<td>0</td>
</tr>
<tr>
<td>DVT Symptomatic</td>
<td>576</td>
<td>0.0035</td>
<td>645</td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td>9,998</td>
<td>0.2700</td>
<td>15,397</td>
</tr>
<tr>
<td>Chronic pulmonary hypertension</td>
<td>69,123</td>
<td>9.2206</td>
<td>253,534</td>
</tr>
<tr>
<td>Pulmonary embolism - fatal</td>
<td>0</td>
<td>12.5578</td>
<td>251,156</td>
</tr>
<tr>
<td>Pulmonary embolism - symptomatic</td>
<td>2,521</td>
<td>0.0041</td>
<td>2,603</td>
</tr>
<tr>
<td>Major bleeding - No long-term sequlae</td>
<td>827</td>
<td>0.0267</td>
<td>1,361</td>
</tr>
<tr>
<td>Major bleeding - Stroke</td>
<td>23,797</td>
<td>10.4943</td>
<td>233,683</td>
</tr>
<tr>
<td>Major bleeding - fatal</td>
<td>0</td>
<td>12.5578</td>
<td>251,156</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopaenia (sensitivity analysis only)</td>
<td>2,714</td>
<td>1.8750</td>
<td>40,213</td>
</tr>
</tbody>
</table>

QALY = Quality-adjusted life-year

(a) Net loss is the sum of the resource cost plus the QALY loss multiplied £20,000
9.4.2 Base case results

Event rates by strategy can be found in Appendix G.

9.4.2.1 Standard duration prophylaxis results

Table 9-38: Base case results – deterministic and probabilistic results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Deterministic INB</th>
<th>Probabilistic INB</th>
<th>% of simulations where strategy was most cost effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td>489</td>
<td>488</td>
<td>38.3%</td>
</tr>
<tr>
<td>IPCD-FID</td>
<td>463</td>
<td>464</td>
<td>24.5%</td>
</tr>
<tr>
<td>UFH_plus_GCS</td>
<td>409</td>
<td>408</td>
<td>4.1%</td>
</tr>
<tr>
<td>LMWH_plus_GCS</td>
<td>349</td>
<td>348</td>
<td>10.1%</td>
</tr>
<tr>
<td>LMWH</td>
<td>348</td>
<td>347</td>
<td>0.3%</td>
</tr>
<tr>
<td>AspirinHD</td>
<td>314</td>
<td>314</td>
<td>0.7%</td>
</tr>
<tr>
<td>UFH</td>
<td>241</td>
<td>241</td>
<td>0.0%</td>
</tr>
<tr>
<td>Fondaparinux_plus_IPCD-FID</td>
<td>130</td>
<td>127</td>
<td>0.2%</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>106</td>
<td>104</td>
<td>0.5%</td>
</tr>
<tr>
<td>VKA</td>
<td>317</td>
<td>75</td>
<td>0.0%</td>
</tr>
<tr>
<td>Nil</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>UFH_plus_AspirinHD</td>
<td>-70</td>
<td>-694</td>
<td>21.3%</td>
</tr>
</tbody>
</table>

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost effective overall.

Figure 9-13: Base case results of the cost effectiveness analysis for general surgery and other internal organ patients: standard duration prophylaxis

£2,400 per QALY gained
‘+’ indicates two interventions used in parallel, UFH=unfractionated heparin, GCS=anti-embolism stockings, LMWH=low molecular weight heparin, IPC/FID=intermittent pneumatic compression device or foot impulse device, warf= vitamin K antagonist, fon=fondaparinux, nil=no prophylaxis, AspHD=high dose aspirin (>300mg)

9.4.3 Base case results – post-discharge prophylaxis

There was one study which investigated extended prophylaxis post-discharge. This study compared LMWH with no prophylaxis and randomised patients 10 -12 days after surgery.

Table 9-39: Results for study post discharge comparing LMWH with no prophylaxis

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Deterministic INB</th>
<th>Probabilistic INB</th>
<th>% of simulations where strategy was most cost effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH</td>
<td>123</td>
<td>49</td>
<td>77.5%</td>
</tr>
<tr>
<td>Nil</td>
<td>0</td>
<td>0</td>
<td>22.5%</td>
</tr>
</tbody>
</table>

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost effective overall

Figure 9-14: Base case results of the cost effectiveness analysis for general surgery and other internal organ patients: post-discharge prophylaxis
### 9.4.4 Deterministic sensitivity analysis

**Table 9-40: Deterministic sensitivity analysis results**

<table>
<thead>
<tr>
<th>Factors changed within the Model</th>
<th>Most Cost Effective Strategy</th>
<th>Standard duration prophylaxis</th>
<th>Post Discharge (LMWH vs Nil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>Base case (probabilistic)</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic Thromboembolic Pulmonary Hypertension and Post Thrombotic Syndrome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% Chronic Thromboembolic Pulmonary Hypertension</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>0.5% Chronic Thromboembolic Pulmonary Hypertension</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>1% Chronic Thromboembolic Pulmonary Hypertension</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>0% Chronic Thromboembolic Pulmonary Hypertension and 0% Post Thrombotic Syndrome</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>High Post Thrombotic Syndrome rate (e.g. 30% after symptomatic DVT and 21% after asymptomatic DVT)</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>Low Post Thrombotic Syndrome (e.g. 15% after symptomatic DVT and 8% after asymptomatic DVT)</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>Low cost for Post Thrombotic Syndrome</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>High cost for Post Thrombotic Syndrome</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>High cost for Chronic Thromboembolic Pulmonary Hypertension</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td><strong>Other Sensitivity Analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.8%, UFH=0.8%)</td>
<td>GCS</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.2%, UFH=2.6%)</td>
<td>GCS</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Using population specific pulmonary embolism relative risk</td>
<td>High dose Aspirin</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Using population specific major bleeding relative risks</td>
<td>GCS</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Low aspirin major bleeding relative risk from Network Meta-analysis (RR = 0.5)</td>
<td>GCS</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>High aspirin major bleeding relative risk from aspirin vs. nil arms (RR = 1.3)</td>
<td>GCS</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Discounted LMWH cost = £1</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>Fatality after PE = 10%</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>Fatality after Major Bleeding = 5%</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>Foot Impulse Device (consumable: £40, pump: £0)</td>
<td>GCS</td>
<td>N / A</td>
<td></td>
</tr>
<tr>
<td>Increased NICE threshold (£30,000/QALY)</td>
<td>GCS</td>
<td>LMWH</td>
<td></td>
</tr>
</tbody>
</table>

QALY=quality-adjusted life-year, N/A=not applicable
Table 9-41: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding

<table>
<thead>
<tr>
<th>PE risk</th>
<th>Major bleeding risk</th>
<th>0%</th>
<th>0.5%</th>
<th>1%</th>
<th>1.5%</th>
<th>2%</th>
<th>2.5%</th>
<th>3%</th>
<th>3.5%</th>
<th>4%</th>
<th>4.5%</th>
<th>5%</th>
<th>5.5%</th>
<th>6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>UFH + GCS</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
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<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
<td></td>
</tr>
<tr>
<td>0.5%</td>
<td>UFH + GCS</td>
<td>UFH</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
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<td>GCS</td>
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<td>GCS</td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>UFH + GCS</td>
<td>UFH</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
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<tr>
<td>1.5%</td>
<td>UFH + GCS</td>
<td>UFH</td>
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</tr>
<tr>
<td>2%</td>
<td>UFH + GCS</td>
<td>UFH</td>
<td>GCS</td>
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<td>GCS</td>
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<tr>
<td>2.5%</td>
<td>UFH + GCS</td>
<td>UFH</td>
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<td></td>
</tr>
<tr>
<td>3%</td>
<td>UFH + GCS</td>
<td>UFH</td>
<td>GCS</td>
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<td>GCS</td>
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<tr>
<td>3.5%</td>
<td>UFH + GCS</td>
<td>UFH</td>
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</tr>
<tr>
<td>4%</td>
<td>UFH + GCS</td>
<td>UFH</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
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<tr>
<td>4.5%</td>
<td>UFH + GCS</td>
<td>UFH</td>
<td>GCS</td>
<td>GCS</td>
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<td></td>
</tr>
<tr>
<td>5%</td>
<td>UFH + GCS</td>
<td>UFH</td>
<td>GCS</td>
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<td>GCS</td>
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<tr>
<td>5.5%</td>
<td>UFH + GCS</td>
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</tr>
<tr>
<td>6%</td>
<td>UFH + GCS</td>
<td>UFH</td>
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<td></td>
</tr>
</tbody>
</table>

Table 9-42: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: post-discharge

<table>
<thead>
<tr>
<th>PE risk</th>
<th>Major bleeding risk</th>
<th>0%</th>
<th>0.5%</th>
<th>1%</th>
<th>1.5%</th>
<th>2%</th>
<th>2.5%</th>
<th>3%</th>
<th>3.5%</th>
<th>4%</th>
<th>4.5%</th>
<th>5%</th>
<th>5.5%</th>
<th>6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>0.5%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>1.5%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>2.5%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
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<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>3%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
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<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>3.5%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>4%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>4.5%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>5%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
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<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>5.5%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
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<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td>6%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
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<td>LMWH</td>
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<td>LMWH</td>
<td></td>
</tr>
</tbody>
</table>

In a threshold sensitivity analysis, we found that post-discharge prophylaxis was no longer cost-effective if greater than 37% of patients require district nurse visits to deliver their prophylaxis.
### 9.4.5 Conclusion

Anti-embolism / Graduated Compression Stockings (GCS) alone was the most cost effective standard duration strategy for general surgery patients in both the deterministic base case and in the probabilistic sensitivity analysis. GCS was the most effective at increasing QALYs (as well as the most cost-effective strategy) since the QALYs lost due to major bleeding seemed to offset the QALY benefits of adjunctive drug prophylaxis. There was only one situation in the deterministic sensitivity analysis in which the most cost effective strategy changed: high dose aspirin alone was the most cost effective strategy when the population specific pulmonary embolism relative risks were used.

The results were highly sensitive to baseline risk of major bleeding and baseline risk of pulmonary embolism (Table 9-41). For patients at lowest risk of major bleeding, we find that combination prophylaxis is cost-effective, rather than mechanical prophylaxis alone.

Post discharge, LMWH was cost effective compared to no VTE prophylaxis in the base case analysis. This was based on trials which included mainly cancer surgery patients. This result was consistent for all deterministic sensitivity analyses. In the probabilistic sensitivity analysis, LMWH was more cost-effective in 77% of the 5000 simulations of the probabilistic sensitivity analysis. To summarise, post-discharge VTE prophylaxis for this population was cost-effective and the result was insensitive to the parameters used in the sensitivity analysis. However, a major limitation of this model was that we assumed life expectancy was the same as the general population aged 60, whereas, having cancer patients’ life expectancy is likely to be lower. In a sensitivity analysis it was found that life expectancy would have to be halved for it to no longer be cost-effective for these patients (Table 9-43).

### 9.5 Patient views

A total of six studies conducted among surgical patients were identified (Evidence Table 61, Appendix D). A summary of these studies is presented below. For patient views about specific thromboprophylaxis agents, see section 6.6.

Two studies looked into use of anti-embolism stockings / graduated compression stockings (GCS) (Evidence Table 61, Appendix D). One was a qualitative study which looked into the experience of patients who had recently worn GCS during their hospital stay. This study found...
that patients lacked information about how to wear the stockings and poor fitting was a problem (chapter 6 and chapter 32). Another observational study conducted in the UK found that overall, 39% of patients wore GCS in a correct manner, and only 4% adhered to the hospital policy of wearing thigh-length stockings.

One study randomised 207 women undergoing surgery for gynaecological malignancy to LMWH or IPCD. Fewer patients (4%) receiving LMWH reported discomfort or side effects compared to the IPCD group (26%).

One study observed that adherence to IPCD in surgical wards was around 60%. Another study where patients used both anti-embolism stockings and IPCD found that only 19% and 25.5% of patients surveyed were wearing correctly fitted IPCD and anti-embolism stockings respectively. In both of these studies, many patients were not wearing correctly fitted IPCDs or stockings (section 6.6).

For patient views about specific prophylaxis agents, see section 6.6.
## 9.6 Summary of evidence

Table 9-44: Summary of evidence from network meta-analysis results for DVT, symptomatic pulmonary embolism and major bleeding outcomes.

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
<th>DVT</th>
<th>PE</th>
<th>MB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis vs no prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td>no prophylaxis</td>
<td>GCS</td>
<td>Not sig</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>IPCD/FID</td>
<td>no prophylaxis</td>
<td>IPCD/FID</td>
<td>Not sig</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>no prophylaxis</td>
<td>Fondaparinux</td>
<td>Not sig</td>
<td></td>
<td>No prophylaxis</td>
</tr>
<tr>
<td>LMWH</td>
<td>no prophylaxis</td>
<td>LMWH</td>
<td></td>
<td></td>
<td>No prophylaxis</td>
</tr>
<tr>
<td>UFH</td>
<td>no prophylaxis</td>
<td>UFH</td>
<td>Not sig</td>
<td></td>
<td>No prophylaxis</td>
</tr>
<tr>
<td>VKA (adjusted dose)</td>
<td>no prophylaxis</td>
<td>VKA</td>
<td>Not sig</td>
<td></td>
<td>No prophylaxis</td>
</tr>
<tr>
<td>Aspirin (high-dose)</td>
<td>no prophylaxis</td>
<td>Aspirin</td>
<td></td>
<td></td>
<td>Not Sig</td>
</tr>
<tr>
<td>Fondaparinux + IPCD/FID</td>
<td>no prophylaxis</td>
<td>Fondaparinux + IPCD/FID</td>
<td>Not sig</td>
<td></td>
<td>No prophylaxis</td>
</tr>
<tr>
<td>LMWH + GCS</td>
<td>no prophylaxis</td>
<td>LMWH + GCS</td>
<td>-</td>
<td></td>
<td>No prophylaxis</td>
</tr>
<tr>
<td>UFH + GCS</td>
<td>no prophylaxis</td>
<td>UFH + GCS</td>
<td>Not sig</td>
<td></td>
<td>No prophylaxis</td>
</tr>
<tr>
<td>UFH + aspirin (high-dose)</td>
<td>no prophylaxis</td>
<td>UFH + aspirin</td>
<td>UFH + aspirin</td>
<td></td>
<td>No prophylaxis</td>
</tr>
</tbody>
</table>

Cost-effectiveness results

GCS was the most clinically effective and cost effective strategy. At lower levels of bleeding risk, combination prophylaxis (e.g. UFH+GCS) was most cost-effective.

There was one situation in the deterministic sensitivity analysis in which the most cost effective strategy changed was that high dose aspirin alone was the most cost effective strategy when the population specific pulmonary embolism relative risks were used.

Post discharge LMWH was cost effective in cancer surgery patients

---

The VTE prophylaxis strategy which is significantly more effective in reducing DVT or PE, or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. No event = outcomes reported in study(ies) but no events were reported. ‘-’ = not reported. MB = Major bleeding
### 9.7 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Offer VTE prophylaxis to patients undergoing gastrointestinal surgery who are assessed to be at increased risk of VTE (see section 5.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Start mechanical VTE prophylaxis at admission. Choose any one of:</td>
</tr>
<tr>
<td></td>
<td>- anti-embolism stockings (thigh or knee length)</td>
</tr>
<tr>
<td></td>
<td>- foot impulse devices</td>
</tr>
<tr>
<td></td>
<td>- intermittent pneumatic compression devices (thigh or knee length)</td>
</tr>
<tr>
<td></td>
<td>Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.</td>
</tr>
<tr>
<td></td>
<td>- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account patient factors and according to clinical judgement. Choose any one of:</td>
</tr>
<tr>
<td></td>
<td>- fondaparinux sodium</td>
</tr>
<tr>
<td></td>
<td>- LMWH</td>
</tr>
<tr>
<td></td>
<td>- UFH (for patients with renal failure).</td>
</tr>
<tr>
<td></td>
<td>Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Offer VTE prophylaxis to patients undergoing gynaecological, thoracic or urologic surgery who are assessed to be at increased risk of VTE (see section 5.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Start mechanical VTE prophylaxis at admission. Choose any one of:</td>
</tr>
<tr>
<td></td>
<td>- anti-embolism stockings (thigh or knee length)</td>
</tr>
<tr>
<td></td>
<td>- foot impulse devices</td>
</tr>
<tr>
<td></td>
<td>- intermittent pneumatic compression devices (thigh or knee length)</td>
</tr>
<tr>
<td></td>
<td>Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.</td>
</tr>
<tr>
<td></td>
<td>- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:</td>
</tr>
</tbody>
</table>
- LMWH
- UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

**Recommendation (From section 5.9)**

Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more of the risk factors shown in Box 1.

**Box 1 – VTE risk factor box**

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m\(^2\))
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

**Relative values of different outcomes**

The outcomes included in the economic model were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). Each of these events had a cost and loss of quality adjusted life year associated with it, the details of which are provided in the methods of cost effectiveness.
Trade off between clinical benefit and harms

The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. In the decision model base case, where the baseline risk of major bleeding was 1.4%, the number of deaths was the same for mechanical-only and combination prophylaxis but the QALYs gained were highest for mechanical-only. The QALY benefits from drug prophylaxis did not outweigh the QALYs lost due to bleeding. However, when the risk was lower, drug prophylaxis or combination prophylaxis increased QALYs.

Economic considerations

Mechanical-only prophylaxis was the most effective (at increasing QALYs) and most cost-effective strategy for general surgery patients. A combination of mechanical prophylaxis and heparin was cost-effective at a lower baseline risk of major bleeding (1.0% compared with 1.4%).

These results were extrapolated to the other patient groups on the basis that their baseline risks were similar.

Quality of evidence

There are 146 RCTs covering this group of patients. All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

Many of these are old, particularly the studies comparing prophylaxis with no prophylaxis. Surgical practice may have changed since these trials were published.

There was little direct evidence for pulmonary embolism as most the trials screened for DVT and may have reduced the risk of pulmonary embolism from developing.

Most of the pooled data investigated prophylaxis in general surgical patients; there were fewer studies in gynaecological patients and less still in urological and thoracic surgery patients. There was no evidence to suggest a difference in the effectiveness of prophylaxis in these groups but these data may not be directly applicable.

Other considerations

The average duration of VTE prophylaxis for ‘general surgery’ patients in the trials was 7 days. This concurs with the licensing conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. It is known in many cases surgical patients are discharged within 5 days of their operation. The guideline development group felt that the risk of VTE may still persist beyond this time period and prophylaxis may be effective after discharge. No economic
analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given.

There are other considerations for each agent when choosing pharmacological prophylaxis (see section 6.8). UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH or fondaparinux. Fondaparinux is a synthetic alternative to heparins which are derived from porcine products, although there may be concerns with an increased risk of bleeding. Fondaparinux only licensed in surgery for major orthopaedic procedures of the lower limb and patients undergoing major abdominal surgery. Consequently, it is not offered as an option for gynaecological, urological or thoracic surgery.

<table>
<thead>
<tr>
<th><strong>Recommendation</strong></th>
<th>Offer VTE prophylaxis to patients undergoing bariatric surgery.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>● Start mechanical VTE prophylaxis at admission. Choose any one of:</td>
</tr>
<tr>
<td></td>
<td>- anti-embolism stockings (thigh or knee length)</td>
</tr>
<tr>
<td></td>
<td>- foot impulse devices</td>
</tr>
<tr>
<td></td>
<td>- intermittent pneumatic compression devices (thigh or knee length)</td>
</tr>
<tr>
<td></td>
<td>Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.</td>
</tr>
<tr>
<td></td>
<td>● Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:</td>
</tr>
<tr>
<td></td>
<td>- fondaparinux sodium</td>
</tr>
<tr>
<td></td>
<td>- LMWH</td>
</tr>
<tr>
<td></td>
<td>- UFH (for patients with renal failure).</td>
</tr>
<tr>
<td></td>
<td>Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).</td>
</tr>
</tbody>
</table>

| **Relative values of different outcomes** | The outcomes included in the economic model for all general surgery patients were thromboembolic events (asymptomatic |
| **Trade off between clinical benefit and harms** | The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism |
were considered against the risk of major bleeding. There is an increased risk of VTE in this group as all patients are obese.

**Economic considerations**

There is no relevant cost-effectiveness evidence specifically for this population subgroup. However, a combination of drug and mechanical prophylaxis was found to be cost-effective for general surgery patients where the risk of major bleeding is less than 1% (Chapter 9.4). It seems likely that combination prophylaxis will also be cost-effective for bariatric surgery patients who are at elevated risk of VTE and relatively low risk of major bleeding.

**Quality of evidence**

There are no studies specific to bariatric surgery. We extrapolated the results from the model investigating gastrointestinal, gynaecological, urological and thoracic surgery together. This included 146 RCTs. All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

**Other considerations**

The average duration of VTE prophylaxis for ‘general surgery’ patients in the trials was 7 days. This concurs with the licensing conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. It is known in many cases surgical patients are discharged within 5 days of their operation. The guideline development group felt that the risk of VTE may still persist beyond this time period and prophylaxis may be effective after discharge. No economic analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given.

There are other considerations for each agent when choosing pharmacological prophylaxis. UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH or fondaparinux sodium. Fondaparinux sodium is only licensed in surgery for major orthopaedic procedures of the lower limb and patients undergoing major abdominal surgery.

**Recommendation**

Extend pharmacological prophylaxis to 28 days postoperatively for patients who have had major cancer surgery in the abdomen or pelvis.

**Relative values of different outcomes**

The outcomes included in the economic model were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of
VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). Each of these events had a cost and loss of quality adjusted life year associated with it, the details of which are provided in the methods of cost effectiveness chapter.

Trade off between clinical benefit and harms
The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. Our decision model indicated that the QALYs lost due to major bleeding were outweighed by the QALYs gained from drug prophylaxis.

Economic considerations
In our economic analysis, post-discharge prophylaxis with LMWH was cost-effective for cancer surgery patients at £4,400 per QALY gained.

Quality of evidence
There are 3 RCTs covering this group of patients. All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

1 of the RCTs investigated cancer surgery patients, the other 2 were a mixture of cancer surgery patients. Overall, the majority of patients had cancer.

There was little direct evidence for pulmonary embolism as most the trials screened for DVT and may have reduced the risk of pulmonary embolism from developing.

Other considerations
Only trials for LMWH for extended duration prophylaxis in this population had been conducted. In these trial, the average duration of VTE prophylaxis was 28 days.

However, some patients may be contraindicated to LMWH and/or offered one of the other agents. The GDG still considered it important to extend pharmacological prophylaxis for 28 days postoperatively in these cases.
9.7.1 Other recommendations

The specific recommendations for patients undergoing gastrointestinal, gynaecological, thoracic and urological surgery in this chapter should be read in conjunction with other relevant recommendations in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- recommendations about patients in critical care (Section 29.7)

9.8 Summary of recommendations

➢ Offer VTE prophylaxis to patients undergoing gastrointestinal surgery who are assessed to be at increased risk of VTE (see section 5.9)

- Start mechanical VTE prophylaxis at admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:
  - fondaparinux sodium
  - LMWH
  - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Offer VTE prophylaxis to patients undergoing gynaecological, thoracic or urologic surgery who are assessed to be at increased risk of VTE (see section 5.9)

- Start mechanical VTE prophylaxis at admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
- intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Offer VTE prophylaxis to patients undergoing bariatric surgery.

- Start mechanical VTE prophylaxis at admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:
  - fondaparinux sodium
  - LMWH
  - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more risk factors in Box 1.
Extend pharmacological prophylaxis to 28 days postoperatively for patients who have had major cancer surgery in the abdomen or pelvis.

Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).
10 Elective hip replacement

10.1 Introduction

Elective total hip replacement is associated with an increased risk of VTE with a particular concern about the reported increased incidence of proximal DVT. The surgery covered in this section of the guideline is performed for primary or secondary degenerative joint disease. Other indications, for example, following fractures of the proximal femur are covered elsewhere. The all risk mortality after hip arthroplasty has been reported as 0.7% \(^{481}\) with a baseline risk of DVT in the absence of prophylaxis of 44% (chapter 5) and an incidence of pulmonary embolism of 3% (chapter 5).

An objection of using chemical VTE prophylaxis is the increased risk of bleeding as a result of anticoagulation. A balance of the benefit of VTE prophylaxis has to be weighed against the risks and consequences of a post-operative bleed. The baseline risk of major or significant bleeding in the absence of chemical VTE prophylaxis is 2% (chapter 5). However, the potential risks of major bleeding including re-operation and its possible link to infection are uncertain with the evidence available and should be clarified with further research.

This guideline is aimed at providing pre-, peri- and post-operative guidance for the reduction of VTE and its sequelae following elective hip replacement. The Guideline takes into account the early complications of VTE and its prophylaxis (e.g. bleeding, PE) and late complications including post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension.

10.2 Evidence of methods of prophylaxis

There were 72 trials included in this section \(^{12,26,28,47,51,126,129,132,142,151-153,174,188,190,193,195,198,201,202,207,209,243,249,259-261,272,293,296,299,327,330,377-380,400,410,420,421,433,465,476,479,507,523,526,527,534,565,573,574,582,587,605,612,619,627,635,638,650,651,659,673,675,684,702,705,708}\. Most of RCTs had their data extracted from systematic reviews. Where applicable the study is cited in the evidence table for that review. Eight systematic reviews included RCTs covering patients having total hip replacement\(^{15,21,125,294,355,451,557,719}\).

One paper reported on two trials \(^{421}\) and 5 trials had compared 3 interventions \(^{12,153,380,619,702}\).

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).
10.2.1 Summary of comparisons identified for any main outcomes

<table>
<thead>
<tr>
<th></th>
<th>No. of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td></td>
</tr>
<tr>
<td>IPCD/FID</td>
<td>2</td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>4 6 1 1 (a)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>11 1</td>
</tr>
<tr>
<td>VKA</td>
<td>1 1</td>
</tr>
<tr>
<td>High dose aspirin</td>
<td>6</td>
</tr>
<tr>
<td>Low dose aspirin</td>
<td>1</td>
</tr>
<tr>
<td>GCS + IPCD/FID</td>
<td>1</td>
</tr>
<tr>
<td>Mech + pharm</td>
<td>5 1 1 2 4 5</td>
</tr>
<tr>
<td>Other comparisons</td>
<td>3 1 2 2 1</td>
</tr>
</tbody>
</table>

**Figure 10-15: Number of studies which compared various types of prophylaxis methods.**

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

(a) Extended duration prophylaxis from surgery to 28-35 days
(b) One of these studies compared extended duration prophylaxis from surgery for 35 days, the other study investigated extended duration rivaroxaban (35 days) compared with standard duration LMWH (14 days)

10.2.2 Results from pairwise comparisons

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Interventions</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID vs nil</td>
<td>2</td>
<td>51/195</td>
<td>102/205</td>
<td>0.53 (0.41, 0.70)</td>
<td>-0.24 (-0.33, -0.14)</td>
<td>ET: 24 FP: 4</td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>4</td>
<td>49/252</td>
<td>100/240</td>
<td>0.40 (0.22, 0.71)</td>
<td>-0.22 (-0.33, -0.12)</td>
<td>ET: 26 FP: 13</td>
</tr>
<tr>
<td>UFH vs nil</td>
<td>8</td>
<td>67/257</td>
<td>116/258</td>
<td>0.53 (b) (0.32, 0.89)</td>
<td>-0.20 (-0.31, -0.09)</td>
<td>ET: 27 FP: 17</td>
</tr>
<tr>
<td>High dose aspirin vs nil</td>
<td>5</td>
<td>63/183</td>
<td>102/200</td>
<td>0.74 (c) (0.48, 1.14)</td>
<td>-0.16 (-0.29, -0.02)</td>
<td>ET: 29 FP: 28</td>
</tr>
<tr>
<td>Low dose aspirin vs nil</td>
<td>1</td>
<td>1/30</td>
<td>11/30</td>
<td>0.09 (0.01, 0.66)</td>
<td>-0.33 (-0.52, -0.15)</td>
<td>ET: 29 FP: 32</td>
</tr>
<tr>
<td>Comparison</td>
<td>No. of studies</td>
<td>Intervention - tion</td>
<td>Control</td>
<td>Relative risk</td>
<td>Absolute effect</td>
<td>Forest plots &amp; Evidence tables</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td><strong>Single proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID vs Vitamin K antagonist</td>
<td>1</td>
<td>11/66</td>
<td>12/72</td>
<td>1.00 (0.47, 2.11)</td>
<td>0.00 (-0.12, 0.12)</td>
<td>Et: 37, Fp: 95</td>
</tr>
<tr>
<td>Dabigatran vs LMWH(d)</td>
<td>1</td>
<td>45/880</td>
<td>58/897</td>
<td>0.80 (0.55, 1.18)</td>
<td>-0.01 (-0.03, 0.01)</td>
<td>Et: 476, Fp: 41</td>
</tr>
<tr>
<td>Rivaroxaban vs LMWH (e)</td>
<td>2</td>
<td>26/2459</td>
<td>124/2427</td>
<td>0.21 (0.14, 0.32)</td>
<td>-0.05 (-0.09, 0.00)</td>
<td>Et: 479, Fp: 261</td>
</tr>
<tr>
<td>LMWH vs UFH</td>
<td>10</td>
<td>191/1210</td>
<td>227/1045</td>
<td>0.76 (0.61, 0.93)</td>
<td>-0.05 (-0.08, -0.02)</td>
<td>Et: 32, Fp: 48</td>
</tr>
<tr>
<td>VKA vs LMWH 195,293</td>
<td>2</td>
<td>130/52</td>
<td>108/86</td>
<td>1.94 (1.53, 2.44)</td>
<td>0.12 (0.07, 0.16)</td>
<td>Et: 34, Fp: 57</td>
</tr>
<tr>
<td>Aspirin (high dose) vs UFH 133</td>
<td>1</td>
<td>10/20</td>
<td>1/20</td>
<td>10.0 (1.41, 70.99)</td>
<td>0.45 (0.21, 0.69)</td>
<td>Et: 36, Fp: 64</td>
</tr>
<tr>
<td>Aspirin (low dose) vs UFH 708</td>
<td>1</td>
<td>7/19</td>
<td>10/25</td>
<td>0.92 (0.43, 1.97)</td>
<td>-0.03 (-0.32, 0.26)</td>
<td>Et: 36, Fp: 68</td>
</tr>
<tr>
<td>Aspirin (high dose) vs. Aspirin (low dose) 1,2,3,59</td>
<td>2</td>
<td>31/78</td>
<td>27/73</td>
<td>1.01 (0.73, 1.41)</td>
<td>0.03 (-0.07, 0.12)</td>
<td>Et: 56, Fp: 78</td>
</tr>
<tr>
<td><strong>Double proph vs single</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID + GCS vs GCS 190</td>
<td>1</td>
<td>4/39</td>
<td>16/40</td>
<td>0.26 (0.09, 0.70)</td>
<td>-0.30 (-0.48, -0.12)</td>
<td>Et: 39, Fp: 117</td>
</tr>
<tr>
<td>Asp (HD) + UFH vs UFH 188</td>
<td>1</td>
<td>4/20</td>
<td>4/20</td>
<td>1.00 (0.29, 3.45)</td>
<td>0.00 (-0.25, 0.25)</td>
<td>Et: 42, Fp: 162</td>
</tr>
<tr>
<td>UFH + GCS vs GCS 465</td>
<td>1</td>
<td>8/35</td>
<td>19/32</td>
<td>0.38 (0.20, 0.75)</td>
<td>0.00 (-0.26, 0.26)</td>
<td>Et: 27, Fp: 142</td>
</tr>
<tr>
<td>LMWH + GCS vs GCS 202,379,373,673</td>
<td>4</td>
<td>128/50</td>
<td>0</td>
<td>141/336</td>
<td>0.62 (0.51, 0.76)</td>
<td>-0.17 (-0.23, -0.10)</td>
</tr>
<tr>
<td>Vitamin K antagonist + GCS vs GCS 299</td>
<td>1</td>
<td>3/17</td>
<td>4/19</td>
<td>0.84 (0.22, 3.22)</td>
<td>-0.03 (-0.29, 0.22)</td>
<td>Et: 41, Fp: 155</td>
</tr>
<tr>
<td>GCS + LMWH vs LMWH 330</td>
<td>1</td>
<td>8/32</td>
<td>12/32</td>
<td>0.67 (0.32, 1.41)</td>
<td>-0.13 (-0.35, 0.10)</td>
<td>Et: 38, Fp: 107</td>
</tr>
<tr>
<td>IPCD/FID + UFH vs UFH 605</td>
<td>1</td>
<td>6/35</td>
<td>10/35</td>
<td>0.60 (0.24, 1.47)</td>
<td>-0.11 (-0.31, 0.08)</td>
<td>Et: 39, Fp: 120</td>
</tr>
<tr>
<td><strong>Double proph vs double</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID + GCS vs UFH + GCS 382</td>
<td>1</td>
<td>9/67</td>
<td>23/65</td>
<td>0.38 (0.19, 0.76)</td>
<td>-0.22 (-0.36, -0.08)</td>
<td>Et: 50, Fp: 200</td>
</tr>
<tr>
<td>IPCD/FID + GCS vs UFH +LMWH + GCS 673</td>
<td>1</td>
<td>24/136</td>
<td>18/138</td>
<td>1.35 (0.77, 2.38)</td>
<td>0.05 (0.04, 0.13)</td>
<td>Et: 49, Fp: 202</td>
</tr>
<tr>
<td>IPCD/FID + GCS vs VKA + GCS 28,193</td>
<td>2</td>
<td>29/148</td>
<td>44/148</td>
<td>0.49 (0.13, 1.89)</td>
<td>-0.12 (-0.28, 0.04)</td>
<td>Et: 48, Fp: 207</td>
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<tr>
<td>Fondaparinux + GCS vs LMWH + GCS 377,651</td>
<td>2</td>
<td>80/169</td>
<td>2</td>
<td>148/1714</td>
<td>0.55 (0.35, 0.85)</td>
<td>-0.04 (-0.06, -0.01)</td>
</tr>
<tr>
<td>LMWH + GCS vs UFH + GCS 635</td>
<td>1</td>
<td>45/136</td>
<td>47/137</td>
<td>0.96 (0.69, 1.35)</td>
<td>-0.01 (-0.12, 0.10)</td>
<td>Et: 45, Fp: 174</td>
</tr>
<tr>
<td>VKA + GCS vs Asp (HD) + GCS 260</td>
<td>1</td>
<td>10/55</td>
<td>18/51</td>
<td>0.52 (0.26, 1.01)</td>
<td>-0.17 (-0.34, -0.01)</td>
<td>Et: 35, Fp: 196</td>
</tr>
<tr>
<td><strong>Other Comparisons</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FID vs UFH then Asp (HD) 619</td>
<td>1</td>
<td>0/25</td>
<td>5/25</td>
<td>0.09 (0.01, 1.56)</td>
<td>-0.20 (-0.37, 0.03)</td>
<td>Et: 37, Fp: 93</td>
</tr>
<tr>
<td>UFH then Asp (HD) + FID vs FID + 619</td>
<td>1</td>
<td>0/25</td>
<td>0/25</td>
<td>0.09 (0.01, 1.56)</td>
<td>-0.00 (-0.07, 0.07)</td>
<td>Et: 37, Fp: 153</td>
</tr>
<tr>
<td>FID vs UFH then Asp (HD) vs UFH then Asp (HD) 619</td>
<td>1</td>
<td>0/25</td>
<td>5/25</td>
<td>0.09 (0.01, 1.56)</td>
<td>-0.20 (-0.37, 0.03)</td>
<td>Et: 39, Fp: 129</td>
</tr>
<tr>
<td>LMWH then FID + GCS vs LMWH + GCS 523</td>
<td>1</td>
<td>3/100</td>
<td>6/100</td>
<td>0.50 (0.13, 1.94)</td>
<td>-0.03 (-0.09, 0.03)</td>
<td>Et: 51, Fp: 214</td>
</tr>
</tbody>
</table>
### Table 10-46: Pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proph vs no proph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID vs nil 296</td>
<td>1</td>
<td>1/152</td>
<td>1/158</td>
<td>1.04 (0.07, 16.47)</td>
<td>0.00 (-0.02, 0.02)</td>
<td>ET: 24, FP: 5</td>
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<tr>
<td>LMWH vs nil 638,630,705</td>
<td>3</td>
<td>1/158</td>
<td>4/154</td>
<td>0.33 (0.05, 2.02)</td>
<td>-0.01 (-0.04, 0.02)</td>
<td>ET: 26, FP: 14</td>
</tr>
<tr>
<td>UFH vs nil 51,410,684</td>
<td>3</td>
<td>20/143</td>
<td>19/140</td>
<td>0.88 (0.30, 2.61)</td>
<td>-0.01 (-0.08, 0.05)</td>
<td>ET: 27, FP: 18</td>
</tr>
<tr>
<td>High dose aspirin vs nil 12,261,433,587,612</td>
<td>6</td>
<td>2/189</td>
<td>7/209</td>
<td>0.42 (0.11, 1.56)</td>
<td>-0.02 (-0.05, 0.01)</td>
<td>ET: 29, FP: 29</td>
</tr>
<tr>
<td>Low dose aspirin vs nil 12</td>
<td>1</td>
<td>0/30</td>
<td>1/30</td>
<td>0.33 (0.01, 7.87)</td>
<td>-0.03 (-0.12, 0.05)</td>
<td>ET: 29, FP: 33</td>
</tr>
<tr>
<td><strong>Single proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID vs LMWH 627</td>
<td>1</td>
<td>0/25</td>
<td>0/25</td>
<td>Not Estimable</td>
<td>0.01 (-0.01, 0.03)</td>
<td>ET: 37, FP: 88</td>
</tr>
<tr>
<td>IPCD/FID vs Vitamin K antagonist 507</td>
<td>1</td>
<td>0/66</td>
<td>0/72</td>
<td>Not Estimable</td>
<td>0.00 (-0.03, 0.03)</td>
<td>ET: 37, FP: 96</td>
</tr>
<tr>
<td>Dabigatran vs LMWH(a) 476</td>
<td>1</td>
<td>5/880</td>
<td>3/897</td>
<td>1.70 (0.41, 7.09)</td>
<td>0.00 (0.00, 0.01)</td>
<td>ET: 476, FP: 42</td>
</tr>
<tr>
<td>Rivaroxaban vs. LMWH(b) 479</td>
<td>2</td>
<td>5/2459</td>
<td>6/2427</td>
<td>0.79 (0.11, 5.87)</td>
<td>0.00 (-0.01, 0.00)</td>
<td>ET: 479, FP: 262</td>
</tr>
<tr>
<td>LMWH vs UFH 26,198,243,327,400,527</td>
<td>6</td>
<td>1/793</td>
<td>8/791</td>
<td>0.34 (0.10, 1.15)</td>
<td>-0.01 (-0.02, 0.00)</td>
<td>ET: 32, FP: 49</td>
</tr>
<tr>
<td>VKA vs LMWH 126</td>
<td>1</td>
<td>12/149</td>
<td>5/151</td>
<td>0.81 (0.38, 1.73)</td>
<td>0.00 (-0.01, 0.00)</td>
<td>ET: 34, FP: 58</td>
</tr>
<tr>
<td>Aspirin (high dose) vs. Aspirin (low dose) 12,239</td>
<td>2</td>
<td>0/78</td>
<td>2/73</td>
<td>0.18 (0.01, 3.64)</td>
<td>-0.02 (-0.07, 0.03)</td>
<td>ET: 56, FP: 79</td>
</tr>
<tr>
<td><strong>Double proph vs single</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH + GCS vs GCS 202,573,673</td>
<td>3</td>
<td>2/414</td>
<td>2/249</td>
<td>0.65 (0.10, 4.37)</td>
<td>0.00 (-0.01, 0.01)</td>
<td>ET: 26, FP: 135</td>
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<tr>
<td>GCS + LMWH vs LMWH 330</td>
<td>1</td>
<td>2/32</td>
<td>3/32</td>
<td>0.67 (0.12, 3.73)</td>
<td>-0.03 (-0.16, 0.10)</td>
<td>ET: 38, FP: 108</td>
</tr>
<tr>
<td>IPCD/FID + UFH vs UFH 605</td>
<td>1</td>
<td>0/35</td>
<td>0/35</td>
<td>Not Estimable</td>
<td>0.00 (-0.05, 0.05)</td>
<td>ET: 39, FP: 121</td>
</tr>
</tbody>
</table>

* FP = forest plot number in Appendix E; ET = evidence table number in Appendix D. Proph = prophylaxis

(a) There is substantial statistical heterogeneity between studies for this population ($I^2$ = 54.4%, $\chi^2$ on 3 df = 6.58, $p$ = 0.09).

(b) There is substantial statistical heterogeneity between studies for this population ($I^2$ = 65.9%, $\chi^2$ on 7 df = 20.52, $p$ = 0.005).

(c) There is substantial statistical heterogeneity between studies for this population ($I^2$ = 53.9%, $\chi^2$ on 4 df = 8.67, $p$ = 0.07).

(d) Extended prophylaxis study. Patients were randomized at surgery and prophylaxis continued for 28-35 days in both arms. Only the results relating to the 220mg dose of Dabigatan was included in this analysis.

(e) Extended prophylaxis study. Patients were randomized at surgery and Rivaroxaban continued for 35 days in one study and 14 days.

(f) There is substantial statistical heterogeneity between studies for this population ($I^2$ = 77.0%, $\chi^2$ on 1 df = 4.35, $p$ = 0.04).

(g) There is substantial statistical heterogeneity between studies for this population ($I^2$ = 63.8%, $\chi^2$ on 1 df = 2.76, $p$ = 0.10).
Double proph vs double

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPCD/FID + GCS vs LMWH + GCS 675</td>
<td>1</td>
<td>1/136</td>
<td>0/138</td>
<td>3.04</td>
<td>(0.13, 74.07)</td>
<td>0.01 (-0.01, 0.03)</td>
</tr>
<tr>
<td>Fondaparinux + GCS vs LMWH + GCS 377,651</td>
<td>2</td>
<td>7/2255</td>
<td>3/2251</td>
<td>2.10</td>
<td>(0.43, 10.37)</td>
<td>0.00 (0.00, 0.01)</td>
</tr>
<tr>
<td>IPCD + Asp (HD) vs GCS Asp (HD) 565</td>
<td>1</td>
<td>0/50</td>
<td>0/50</td>
<td>Not Estimable</td>
<td></td>
<td>0.00 (-0.04, 0.04)</td>
</tr>
<tr>
<td>LMWH + GCS vs UFH + GCS 635</td>
<td>1</td>
<td>2/167</td>
<td>6/168</td>
<td>0.34</td>
<td>(0.07, 1.64)</td>
<td>-0.02 (-0.06, 0.01)</td>
</tr>
<tr>
<td>VKA + GCS vs Asp (HD) + GCS 260</td>
<td>1</td>
<td>0/55</td>
<td>0/51</td>
<td>Not Estimable</td>
<td></td>
<td>0.00 (-0.04, 0.04)</td>
</tr>
</tbody>
</table>

Other Comparisons

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asp (HD) + IPCD + GCS vs IPCD + GCS 702</td>
<td>1</td>
<td>1/72</td>
<td>0/75</td>
<td>3.16</td>
<td>(0.13, 76.44)</td>
<td>0.01 (-0.02, 0.05)</td>
</tr>
<tr>
<td>VKA + GCS + IPCD vs GCS + IPCD 702</td>
<td>1</td>
<td>0/69</td>
<td>0/75</td>
<td>Not Estimable</td>
<td></td>
<td>0.00 (-0.03, 0.03)</td>
</tr>
<tr>
<td>VKA + IPCD + GCS vs Asp + IPCD + GCS 702</td>
<td>1</td>
<td>0/69</td>
<td>1/72</td>
<td>0.35</td>
<td>(0.01, 8.39)</td>
<td>-0.01 (-0.05, 0.02)</td>
</tr>
<tr>
<td>LMWH then FID + GCS vs LMWH + GCS 523</td>
<td>1</td>
<td>0/100</td>
<td>0/100</td>
<td>Not Estimable</td>
<td></td>
<td>0.00 (-0.02, 0.02)</td>
</tr>
</tbody>
</table>

Post Discharge

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH 47,132,42,272,378,526</td>
<td>6</td>
<td>0/923</td>
<td>5/894</td>
<td>0.16</td>
<td>(0.02, 1.35)</td>
<td>0.00 (-0.01, 0.01)</td>
</tr>
<tr>
<td>Vitamin K antagonist 534</td>
<td>1</td>
<td>0/184</td>
<td>1/176</td>
<td>0.32</td>
<td>(0.01, 7.78)</td>
<td>0.00 (-0.02, 0.01)</td>
</tr>
</tbody>
</table>

* FP – forest plot number in Appendix E; ET – evidence table number in Appendix D

Proph – prophylaxis

(a) – Extended prophylaxis study. Patients were randomized at surgery and prophylaxis continued for 28-35 days in both arms. Only the results relating to the 220mg dose of Dabigatran was included in this analysis.

(b) - Extended prophylaxis study. Patients were randomized at surgery and Rivaroxaban continued for 35 days Enoxaparin was continued for 35 days in one study and 14 days in the other.

Table 10-47: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil 380,650</td>
<td>2</td>
<td>2/168</td>
<td>4/166</td>
<td>0.50</td>
<td>(0.09, 2.66)</td>
<td>-0.01 (-0.04, 0.02)</td>
</tr>
<tr>
<td>UFH vs nil 51,151,153,249,410,421,659,684</td>
<td>9</td>
<td>26/342</td>
<td>19/345</td>
<td>1.42</td>
<td>(0.84, 2.41)</td>
<td>0.00 (-0.01, 0.02)</td>
</tr>
<tr>
<td>High dose aspirin vs nil 12,153,261,887</td>
<td>4</td>
<td>0/162</td>
<td>0/178</td>
<td>Not Estimable</td>
<td></td>
<td>0.00 (-0.02, 0.02)</td>
</tr>
</tbody>
</table>

Single proph vs single

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPCD/FID vs Vitamin K antagonist 507</td>
<td>1</td>
<td>0/66</td>
<td>0/72</td>
<td>Not Estimable</td>
<td></td>
<td>0.00 (-0.03, 0.03)</td>
</tr>
<tr>
<td>Dabigatran vs LMWH(a) 476</td>
<td>1</td>
<td>23/114</td>
<td>18/115</td>
<td>1.29</td>
<td>(0.70, 2.37)</td>
<td>0.00 (-0.01, 0.02)</td>
</tr>
<tr>
<td>Rivaroxaban vs LMWH(b) 479</td>
<td>2</td>
<td>7/3437</td>
<td>3/3453</td>
<td>2.29</td>
<td>(0.57, 9.16)</td>
<td>0.00 (0.00, 0.00)</td>
</tr>
<tr>
<td>LMWH vs UFH 129,174,243,380,400,527</td>
<td>6</td>
<td>29/119</td>
<td>39/119</td>
<td>0.59</td>
<td>(0.34, 1.01)</td>
<td>-0.01 (-0.03, 0.01)</td>
</tr>
<tr>
<td>VKA vs LMWH 126,159,293</td>
<td>4</td>
<td>30/228</td>
<td>91/279</td>
<td>0.57</td>
<td>(0.38, 0.85)</td>
<td>-0.01 (-0.04, 0.01)</td>
</tr>
<tr>
<td>Aspirin (high dose) vs UFH 153</td>
<td>1</td>
<td>0/20</td>
<td>1/21</td>
<td>0.33</td>
<td>(0.01, 7.72)</td>
<td>-0.05 (-0.18, 0.08)</td>
</tr>
</tbody>
</table>
### Comparison

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (high dose) vs. Aspirin (low dose)</td>
<td>1</td>
<td>0/30</td>
<td>0/30</td>
<td>Not estimable</td>
<td>0.00 (-0.06, 0.06)</td>
<td>ET: 56 FP: 80</td>
</tr>
<tr>
<td>Double proph vs single</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (HD) vs UFH</td>
<td>1</td>
<td>1/20</td>
<td>0/20</td>
<td>3.00 (0.13, 69.52)</td>
<td>0.05 (-0.08, 0.18)</td>
<td>ET: 42 FP: 164</td>
</tr>
<tr>
<td>LMWH + GCS vs GCS</td>
<td>2</td>
<td>7/391</td>
<td>1/186</td>
<td>2.02 (0.28, 14.72)</td>
<td>0.01 (0.00, 0.03)</td>
<td>ET: 26 FP: 136</td>
</tr>
<tr>
<td>Fondaparinux + GCS vs GCS</td>
<td>1</td>
<td>2/81</td>
<td>0/82</td>
<td>5.06 (0.25, 103.81)</td>
<td>0.02 (-0.02, 0.07)</td>
<td>ET: 40 FP: 130</td>
</tr>
<tr>
<td>Vitamin K antagonist + GCS vs GCS</td>
<td>1</td>
<td>1/17</td>
<td>1/19</td>
<td>1.12 (0.08, 16.52)</td>
<td>0.01 (-0.14, 0.16)</td>
<td>ET: 41 FP: 156</td>
</tr>
<tr>
<td>Double proph vs double</td>
<td>188</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID + GCS vs Warfarin + GCS</td>
<td>1</td>
<td>0/50</td>
<td>0/45</td>
<td>Not estimable</td>
<td>0.00 (-0.04, 0.04)</td>
<td>ET: 48 FP: 208</td>
</tr>
<tr>
<td>Fondaparinux vs LMWH + GCS</td>
<td>2</td>
<td>67/226</td>
<td>43/226</td>
<td>LL: 1.55 (1.06, 2.26)</td>
<td>0.01 (0.00, 0.02)</td>
<td>ET: 44 FP: 173</td>
</tr>
<tr>
<td>LMWH + GCS vs UFH + GCS</td>
<td>1</td>
<td>2/167</td>
<td>2/168</td>
<td>LL: 0.75 (0.32, 1.77)</td>
<td>0.00 (-0.01, 0.01)</td>
<td>ET: 45 FP: 176</td>
</tr>
<tr>
<td>VKA + GCS vs Asp (HD) + GCS</td>
<td>1</td>
<td>10/55</td>
<td>1/51</td>
<td>LL: 9.27 (1.23, 69.90)</td>
<td>0.16 (0.05, 0.27)</td>
<td>ET: 35 FP: 198</td>
</tr>
<tr>
<td>Other Comparisons</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH then FID + GCS vs LMWH + GCS</td>
<td>1</td>
<td>0/100</td>
<td>0/100</td>
<td>Not estimable</td>
<td>0.00 (-0.02, 0.02)</td>
<td>ET: 51 FP: 216</td>
</tr>
<tr>
<td>Post Discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>523</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>420</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin K antagonist</td>
<td>534</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* FP – forest plot number in Appendix E; ET – evidence table number in Appendix D

Proph - prophylaxis

(a) – Extended prophylaxis study. Patients were randomized at surgery and prophylaxis continued for 28-35 days in both arms. Only the results relating to the 220mg dose of Dabigatran was included in this analysis.

(b) - Extended prophylaxis study. Patients were randomized at surgery and Rivaroxaban continued for 35 days Enoxaparin was continued for 35 days in one study and 14 days in the other.

### 10.2.3 Additional information

#### 10.2.3.1 All cause mortality

All cause mortality was not identified as a key outcome during the development of the surgical guideline. Much of the data were identified from systematic reviews where all cause mortality was not reported. There was not time during the development of this guideline to review all cause mortality for this population. In the National Joint Registry data\(^ {481}\) the mortality at 3 months after total hip replacement was 0.7% not adjusting for prophylaxis method. It is estimated that at this event rate, a sample size of 200,000 patients in each arm is required to detect a 10% reduction in mortality with 80% power and a p value of 0.05 (\(\alpha=0.05\), two sided). Smaller reductions in mortality would require even larger sample sizes. None of the published studies nor the total sample size in the meta-analysis was powered to detect a difference in mortality.

#### 10.2.3.2 Other outcomes
No studies reported chronic thromboembolic pulmonary hypertension, post thrombotic syndrome or heparin induced thrombocytopenia.

10.2.3.3 Additional studies

Eighteen (18) RCTs reported evidence for both hip and knee replacement patients without distinguishing between the two groups. The results of these studies are presented in the evidence tables (Appendix D) and forest plots (Appendix E).

10.3 Network meta-analysis results

10.3.1 Introduction

A network meta-analysis was completed for DVT, pulmonary embolism and major bleeding. Details on the network meta-analysis methods can be found in section 3.10.

For elective total hip replacement the studies for standard duration prophylaxis (e.g. prophylaxis given for a maximum of 21 days) were analysed in the network meta-analysis. Prophylaxis extending beyond this period were analysed separately. As the only studies for dabigatran and rivaroxaban extended prophylaxis for 28-35 days it is not included in the network meta-analyses of DVT and PE (the network meta-analysis of major bleeding is conducted for all population subgroups pooled together).

10.3.2 Results

DVT results

There were 46 studies included in the network meta-analysis for DVT. The results of these studies are presented in the evidence tables (Appendix D) and forest plots (Appendix E).
Figure 10-16: Network diagram for DVT. Numbers indicate the number of studies which contributed results for each comparison.

Figure 10-17: DVT results – network meta-analysis results of interventions compared to no prophylaxis.
Table 10-48: DVT – network meta-analysis results

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fon + GCS</td>
<td>0.11 (0.03, 0.38)</td>
</tr>
<tr>
<td>IPCD/FID + UFH then Asp high</td>
<td>0.13 (0.00, 1.81)</td>
</tr>
<tr>
<td>UFH + GCS</td>
<td>0.17 (0.04, 0.57)</td>
</tr>
<tr>
<td>LMWH + GCS</td>
<td>0.21 (0.05, 0.59)</td>
</tr>
<tr>
<td>IPCD/FID + UFH</td>
<td>0.28 (0.08, 0.79)</td>
</tr>
<tr>
<td>VKA + GCS</td>
<td>0.35 (0.04, 1.44)</td>
</tr>
<tr>
<td>LMWH</td>
<td>0.36 (0.25, 0.48)</td>
</tr>
<tr>
<td>GCS</td>
<td>0.43 (0.11, 1.05)</td>
</tr>
<tr>
<td>Asp (low dose)</td>
<td>0.47 (0.22, 0.81)</td>
</tr>
<tr>
<td>Asp (high) + UFH</td>
<td>0.50 (0.10, 1.39)</td>
</tr>
<tr>
<td>UFH</td>
<td>0.50 (0.37, 0.64)</td>
</tr>
<tr>
<td>IPCD / FID</td>
<td>0.54 (0.34, 0.81)</td>
</tr>
<tr>
<td>VKA</td>
<td>0.64 (0.39, 0.92)</td>
</tr>
<tr>
<td>Asp (high dose)</td>
<td>0.66 (0.45, 0.91)</td>
</tr>
<tr>
<td>Asp (high) + GCS</td>
<td>0.71 (0.07, 1.91)</td>
</tr>
<tr>
<td>UFH then Asp (high)</td>
<td>2.06 (1.04, 2.19)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals. The residual deviance was 106.1, which is quite close to the number of data points of 96, implying that the model fits the data well.

When comparing these results with the direct meta-analysis evidence, we did notice some evidence of inconsistency between comparisons. The direct comparison of low-dose aspirin with nil (one study n=60) indicated a relative risk of 0.09, whereas these results indicate a relative risk of 0.47. This seems to be due to the weight of the indirect evidence which finds that low-dose aspirin has a similar level of effectiveness to unfractionated heparin.
**Pulmonary embolism results**

There were 24 studies included in the network meta-analysis for PE.

> **Figure 10-18:** Network diagram for pulmonary embolism. Numbers indicate the number of studies which contributed results for each comparison.

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH + GCS</td>
<td>0.07 (0.00, 1.62)</td>
</tr>
<tr>
<td>GCS</td>
<td>0.08 (0.00, 3.74)</td>
</tr>
<tr>
<td>VKA</td>
<td>0.10 (0.01, 0.96)</td>
</tr>
<tr>
<td>LMWH</td>
<td>0.12 (0.02, 0.59)</td>
</tr>
<tr>
<td>Aspirin (high dose)</td>
<td>0.16 (0.02, 1.12)</td>
</tr>
<tr>
<td>Fon + GCS</td>
<td>0.17 (0.00, 5.43)</td>
</tr>
<tr>
<td>UFH + GCS</td>
<td>0.25 (0.00, 8.83)</td>
</tr>
<tr>
<td>IPCD/FID + UFH then Asp (high)</td>
<td>0.26 (0.00, 24.61)</td>
</tr>
<tr>
<td>Aspirin (low dose)</td>
<td>0.77 (0.02, 11.93)</td>
</tr>
<tr>
<td>UFH</td>
<td>0.86 (0.21, 2.52)</td>
</tr>
<tr>
<td>IPCD/FID</td>
<td>1.09 (0.03, 16.74)</td>
</tr>
<tr>
<td>UFH then Aspirin (high)</td>
<td>9.31 (0.06, 28.91)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals. The residual deviance was 47.7, which is quite close to the number of data points of 50, implying that the model fits the data well.

> **Figure 10-19:** Pulmonary embolism – network meta-analysis results of interventions compared to no prophylaxis.
**Major bleeding results**

A network meta-analysis for major bleeding was conducted using studies across hip fracture surgery, hip replacement surgery, knee replacement surgery, general medical patients and general surgical patients.

One hundred and twenty eight (128) studies were included in the analysis of which:

- 10 studies were in **medical patients**45,121,191,256,257,350,387,390,394,579,
- 48 studies were in **general surgery patients**10,14,29,40,50,52,72,73,75,113,199,210,227,230,238,262,266,267,269,280,283,321,324,329,350,387,390,394,579,366,385,439,496,499,503,504,516,517,530,533,552,553,570,573,575,579,633,639,641,645,657,667,703,711,713,
- 28 studies were in **elective hip replacement patients**126,129,151,153,174,188,195,201,202,243,260,293,299,377,380,400,409,421,465,527,573,574,635,650,651,659,684,
- 9 studies were in patients undergoing **hip fracture surgery**175,178,204,248,463,533,609,704,715,
- 15 studies were in **elective knee replacement patients**36,66,130,186,201,202,274,388,399,436,476,479,
- 7 studies were in **mixed orthopaedic surgery patients**69,200,242,250,292,459,531,
- 11 studies were in **mixed surgery patients**54,166,270,271,340-344,396,416,486,568,575,585,655.

Seven of these studies included three comparison arms153,299,380,504,533,633,655.

![Network diagram for major bleeding](image)

**Figure 10-20:** Network diagram for major bleeding. Numbers indicate the number of studies which contributed results for each comparison.
Only the results for interventions included in the network meta-analysis for DVT were included in the results.

Table 10-50: Major bleeding – network meta-analysis results

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asp (high dose)</td>
<td>0.68 (0.26, 1.57)</td>
</tr>
<tr>
<td>VKA</td>
<td>1.82 (1.22, 2.73)</td>
</tr>
<tr>
<td>LMWH</td>
<td>1.85 (1.37, 2.73)</td>
</tr>
<tr>
<td>UFH</td>
<td>2.11 (1.58, 2.83)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>3.29 (1.91, 5.83)</td>
</tr>
<tr>
<td>Asp (high dose) + UFH</td>
<td>4.00 (1.50, 10.68)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals. The residual deviance was 291.5, which is quite close to the number of data points of 263, implying that the model fits the data well.

Figure 10-21: Major bleeding – network meta-analysis results of interventions compared to no prophylaxis
10.4 Cost-effectiveness evidence

10.4.1 Introduction

General assumptions and methods for model are described in chapter 4.

The results are driven by the network meta-analysis, above. Other data used for the cost-effectiveness analysis, which are specific to elective total hip replacement patients can be found in Table 10-51 and Table 10-52

Table 10-51: Baseline risk and other population specific parameters used in the economic model for total hip replacement patients

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Source</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>Hospital Episode Statistics Data (2005-6)</td>
<td>70</td>
</tr>
<tr>
<td>% Male</td>
<td></td>
<td>38%</td>
</tr>
<tr>
<td>Standardised Mortality Ratio (a)</td>
<td>Ramiah, 2007</td>
<td>Men: 85% Women: 98% (10 years)</td>
</tr>
<tr>
<td>Mean duration of prophylaxis</td>
<td>Systematic review of RCTs (b)</td>
<td>10 days</td>
</tr>
<tr>
<td>Proportion of DVTs that are symptomatic (Ratio of symptomatic DVTs to all DVTs)</td>
<td>Published systematic review</td>
<td>21.0%</td>
</tr>
<tr>
<td>Major Bleed Fatality Rate (c)</td>
<td>Systematic review of RCTs</td>
<td>0.8%</td>
</tr>
<tr>
<td>PE Fatality Rate (d)</td>
<td>Systematic review of RCTs (all elective surgery)</td>
<td>6.0% =11/184</td>
</tr>
<tr>
<td>Re-operation rate</td>
<td>Review of fondaparinux and dabigatran studies</td>
<td>13%</td>
</tr>
<tr>
<td>DVT risk</td>
<td>Systematic review of RCTs (b)</td>
<td>45.0%</td>
</tr>
<tr>
<td>Symptomatic PE risk</td>
<td>Systematic review of RCTs (b)</td>
<td>3.4%</td>
</tr>
<tr>
<td>Major bleeding risk</td>
<td>Systematic review of RCTs (b)</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

(a) Ratio of the death rate in the surgical group compared with the death rate in the general population, adjusting for age and sex
(b) This refers to the systematic review of RCTs for the current guideline
(c) Fatal major bleeds divided by all major bleeds
(d) Fatal PEs divided by all symptomatic PEs

Table 10-52: Weights used for events in the base case analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Cost (£)</th>
<th>QALYs lost</th>
<th>Net loss (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT Asymptomatic</td>
<td>0</td>
<td>0.0000</td>
<td>0</td>
</tr>
<tr>
<td>DVT Symptomatic</td>
<td>576</td>
<td>0.0035</td>
<td>645</td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td>7,565</td>
<td>0.1997</td>
<td>11,559</td>
</tr>
<tr>
<td>Chronic pulmonary hypertension</td>
<td>69,123</td>
<td>6.1647</td>
<td>192,417</td>
</tr>
<tr>
<td>Pulmonary embolism - fatal</td>
<td>0</td>
<td>9.5019</td>
<td>190,039</td>
</tr>
<tr>
<td>Pulmonary embolism - symptomatic</td>
<td>2,521</td>
<td>0.0041</td>
<td>2,603</td>
</tr>
<tr>
<td>Major bleeding - No long-term sequelae</td>
<td>908</td>
<td>0.0267</td>
<td>1,441</td>
</tr>
<tr>
<td>Major bleeding - Stroke</td>
<td>23,877</td>
<td>7.4385</td>
<td>172,647</td>
</tr>
<tr>
<td>Major bleeding - fatal</td>
<td>0</td>
<td>9.5019</td>
<td>190,039</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia (sensitivity analysis only)</td>
<td>2,615</td>
<td>1.4176</td>
<td>30,966</td>
</tr>
</tbody>
</table>

QALY=quality-adjusted life-year
(a) Net loss is the sum of the resource cost plus the QALY loss: Net loss=cost+ (20,000 x QALYs lost)
10.4.2 Results for elective total hip replacement patients

Event rates by strategy can be found in Appendix G.

10.4.2.1 Base case results (standard duration prophylaxis)

Table 10-53: Base case results (standard duration prophylaxis) – deterministic and probabilistic results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Deterministic INB</th>
<th>Probabilistic INB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td>LMWH_plus_GCS</td>
<td>971</td>
<td>964</td>
</tr>
<tr>
<td>UFH_plus_GCS</td>
<td>962</td>
<td>957</td>
</tr>
<tr>
<td>Fondaparinux_plus_GCS</td>
<td>916</td>
<td>910</td>
</tr>
<tr>
<td>LMWH</td>
<td>818</td>
<td>818</td>
</tr>
<tr>
<td>AspirinLD</td>
<td>802</td>
<td>799</td>
</tr>
<tr>
<td>GCS</td>
<td>793</td>
<td>784</td>
</tr>
<tr>
<td>UFH_plus_IPCD-FID</td>
<td>764</td>
<td>765</td>
</tr>
<tr>
<td>IPCD-FID</td>
<td>644</td>
<td>639</td>
</tr>
<tr>
<td>WarfarinAD_plus_GCS</td>
<td>620</td>
<td>603</td>
</tr>
<tr>
<td>UFH</td>
<td>538</td>
<td>541</td>
</tr>
<tr>
<td>AspirinHD</td>
<td>516</td>
<td>515</td>
</tr>
<tr>
<td>WarfarinAD</td>
<td>360</td>
<td>357</td>
</tr>
<tr>
<td>AspirinHD_plus_GCS</td>
<td>268</td>
<td>257</td>
</tr>
<tr>
<td>UFH_plus_AspirinHD</td>
<td>117</td>
<td>121</td>
</tr>
</tbody>
</table>

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost effective overall.

Figure 10-22: Base case results of the cost-effectiveness analysis for total hip replacement patients (probabilistic analysis): standard duration(a)

Fon = fondaparinux, Asp HD = High dose Aspirin, Warf = Warfarin.
(a) UFH+AspHD has been omitted for ease of presentation. Due to increased bleeding this strategy lies in the top left quadrant of the cost-effectiveness plane (that is it increases cost and reduces QALYs compared with no prophylaxis).
10.4.2.2 Base case results (post-discharge)

Six studies \(^{47,132,142,272,378,526}\) randomised patients at discharge to receive LMWH or no prophylaxis and evaluated only events occurring after the initial hospital stay.

Table 10-54: Base case results for post-discharge prophylaxis comparing LMWH with no prophylaxis

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Deterministic INB</th>
<th>Probabilistic INB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td>LMWH</td>
<td>238</td>
<td>250</td>
</tr>
<tr>
<td>Nil</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost-effective overall.

Figure 10-23: Base case results of the cost-effectiveness analysis for total hip replacement patients (probabilistic analysis): post-discharge prophylaxis

10.4.2.3 Base case results (extended duration)

One study\(^{476}\) randomised patients to either LMWH or dabigatran at the time of surgery and evaluated all events occurring from that point. Two studies\(^{479}\) compared Rivaroxaban with LMWH. Rivaroxaban was found to be the most cost-effective intervention in the base case analysis.
Table 10-55: Base case results for extended duration prophylaxis comparing LMWH with Dabigatran and Rivaroxaban

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Deterministic INB Mean</th>
<th>Probabilistic INB Mean</th>
<th>% of simulations where strategy was most cost-effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>208</td>
<td>121</td>
<td>80.7%</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>37</td>
<td>27</td>
<td>16.0%</td>
</tr>
<tr>
<td>LMWH</td>
<td>0</td>
<td>0</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost effective overall.

Figure 10-24: Base case results of the cost-effectiveness analysis for total hip replacement patients (probabilistic analysis): extended duration prophylaxis.
### 10.4.2.4 Deterministic sensitivity analysis

#### Table 10-56: Deterministic sensitivity analysis results

<table>
<thead>
<tr>
<th>Factors changed within the Model</th>
<th>Standard duration prophylaxis</th>
<th>Post Discharge (LMWH vs nil)</th>
<th>Extended Duration (LMWH vs dabigatran vs Rivaroxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case</strong></td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td><strong>Base case (probabilistic)</strong></td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td><strong>Chronic Thromboembolic Pulmonary Hypertension and Post Thrombotic Syndrome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% Chronic Thromboembolic Pulmonary Hypertension</td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>0.5% Chronic Thromboembolic Pulmonary Hypertension</td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>1% Chronic Thromboembolic Pulmonary Hypertension</td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>0% Chronic Thromboembolic Pulmonary Hypertension and 0% Post Thrombotic Syndrome</td>
<td>Low-dose aspirin</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>High Post Thrombotic Syndrome rate (e.g. 30% after symptomatic DVT and 21% after asymptomatic DVT)</td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Low Post Thrombotic Syndrome (e.g. 15% after symptomatic DVT and 8% after asymptomatic DVT)</td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Low cost for Post Thrombotic Syndrome</td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>High cost for Post Thrombotic Syndrome</td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>High cost for Chronic Thromboembolic Pulmonary Hypertension</td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td><strong>Other Sensitivity Analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.5%, UFH=5%)</td>
<td>Fon+GCS</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.2%, UFH=2.6%)</td>
<td>Fon+GCS</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Using population specific pulmonary embolism result</td>
<td>LMWH+GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Using population specific major bleeding relative risks</td>
<td>Fon+GCS</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Low aspirin major bleeding relative risk from Network Meta-analysis (RR = 0.49)</td>
<td>LMWH + GCS</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>High aspirin major bleeding relative risk from aspirin vs. nil arms (RR = 1.3)</td>
<td>LMWH + GCS</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Discounted LMWH/Dabigatran cost = £1</td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Fatality after pulmonary embolism = 10%</td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Fatality after Major Bleeding = 5%</td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Foot Impulse Device (consumable: £18, pump: £0)</td>
<td>LMWH + GCS</td>
<td>N / A</td>
<td>N / A</td>
</tr>
<tr>
<td>Increased NICE threshold (£30,000/ QALY)</td>
<td>LMWH + GCS</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
</tr>
</tbody>
</table>

QALY=quality-adjusted life-year, fon=fondaparinux
Table 10-57: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: standard duration prophylaxis

<table>
<thead>
<tr>
<th>Major bleeding risk</th>
<th>0%</th>
<th>0.5%</th>
<th>1%</th>
<th>1.5%</th>
<th>2%</th>
<th>2.5%</th>
<th>3%</th>
<th>3.5%</th>
<th>4%</th>
<th>4.5%</th>
<th>5%</th>
<th>5.5%</th>
<th>6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE risk</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>0% Fon +GCS</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>AspLD</td>
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</tr>
<tr>
<td>0.5% Fon +GCS</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>AspLD</td>
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<tr>
<td>1% Fon +GCS</td>
<td>LMWH</td>
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<td>1.5% Fon +GCS</td>
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<td>2% Fon +GCS</td>
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<td>2.5% Fon +GCS</td>
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<td>3% Fon +GCS</td>
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<td>3.5% Fon +GCS</td>
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<tr>
<td>4% Fon +GCS</td>
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<tr>
<td>4.5% Fon +GCS</td>
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<td>5% Fon +GCS</td>
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<td>5.5% Fon +GCS</td>
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<td>6% Fon +GCS</td>
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</tbody>
</table>

Fon=fondaparinux; Asp LD = Low dose aspirin (<300mg/day)

Table 10-58: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: post discharge prophylaxis

<table>
<thead>
<tr>
<th>Major bleeding risk</th>
<th>0%</th>
<th>0.5%</th>
<th>1%</th>
<th>1.5%</th>
<th>2%</th>
<th>2.5%</th>
<th>3%</th>
<th>3.5%</th>
<th>4%</th>
<th>4.5%</th>
<th>5%</th>
<th>5.5%</th>
<th>6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0% LMWH</td>
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<td>0.5% LMWH</td>
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<td>1% LMWH</td>
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<td>1.5% LMWH</td>
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<tr>
<td>2% LMWH</td>
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<td>2.5% LMWH</td>
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<td>3% LMWH</td>
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<td>6% LMWH</td>
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Table 10-59: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: extended duration prophylaxis

<table>
<thead>
<tr>
<th>PE risk</th>
<th>0%</th>
<th>0.5%</th>
<th>1%</th>
<th>1.5%</th>
<th>2%</th>
<th>2.5%</th>
<th>3%</th>
<th>3.5%</th>
<th>4%</th>
<th>4.5%</th>
<th>5%</th>
<th>5.5%</th>
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<tbody>
<tr>
<td>Rivar</td>
<td>Rivar</td>
<td>Rivar</td>
<td>Rivar</td>
<td>Dabig</td>
<td>LMWH</td>
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</table>

Rivar=Rivaroxaban, Dabig = Dabigatran

In a threshold sensitivity analysis, we found that post-discharge LMWH prophylaxis was no longer cost-effective if greater than 60% of patients require district nurse visits to deliver their prophylaxis.

10.4.3 Conclusion of cost-effectiveness analysis

A combined strategy of low molecular weight heparin and GCS was the most clinically effective and cost-effective standard duration prophylaxis strategy in the deterministic base case and in the probabilistic analysis. A combination of pharmacological and mechanical (GCS, IPCD or FID) prophylaxis was found to be the most cost-effective strategy in over 70% of the simulations in the standard duration prophylaxis probabilistic sensitivity analysis.

Most of the results in the deterministic sensitivity analysis did not differ from the base case of LMWH + GCS. The following analyses returned different results:

- Fondaparinux + GCS was the most cost-effective strategy when heparin Induced thrombocytopenia was considered.

- Fondaparinux + GCS was the most cost-effective strategy when the major bleeding relative risks for only the total hip replacement population were used to estimate the incidence of major bleeding rather than the relative risks estimated using the network meta-analysis across all populations.

- Low-dose aspirin was most cost-effective when the risk of chronic thromboembolic pulmonary hypertension and post thrombotic syndrome are zero.

At the lowest levels of bleeding risk, fondaparinux + GCS was most cost-effective but as bleeding risk increases LMWH+GCS became the optimal strategy. At the highest levels of bleeding risk, low-dose aspirin was the most cost-effective strategy – this might be an artefact since we did not have an estimate of bleeding increase for
aspirin. If we exclude low-dose aspirin then mechanical-only prophylaxis is most cost-effective for patients at highest risk of bleeding.

Low molecular weight heparin was more cost-effective than no prophylaxis post hospital discharge. This remained the most cost-effective strategy in all sensitivity analyses.

Rivaroxaban was more cost-effective than either dabigatran or LMWH on the basis of the extended duration prophylaxis trials. In all of the deterministic sensitivity analyses completed for extended duration prophylaxis, rivaroxaban was most cost-effective. In a 2-way sensitivity analysis comparing the effect of different baselines risks of pulmonary embolism and major bleeding, LMWH and dabigatran became cost-effective at higher levels of major bleeding risk.

10.5 Patient views

A total of 7 studies included patients with hip replacement procedures 16,102,128,247,506,525,555 (Evidence tables 61-3, Appendix D). All these studies involved a mixture of elective hip and knee replacement patients 16,102,128,506,525,555, except one 247. Another study also had trauma patients 506. More information about patient views and adherence from these studies are presented in Section 6.6. The following is a summary of the main findings.

Haddad et al 247 observed the adherence to IPCD (% time used, measure using an external device) among elective hip replacement patient to be around 80%, both before and after the education initiative.

Four studies looked at the adherence and patient views of FID 16,102,525,555. The adherence reported ranged from 30% to 95%, depending on timing of observation and definitions used. Although the majority of patients found FID comfortable, interference with sleep was quite widely reported (28% to 58%) among studies where patients were required to wear the devices continuously.

One of these FID studies compared the acceptability of FID to subcutaneous LMWH injections 16. All patients received both prophylaxes, and were generally comfortable with them. Slightly more patients found LMWH painful (14.1% vs 11% in FID). However, significantly more patients would rather not have FIDs (37%) compared to LMWH (14.0%) or continue prophylaxis for 4 weeks (76.7% vs. 51.2%).

In another study, the FID (n=120) was compared to IPCD plus (GCS) (n=104) 555. Significantly more patients were "comfortable" or had no complaints with the FID (71% vs. 55%). Among 35 participants in the FID group who had used an IPCD in a previous surgery, more (69%) preferred the FID than IPCD (20%). The rest had no preference.

One study looked into the ability to self-administer subcutaneous LMWH and adhere to the injection regimen for 21 days in 51 patients 128. Patients received instructions and a demonstration by the staff nurses. On discharge, written and video instructional materials were provided. Among the 40 patients who completed the study, most (86%) performed self-injections while 14% were assisted by a family or friend. Most patients (98%) understood the importance of heparin and 68% (34/ 50) felt comfortable with self-injection.

For patient views about specific prophylaxis agents, see Section6.6.
## 10.6 Summary of evidence

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DVT</td>
<td>PE</td>
</tr>
<tr>
<td><strong>Prophylaxis vs no prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td>No prophylaxis</td>
<td>Not sig</td>
</tr>
<tr>
<td>IPCD / FID</td>
<td>No prophylaxis</td>
<td>IPCD / FID</td>
</tr>
<tr>
<td>Asp (low dose)</td>
<td>No prophylaxis</td>
<td>Asp (low dose)</td>
</tr>
<tr>
<td>Asp (high dose)</td>
<td>No prophylaxis</td>
<td>Asp (high dose)</td>
</tr>
<tr>
<td>VKA (adjusted dose)</td>
<td>No prophylaxis</td>
<td>VKA (adjusted dose)</td>
</tr>
<tr>
<td>UFH</td>
<td>No prophylaxis</td>
<td>UFH</td>
</tr>
<tr>
<td>LMWH</td>
<td>No prophylaxis</td>
<td>LMWH</td>
</tr>
<tr>
<td>Aspirin (high) + GCS</td>
<td>No prophylaxis</td>
<td>Not sig</td>
</tr>
<tr>
<td>VKA + GCS</td>
<td>No prophylaxis</td>
<td>Not sig</td>
</tr>
<tr>
<td>UFH + GCS</td>
<td>No prophylaxis</td>
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<tr>
<td>LMWH + GCS</td>
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<td>LMWH + GCS</td>
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<tr>
<td>Fon + GCS</td>
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<td>Fon + GCS</td>
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<tr>
<td>IPCD/ FID + UFH</td>
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<td>IPCD/FID + UFH</td>
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<tr>
<td>IPCD/ FID + UFH then Asp (high)</td>
<td>No prophylaxis</td>
<td>Not sig</td>
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<tr>
<td>Aspirin (high) + UFH</td>
<td>No prophylaxis</td>
<td>Not sig</td>
</tr>
<tr>
<td>UFH then Aspirin (high)</td>
<td>No prophylaxis</td>
<td>Nil</td>
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</tbody>
</table>

**Post Discharge (from direct evidence)**

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DVT</td>
<td>PE</td>
</tr>
<tr>
<td>LMWH</td>
<td>No prophylaxis post discharge</td>
<td>LMWH</td>
</tr>
<tr>
<td>UFH</td>
<td>No prophylaxis post discharge</td>
<td>Not sig</td>
</tr>
<tr>
<td>VKA</td>
<td>No prophylaxis post discharge</td>
<td>-</td>
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</table>

**Extended Prophylaxis (randomised at surgery for 28 days) (from direct evidence)**

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>LMWH</td>
<td>Not sig</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>LMWH</td>
<td>Rivaroxaban</td>
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</tbody>
</table>

There were no statistical significant difference of effectiveness between LMWH, UFH and Fondaparinux in reducing DVT, PE or major bleeding outcomes.

### Cost-effectiveness

LMWH in combination with GCS was the most clinically effective and cost-effective strategy in the deterministic base case and in the probabilistic analysis. Most of the results in the deterministic sensitivity analysis did not differ from the base case, i.e. LMWH+GCS was still most cost-effective.

Post-discharge, LMWH was more cost-effective than no prophylaxis and remained -effective in all deterministic sensitivity analyses.

Rivaroxaban was more cost-effective than LMWH or dabigatran for extended duration prophylaxis (that is in-hospital plus post-discharge) and remained so in all of the deterministic sensitivity analyses completed.

The prophylaxis strategy, which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. "-" = not reported

nil = no prophylaxis; GCS = anti-embolism / graduated compression stockings; IPCD/FID = intermittent pneumatic compression or foot impulse devices; LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; asp = aspirin; high dose aspirin is >300mg. MB = Major bleeding
10.7 Recommendations and link to evidence

**Recommendation**

Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing elective hip replacement surgery:

- Start mechanical VTE prophylaxis at admission. Choose any one of the following based, on individual patient factors:
  - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of:
  - dabigatran etexilate, starting 1-4 hours after surgery*
  - fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established
  - LMWH, starting 6–12 hours after surgery
  - rivaroxaban, starting 6-10 hours after surgery)§
  - UFH (for patients with renal failure), starting 6–12 hours after surgery.

Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used.

* Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157 (2008).476

§ Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).479

**Relative values of different outcomes**

The orthopaedic subgroup noted that although all cause mortality is the most important outcome for this population the studies were not powered to detect a difference in mortality for
any of the interventions under consideration. The next most important outcome was thought to be the risk of symptomatic venous thromboembolism balanced against the risk of major bleeding. The relative risk reduction for all DVT events was used as a surrogate for symptomatic VTE events as the orthopaedic subgroup group accepted that there was a relationship between the risk reduction in DVT and PE.

Trade off between clinical benefit and harms

The benefit of reducing VTE events was balanced with the potential harms of bleeding. The economic model included consideration of long-term sequelae such as the cost of reoperation due to bleeding, post thrombotic syndrome, chronic thromboembolic pulmonary hypertension and stroke. Our decision model indicated that the QALYs lost due to major bleeding were outweighed by the QALYs gained from drug prophylaxis.

Economic considerations

An original economic model was developed for this population. This model concluded that anti-embolism stockings (GCS) in combination with LMWH, UFH or fondaparinux were the most cost-effective interventions for reducing the risk of VTE for the period of hospitalisation within the standard duration prophylaxis trials (approximately 10 days) – dabigatran could not be compared in this analysis.

The economic model showed that extending thromboprophylaxis after hospitalisation with LMWH for 4 weeks post-discharge was cost-effective for total hip replacement patients. In addition, rivaroxaban was found to be cost-effective compared with dabigatran and LMWH as thromboprophylaxis from surgery for 4-5 weeks.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which themselves had been critically appraised to be of a high quality (level 1+ or level 1++).

Overall the quality of the evidence is good. There is a large body of evidence for this population comprising 72 RCTs providing thromboprophylaxis for between 7-21 days, of which 46 were included in the network meta-analysis. The remaining 25 were not included as they did not contain interventions that linked into the main network. In addition, there were 9 studies investigating extended duration in hip replacement patients for 28-35 days. These studies were all published since 1996.

There was an inconsistency across studies in the definition of major bleeding outcomes used. The definition as used within each paper was accepted.

Other considerations

Initiation of pharmaceutical thromboprophylaxis: The orthopaedic subgroup were mindful of the increase in bleeding risk in the period immediately after surgery and agreed that prophylaxis should be started only once the immediate bleeding risk had reduced.
Only one RCT compared pre-op start times with post-op start for LMWH and this showed no significant difference in major bleeding.

The summary of product characteristics states a postoperative start time for dabigatran, rivaroxaban and fondaparinux, and a preoperative start time for most LMWHs although the actual start times vary depending on the specific LMWH. In this guideline it is recommended that LMWH is started postoperatively which is off-label because concerns about the risk of bleeding into the joint. Patients would be protected preoperatively against VTE by mechanical prophylaxis. Some of the LMWH studies included in our analyses also started LMWH post-operatively. Further information should be sought from the summary of product characteristics for each anticoagulant.

**Mechanical thromboprophylaxis:** There was a discussion within the orthopaedic subgroup about the practicality of using anti-embolism stockings after hip replacement surgery. Patients are likely to have swollen legs post-operatively and it was felt important to ensure that patient’s legs are re-measured after surgery to confirm that the stockings remained correctly fitted. The evidence demonstrates that IPCD/FID was effective in reducing DVT and was a more practical solution in these patients. The orthopaedic subgroup therefore recommended that IPCD/FID were available as an alternative to anti-embolism stockings. The orthopaedic subgroup was aware of potential patient compliance issues with the use of IPC devices and difficulty in their use when patients regained mobility but agreed that they should be continued until the patient was discharged or no longer significantly immobile.

Mechanical prophylaxis (GCS, IPCD or FID) was felt to be particularly important in the period around the operation where patients were not protected by chemical prophylaxis. The orthopaedic subgroup agreed that by providing mechanical methods from admission the risk of developing DVT in the peri-operative period was reduced.

### 10.7.1 Other recommendations of relevance

The specific recommendations for patients having elective hip replacements in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information including when patients are discharged with prophylaxis (Section 32.5)
10.8 Summary of recommendations

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing elective hip replacement surgery:

  - Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:
    - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of the following:

  - dabigatran etexilate, starting 1-4 hours after surgery*
  - fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established
  - LMWH, starting 6–12 hours after surgery
  - rivaroxaban, starting 6–10 hours after surgery$
  - UFH (for patients with renal failure), starting 6–12 hours after surgery.

  Continue pharmacological VTE prophylaxis for 28–35 days, according to the summary of product characteristics for the individual agent being used.

* Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157 (2008).476

$ Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).479
11 Elective knee replacement

11.1 Introduction

Elective total knee replacement for primary or secondary degenerative joint disease is a highly successful procedure involving a large number of patients per annum, usually in an elderly population but with an increasing application in younger age groups. The general risks of this surgery including infection are well documented. The baseline risk for VTE is not as significant as that reported in THR, particularly, with fatal and non-fatal pulmonary embolism (probably less than 1%). Regrettably there is no significant evidence on the effects of thromboprophylaxis on fatal and non fatal PE in TKR, there is only evidence which relates to DVT and these studies suggest that DVT rates including asymptomatic DVT may be as high as 60%.

Uncertainties remain therefore as to whether the studies which show a reduction in DVT rates by thromboprophylaxis can be extrapolated to PE rates and whether there is sufficient morbidity from DVT apart from PE to merit prophylaxis. There is some evidence that links DVT in TKR to morbidity related to post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension but there has been minimal reporting of these morbidities in the British and American literature and many knee surgeons rarely, if ever, see these problems in their clinics. There is discrepancy between this view and the experience of other specialities involved in the subsequent management of DVT sequelae.

The other uncertainty in chemical VTE prophylaxis in TKR is that of “major bleeding” and its potential association with an increased risk of wound haematoma, re-operation and deep infection. Current evidence in this area is weak but suggests a risk in the order of 1%.

Clearly further research is required to try to resolve these uncertainties and extremely large numbers of patients will be needed to provide statistically significant data on risks less than 1%. Until this evidence is available, these patients should be offered the most effective thromboprophylaxis available with the minimum of side effects. A fatal and non fatal PE rate of less than 1% cannot be ignored as this involves several hundred deaths or emergency admissions each year. A high DVT rate cannot be ignored even if the morbidity rates are unclear. Equally, a possible bleeding complication rate of 1% cannot be ignored and thromboprophylaxis must be as safe as possible in this respect.

The VTE prophylaxis recommendation will therefore attempt to meet as many of their concerns as possible by paying attention to the timing of chemical prophylaxis and its duration plus the best means of combining chemical and mechanical (GCS, IPCD or FID) prophylaxis.
11.2 Evidence of methods of thromboprophylaxis

There were 23 RCTs identified for knee replacement patients which included one study with comparing 3 interventions. Most of RCTs had their data extracted from systematic reviews. Where applicable the study is cited in the evidence table for that review. Seven systematic reviews included RCTs covering patients having total knee replacement.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++)..

11.2.1 Summary of comparisons identified for any outcome

![Table of comparisons]

Figure 11-25: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis
11.2.2 Results from pairwise comparisons

Table 11-60: DVT – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Interventions</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID vs nil [436, 697]</td>
<td>2</td>
<td>6/38</td>
<td>28/44</td>
<td>0.26 (0.12, 0.57)</td>
<td>-0.51 (-0.74, -0.28)</td>
<td>ET: 24 FP: 4</td>
</tr>
<tr>
<td>LMWH vs nil [388]</td>
<td>1</td>
<td>11/65</td>
<td>37/64</td>
<td>0.29 (0.16, 0.52)</td>
<td>-0.41 (-0.56, -0.26)</td>
<td>ET: 26 FP: 13</td>
</tr>
<tr>
<td>High dose aspirin vs. nil [436]</td>
<td>1</td>
<td>8/21</td>
<td>9/12</td>
<td>0.51 (0.27, 0.96)</td>
<td>-0.37 (-0.69, -0.05)</td>
<td>ET: 29 FP: 28</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID vs LMWH [66, 676]</td>
<td>2</td>
<td>91/162</td>
<td>64/156</td>
<td>1.51 (0.71, 3.20)</td>
<td>0.17 (-0.09, 0.43)</td>
<td>ET: 37 FP: 87</td>
</tr>
<tr>
<td>IPCD/FID vs High dose aspirin [245, 436]</td>
<td>2</td>
<td>21/71</td>
<td>40/79</td>
<td>0.59 (0.40, 0.88)</td>
<td>-0.25 (-0.39, -0.10)</td>
<td>ET: 37 FP: 98</td>
</tr>
<tr>
<td>VKA vs. LMWH [186, 274, 389]</td>
<td>3</td>
<td>274/609</td>
<td>182/611</td>
<td>1.50 (1.29, 1.74)</td>
<td>0.15 (0.10, 0.20)</td>
<td>ET: 34 FP: 57</td>
</tr>
<tr>
<td>Dabigatran vs LMWH [476]</td>
<td>2</td>
<td>363/1107</td>
<td>350/1155</td>
<td>1.08 (0.86, 1.36)</td>
<td>0.02 (-0.04, 0.09)</td>
<td>ET: 476 FP: 41</td>
</tr>
<tr>
<td>Rivaroxaban vs LMWH [479]</td>
<td>2</td>
<td>140/178</td>
<td>246/183</td>
<td>0.38 (0.22, 0.65)</td>
<td>-0.06 (-0.12, 0.01)</td>
<td>ET: 479 FP: 261</td>
</tr>
<tr>
<td>LMWH vs. UFH [130]</td>
<td>1</td>
<td>54/145</td>
<td>74/143</td>
<td>0.72 (0.55, 0.94)</td>
<td>-0.15 (-0.26, -0.03)</td>
<td>ET: 32 FP: 48</td>
</tr>
<tr>
<td>Double proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID + Asp high dose vs Aspirin high dose [291]</td>
<td>1</td>
<td>1/13</td>
<td>4/14</td>
<td>0.27 (0.03, 2.11)</td>
<td>-0.21 (-0.49, 0.07)</td>
<td>ET: 39 FP: 114</td>
</tr>
<tr>
<td>LMWH + GCS vs GCS [202, 399]</td>
<td>2</td>
<td>113/332</td>
<td>108/182</td>
<td>0.56 (0.46, 0.69)</td>
<td>-0.27 (-0.36, -0.18)</td>
<td>ET: 26 FP: 134</td>
</tr>
<tr>
<td>IPCD + FID vs LMWH [493]</td>
<td>1</td>
<td>4/15</td>
<td>0/14</td>
<td>8.44 (0.50, 144)</td>
<td>0.27 (0.03, 0.50)</td>
<td>ET: 37 FP: 104</td>
</tr>
<tr>
<td>Double proph vs double</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fon + GCS vs LMWH + GCS [36]</td>
<td>1</td>
<td>45/361</td>
<td>98/361</td>
<td>0.46 (0.33, 0.63)</td>
<td>-0.15 (-0.20, -0.09)</td>
<td>ET: 44 FP: 171</td>
</tr>
<tr>
<td>LMWH + IPCD/FID vs Asp High dose + IPCD/FID [486]</td>
<td>1</td>
<td>17/135</td>
<td>18/129</td>
<td>0.90 (0.49, 1.67)</td>
<td>-0.01 (-0.10, 0.07)</td>
<td>ET: 46 FP: 190</td>
</tr>
<tr>
<td>LMWH + GCS vs UFH + GCS [183]</td>
<td>1</td>
<td>21/92</td>
<td>25/93</td>
<td>0.85 (0.51, 1.40)</td>
<td>-0.04 (-0.16, 0.08)</td>
<td>ET: 45 FP: 174</td>
</tr>
<tr>
<td>Post discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH [132]</td>
<td>1</td>
<td>33/155</td>
<td>37/144</td>
<td>0.83 (0.55, 1.25)</td>
<td>-0.04 (-0.14, 0.05)</td>
<td>ET: 58 FP: 225</td>
</tr>
</tbody>
</table>

* FP – forest plot number in Appendix E; ET – evidence table number in Appendix D

Proph - prophylaxis

a) There is substantial statistical heterogeneity between studies for this population ($I^2=86.8\%$, $\chi^2$ on 1 df = 7.56, $p=0.006$).

b) There is substantial statistical heterogeneity between studies for this population ($I^2=72.1\%$, $\chi^2$ on 1 df = 3.58, $p=0.06$).

c) There is substantial heterogeneity between studies for this population population ($I^2=50.3\%$, $\chi^2$ on 1 df = 32.01, $p=0.16$).
### Table 11-61: Pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proph vs no proph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID vs nil</td>
<td>2</td>
<td>1/38</td>
<td>4/44</td>
<td>0.30</td>
<td>-0.09</td>
<td>(0.04, 2.27) ET: 24 FP: 5</td>
</tr>
<tr>
<td></td>
<td>High dose aspirin vs. nil</td>
<td>1</td>
<td>3/21</td>
<td>4/12</td>
<td>0.43</td>
<td>-0.19</td>
</tr>
<tr>
<td><strong>Single proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID vs IPCD/FID</td>
<td>1</td>
<td>0/63</td>
<td>0/67</td>
<td>N/A</td>
<td>0.00</td>
<td>(-0.03, 0.03) ET: 37 FP: 88</td>
</tr>
<tr>
<td></td>
<td>IPCD/FID vs High dose aspirin</td>
<td>2</td>
<td>4/71</td>
<td>4/79</td>
<td>1.34</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>VKA vs. LMWH</td>
<td>3</td>
<td>3/609</td>
<td>2/611</td>
<td>1.39</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Dabigatran vs LMWH</td>
<td>2</td>
<td>6/1107</td>
<td>5/1155</td>
<td>1.28</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban vs LMWH</td>
<td>2</td>
<td>4/2727</td>
<td>12/2725</td>
<td>0.54</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>LMWH vs. UFH</td>
<td>1</td>
<td>0/145</td>
<td>1/143</td>
<td>0.33</td>
<td>-0.01</td>
</tr>
<tr>
<td><strong>Double proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH + GCS vs GCS</td>
<td>2</td>
<td>3/358</td>
<td>1/203</td>
<td>1.15</td>
<td>0.01</td>
<td>(0.17, 7.80) ET: 26 FP: 135</td>
</tr>
<tr>
<td><strong>Double proph vs double</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fon + GCS vs LMWH + GCS</td>
<td>1</td>
<td>1/517</td>
<td>4/517</td>
<td>0.25</td>
<td>-0.01</td>
<td>(0.03, 2.23) ET: 44 FP: 172</td>
</tr>
<tr>
<td>LMWH + IPCD/FID vs Asp</td>
<td>1</td>
<td>0/135</td>
<td>1/129</td>
<td>0.32</td>
<td>-0.01</td>
<td>(0.01, 7.75) ET: 46 FP: 191</td>
</tr>
<tr>
<td>High dose + IPCD/FID</td>
<td>1</td>
<td>0/92</td>
<td>0/93</td>
<td>N/A</td>
<td>0.00</td>
<td>(-0.02, 0.02) ET: 45 FP: 175</td>
</tr>
<tr>
<td>LMWH + GCS vs UFH + GCS</td>
<td>1</td>
<td>0/92</td>
<td>0/93</td>
<td>N/A</td>
<td>0.00</td>
<td>(-0.02, 0.02) ET: 45 FP: 175</td>
</tr>
<tr>
<td><strong>Extended duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>2</td>
<td>3/583</td>
<td>4/578</td>
<td>0.80</td>
<td>0.00</td>
<td>(0.13, 4.86) ET: 58 FP: 226</td>
</tr>
</tbody>
</table>

* FP – forest plot number in Appendix E; ET – evidence table number in Appendix D
  Proph – prophylaxis
### Table 11-62: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proph vs no proph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil 388</td>
<td>1</td>
<td>0/66</td>
<td>1/65</td>
<td>0.33</td>
<td>(-0.02)</td>
<td>ET: 26 FP: 15</td>
</tr>
<tr>
<td>High dose aspirin vs. nil 436</td>
<td>1</td>
<td>1/21</td>
<td>0/12</td>
<td>1.77</td>
<td>(0.05)</td>
<td>ET: 29 FP: 29</td>
</tr>
<tr>
<td><strong>Single proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID vs LMWH 46</td>
<td>1</td>
<td>0/63</td>
<td>1/67</td>
<td>0.35</td>
<td>(-0.01)</td>
<td>ET: 37 FP: 89</td>
</tr>
<tr>
<td>IPCD/FID vs High dose aspirin 436</td>
<td>1</td>
<td>0/10</td>
<td>1/21</td>
<td>0.67</td>
<td>(-0.05)</td>
<td>ET: 37 FP: 100</td>
</tr>
<tr>
<td>VKA vs. LMWH 186,274,389</td>
<td>3</td>
<td>22/789</td>
<td>38/786</td>
<td>0.58</td>
<td>(-0.02)</td>
<td>ET: 34 FP: 59</td>
</tr>
<tr>
<td>Dabigatran vs LMWH 476</td>
<td>2</td>
<td>15/1536</td>
<td>21/1562</td>
<td>0.72 (a)</td>
<td>(0.00)</td>
<td>ET: 476 FP: 43</td>
</tr>
<tr>
<td>Rivaroxaban vs LMWH 479</td>
<td>2</td>
<td>17/276</td>
<td>10/274</td>
<td>1.67</td>
<td>(0.00)</td>
<td>ET: 479 FP: 263</td>
</tr>
<tr>
<td>LMWH vs. UFH 130</td>
<td>1</td>
<td>3/228</td>
<td>3/225</td>
<td>0.99</td>
<td>(0.00)</td>
<td>ET: 32 FP: 50</td>
</tr>
<tr>
<td><strong>Double proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fon + GCS vs GCS 201</td>
<td>1</td>
<td>1/84</td>
<td>1/87</td>
<td>1.04</td>
<td>(0.00)</td>
<td>ET: 40 FP: 132</td>
</tr>
<tr>
<td>LMWH + GCS vs GCS 202,399</td>
<td>2</td>
<td>7/397</td>
<td>7/214</td>
<td>0.53</td>
<td>(-0.01)</td>
<td>ET: 26 FP: 136</td>
</tr>
<tr>
<td><strong>Double proph vs double</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fon + GCS vs LMWH + GCS 36</td>
<td>1</td>
<td>11/517</td>
<td>1/517</td>
<td>11.00</td>
<td>(0.02)</td>
<td>ET: 44 FP: 173</td>
</tr>
<tr>
<td>LMWH + IPCD/FID vs Asp high dose + IPCD/FID 686</td>
<td>1</td>
<td>0/135</td>
<td>0/129</td>
<td>N/A</td>
<td>(0.00)</td>
<td>ET: 46 FP: 192</td>
</tr>
<tr>
<td><strong>Extended duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH 132,272</td>
<td>2</td>
<td>2/583</td>
<td>3/568</td>
<td>0.72 (0.01)</td>
<td>(0.00)</td>
<td>ET: 58 FP: 227</td>
</tr>
</tbody>
</table>

* FP – forest plot number in Appendix E; ET – evidence table number in Appendix D

**Proph** - prophylaxis

(a) There is substantial statistical heterogeneity between studies for this population ($I^2 = 50.2\%$, $\chi^2$ on 1 df = 2.01, p = 0.16).

### 11.2.3 Additional information

#### 11.2.3.1 All cause mortality

All cause mortality was not identified as a key outcome during the development of the surgical guideline. Much of the data were identified from systematic reviews where all cause mortality was not reported. There was not enough time during the development of this guideline to review all cause mortality for this population. In the national joint registry data\(^{481}\) the mortality rate at 3 months after total knee replacement was 0.5%, not adjusting for thromboprophylaxis method. It is estimated that at this event rate, a sample size of 300,000 patients in each arm is required to detect a 10% reduction in mortality with 80% power and a p value of 0.05 ($\alpha = 0.05$, two sided). Smaller reductions in mortality would require even larger sample sizes. None of the published
11.2.3.2 Other outcomes

No RCTs or systematic reviews reported results post thrombotic syndrome, chronic thromboembolic pulmonary hypertension, heparin induced thrombocytopenia, quality of life or length of stay as outcomes for this population.

11.2.3.3 Additional studies

Eighteen (18) RCTs reported evidence for both hip and knee replacement patients without distinguishing between the two groups [20,27,69,127,200,220,242,250,290,292,299,322,402,408,514,531,541,601]. The results of these studies are presented in evidence tables (Appendix D) and forest plots (Appendix E) for those comparisons.

11.3 Network meta-analysis

A network meta-analysis was completed for DVT and major bleeding. Details on the network meta-analysis methods can be found in section 3.10.

**DVT results**

There were 18 studies included in the network meta-analysis for asymptomatic and symptomatic DVT [36,66,130,186,245,274,291,388,389,436,476,479,676,686,697]. One study compared three interventions [436].

![Network diagram for all DVT](image)

**Figure 11-26: Network diagram for all DVT.** Numbers indicate the number of studies which contributed results for each comparison.
Table 11-63: DVT – network meta-analysis results

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux</td>
<td>0.08 (0.03, 0.23)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.12 (0.04, 0.28)</td>
</tr>
<tr>
<td>IPCD/FID + LMWH</td>
<td>0.14 (0.01, 0.97)</td>
</tr>
<tr>
<td>IPCD/FID + Asp (high)</td>
<td>0.15 (0.01, 0.91)</td>
</tr>
<tr>
<td>LMWH</td>
<td>0.20 (0.09, 0.39)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>0.22 (0.09, 0.47)</td>
</tr>
<tr>
<td>IPCD/FID + LMWH</td>
<td>0.31 (0.14, 0.55)</td>
</tr>
<tr>
<td>UFH</td>
<td>0.34 (0.11, 0.73)</td>
</tr>
<tr>
<td>VKA</td>
<td>0.36 (0.15, 0.67)</td>
</tr>
<tr>
<td>Asp (high)</td>
<td>0.62 (0.28, 1.04)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals.

The residual deviance was 37.9, which is quite close to the number of data points of 30, implying that the model fits the data well.

Pulmonary embolism results

There was not enough evidence to complete a network meta-analysis for this outcome.

Major bleeding results

A network meta-analysis for major bleeding was conducted using studies across hip fracture surgery, hip replacement surgery, knee replacement surgery, general medical patients and general surgical patients.

One hundred and twenty eight (128) studies were included in the analysis of which:

- 10 studies were in medical patients
- 48 studies were in general surgery patients
- 28 studies were in elective hip replacement patients
- 9 studies were in patients undergoing hip fracture surgery

Figure 11-27: DVT – network meta-analysis results of interventions compared to no prophylaxis
- 15 studies were in elective knee replacement patients. 

- 7 studies were in mixed orthopaedic surgery patients.

- 11 studies were in mixed surgery patients.

Seven of these studies included three comparison arms.

![Figure 11-28: Network diagram for major bleeding. Numbers indicate the number of studies which contributed results for each comparison]

Only the results for interventions included in the network meta-analysis for DVT were included in the results.
Table 11-64: Major bleeding – network meta-analysis results

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (high dose)</td>
<td>0.44 (0.17, 1.04)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>0.87 (0.30, 2.45)</td>
</tr>
<tr>
<td>VKA</td>
<td>1.21 (0.81, 1.82)</td>
</tr>
<tr>
<td>LMWH</td>
<td>1.23 (0.91, 1.68)</td>
</tr>
<tr>
<td>UFH</td>
<td>1.40 (1.05, 1.89)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2.12 (0.70, 6.29)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.21 (1.27, 3.94)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals.

The residual deviance was 291.5, which is quite close to the number of data points of 263, implying that the model fits the data well.

Figure 11-29: Major Bleeding – network meta-analysis results of interventions compared to no prophylaxis

11.4 Cost-effectiveness evidence

11.4.1 Introduction

The general assumptions and methods for the cost-effectiveness model are described in chapter 4.

The results are driven by the network meta-analysis, above. Other data used for the cost-effectiveness analysis which are specific to knee replacement patients can be found in Table 11-65 and Table 11-66.
### Table 11-65: Baseline risk and other population specific parameters used in the economic model for knee replacement patients

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Source</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>Hospital Episode Statistics Data (2005-6)</td>
<td>70</td>
</tr>
<tr>
<td>% Male</td>
<td>Hospital Episode Statistics Data (2005-6)</td>
<td>42</td>
</tr>
<tr>
<td>Standardised Mortality Ratio (a)</td>
<td>Nunley 2003</td>
<td>52% (1 year)</td>
</tr>
<tr>
<td>Mean duration of prophylaxis</td>
<td>Systematic review of RCTs (b)</td>
<td>10 days</td>
</tr>
<tr>
<td>Proportion of DVTs that are symptomatic (Ratio of symptomatic DVTs to all DVTs)</td>
<td>Published systematic review 542</td>
<td>5.0%</td>
</tr>
<tr>
<td>Major Bleed Fatality Rate (c)</td>
<td>Muntz (2004) systematic review of thromboprophylaxis RCTs</td>
<td>0.8%</td>
</tr>
<tr>
<td>PE Fatality Rate (d)</td>
<td>Systematic review of RCTs all elective surgery</td>
<td>6.0% / 11/184</td>
</tr>
<tr>
<td>Re-operation rate</td>
<td>From a review of recent fondaparinux and dabigatran trials 36,175,377,476,651</td>
<td>13%</td>
</tr>
<tr>
<td>DVT risk</td>
<td>No prophylaxis/placebo arms of RCTs from systematic review (b)</td>
<td>60.0%</td>
</tr>
<tr>
<td>Symptomatic PE risk</td>
<td>This figure is an estimate as no studies have presented results for symptomatic PE in the absence of prophylaxis. Symptomatic PE in cohort studies with prophylaxis range from 0.2-1.9% 422,674,678,689</td>
<td>1.0%</td>
</tr>
<tr>
<td>Major bleeding risk</td>
<td>No prophylaxis/placebo arms of RCTs from systematic review (b)</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

- **a)** Ratio of the death rate in the surgical group compared with the death rate in the general population, adjusting for age and sex
- **b)** This refers to the systematic review of RCTs for the current guideline
- **c)** Fatal major bleeds divided by all major bleeds
- **d)** Fatal PEs divided by all symptomatic PEs

### Table 11-66: Weights used for events in the base case analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Cost (£)</th>
<th>QALYs lost</th>
<th>Net loss (a)(£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT Asymptomatic</td>
<td>0</td>
<td>0.0000</td>
<td>0</td>
</tr>
<tr>
<td>DVT Symptomatic</td>
<td>576</td>
<td>0.0035</td>
<td>645</td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td>7,475</td>
<td>0.1971</td>
<td>11,417</td>
</tr>
<tr>
<td>Chronic pulmonary hypertension</td>
<td>69,123</td>
<td>6.0517</td>
<td>190,156</td>
</tr>
<tr>
<td>Pulmonary embolism - fatal</td>
<td>0</td>
<td>9.3889</td>
<td>187,778</td>
</tr>
<tr>
<td>Pulmonary embolism - symptomatic</td>
<td>2,521</td>
<td>0.0041</td>
<td>2,603</td>
</tr>
<tr>
<td>Major bleeding - No long-term sequelae</td>
<td>908</td>
<td>0.0267</td>
<td>1,441</td>
</tr>
<tr>
<td>Major bleeding - Stroke</td>
<td>23,877</td>
<td>7.3254</td>
<td>170,386</td>
</tr>
<tr>
<td>Major bleeding - fatal</td>
<td>0</td>
<td>9.3889</td>
<td>187,778</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia (sensitivity analysis only)</td>
<td>2,610</td>
<td>1.4006</td>
<td>30,623</td>
</tr>
</tbody>
</table>

QALY=quality-adjusted life-year

(a) Net loss is the sum of the resource cost plus the QALY loss:
Net loss=cost+ (20,000 x QALYs lost)

Event rates by strategy can be found in Appendix G.
11.4.2 Results for knee replacement patients

Table 11-67: Base case results – deterministic and probabilistic results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Deterministic INB</th>
<th>Probabilistic INB</th>
<th>% of simulations where strategy was most cost-effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux</td>
<td>864</td>
<td>910</td>
<td>17.2%</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>902</td>
<td>904</td>
<td>15.8%</td>
</tr>
<tr>
<td>LMWH</td>
<td>881</td>
<td>890</td>
<td>1.9%</td>
</tr>
<tr>
<td>AspirinHD_plus_IPCD-FID</td>
<td>884</td>
<td>890</td>
<td>44.7%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>815</td>
<td>869</td>
<td>16.5%</td>
</tr>
<tr>
<td>LMWH_plus_IPCD-FID</td>
<td>800</td>
<td>815</td>
<td>3.0%</td>
</tr>
<tr>
<td>IPCD-FID</td>
<td>792</td>
<td>790</td>
<td>0.8%</td>
</tr>
<tr>
<td>WarfarinAD</td>
<td>675</td>
<td>680</td>
<td>0.0%</td>
</tr>
<tr>
<td>UFH</td>
<td>652</td>
<td>669</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost effective overall.

Figure 11-30: Base case results of the cost-effectiveness analysis for total knee replacement patients (probabilistic analysis)

Fon = fondaparinux, Asp HD = High dose Aspirin, Warf = Warfarin, Dabig= Dabigatran

£22,000 per QALY gained
### 11.4.3 Deterministic sensitivity analysis

**Table 11-68: Deterministic sensitivity analysis results**

<table>
<thead>
<tr>
<th>Factors changed within the Model</th>
<th>Most Cost-effective Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>Base case (probabilistic)</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td><strong>Chronic Thromboembolic Pulmonary Hypertension and Post Thrombotic Syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>0% Chronic Thromboembolic Pulmonary Hypertension</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>0.5% Chronic Thromboembolic Pulmonary Hypertension</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>1% Chronic Thromboembolic Pulmonary Hypertension</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>0% Chronic Thromboembolic Pulmonary Hypertension and 0% Post Thrombotic Syndrome</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>High Post Thrombotic Syndrome rate (e.g. 30% after symptomatic DVT and 21% after asymptomatic DVT)</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>Low Post Thrombotic Syndrome (e.g. 15% after symptomatic DVT and 8% after asymptomatic DVT)</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>Low cost for Post Thrombotic Syndrome</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>High cost for Post Thrombotic Syndrome</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>High cost for Chronic Thromboembolic Pulmonary Hypertension</td>
<td>Dabigatran</td>
</tr>
<tr>
<td><strong>Other Sensitivity Analyses</strong></td>
<td></td>
</tr>
<tr>
<td>Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.5%, UFH=5%)</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.2%, UFH=2.6%)</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>Using population specific major bleeding relative risks</td>
<td>LMWH</td>
</tr>
<tr>
<td>Discounted LMWH / Dabigatran cost = £1</td>
<td>LMWH</td>
</tr>
<tr>
<td>Fatality after PE = 10%</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>Fatality after Major Bleeding = 5%</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>Low aspirin major bleeding relative risk from Network Meta-analysis (RR = 0.49)</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>Higher aspirin &amp; dabigatran major bleeding relative risk</td>
<td>LMWH</td>
</tr>
<tr>
<td>Foot Impulse Device (consumable: £18, pump: £0)</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>Increased NICE threshold (£30,000/QALY)</td>
<td>Dabigatran</td>
</tr>
</tbody>
</table>

QALY=quality-adjusted life-year
### Table 11-69: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: standard duration prophylaxis

<table>
<thead>
<tr>
<th>PE risk</th>
<th>0%</th>
<th>0.5%</th>
<th>1%</th>
<th>1.5%</th>
<th>2%</th>
<th>2.5%</th>
<th>3%</th>
<th>3.5%</th>
<th>4%</th>
<th>4.5%</th>
<th>5%</th>
<th>5.5%</th>
<th>6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
</tr>
<tr>
<td>0.5%</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
</tr>
<tr>
<td>1%</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
</tr>
<tr>
<td>1.5%</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
</tr>
<tr>
<td>2%</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
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<td>Fon</td>
</tr>
<tr>
<td>2.5%</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
</tr>
<tr>
<td>3%</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
</tr>
<tr>
<td>3.5%</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
</tr>
<tr>
<td>4%</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
</tr>
<tr>
<td>4.5%</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
</tr>
<tr>
<td>5%</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
</tr>
<tr>
<td>5.5%</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
</tr>
<tr>
<td>6%</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Dabig</td>
<td>Dabig</td>
<td>Fon</td>
<td>Fon</td>
</tr>
</tbody>
</table>

Fon = Fondaparinux; Dabig = Dabigatran

#### 11.4.4 Conclusion of cost-effectiveness results

It was noted that for total knee replacement surgery dabigatran was the most cost-effective strategy in the deterministic analysis. However, fondaparinux was more cost-effective in the probabilistic analysis.

Dabigatran and fondaparinux were the most cost-effective strategies in the base case and in most of the deterministic sensitivity analyses. LMWH was the most cost-effective strategy when

- discounted drug costs were used or
- when population specific major bleeding relative risks or
- when the major bleeding risk for dabigatran was assumed the same as for LMWH.

Rivaroxaban had a similar level of cost-effectiveness to LMWH, dabigatran and fondaparinux, as was found in the NICE Technology Appraisal TA170. In the manufacturers model, rivaroxaban was slightly more cost-effective than the others but the TA committee noted that the model had inappropriately ignored non-significant differences and had not taken account of health loss attributable to intra-cranial bleeding.

Aspirin_HD_plus_IPCD-FID also came out as relatively cost-effective in the base case analysis but this was on the basis that aspirin does not increase the risk of major bleeding. When an increased risk of bleeding similar to LMWH was assumed then aspirin was no longer cost-effective.

A cost-effectiveness analysis of post discharge prophylaxis or extended duration prophylaxis has not been completed for this population.
11.5 Patient views

A total of eight studies included some patients undergoing knee replacement surgery (Evidence tables 61-63, Appendix D). More information about patient views and adherence from these studies are presented in section 6.6. The following is a summary of the main findings.

Two studies investigated the patient views and adherence of self injection with LMWH. Spahn et al. evaluated postoperative self-injection of LMWH for about 10 days in 300 patients. Fully completed questionnaires from 207 patients showed that after training for self-injection, most (92.2%) chose self-administration rather than a nursing service. Of those who chose self-administration, 16% required family or friends to help. Fewer patients who self-injected without any help found it ‘very unpleasant’ compared to those who received help. Overall, adherence was incomplete in 28.3% patients who did not use the nursing service.

Colwell et al. looked into the ability to self-administer subcutaneous LMWH and adhere to the injection regimen for 21 days in 51 patients. Patients received instructions and a demonstration by the staff nurses. On discharge, written and video instructional materials were provided. Among the 40 patients who completed the study, 86% performed self-injections while 14% were assisted by a family or friend. Most patients (98%) understood the importance of heparin and 68% felt comfortable with self-injection.

Five studies looked at the adherence and patient views of foot impulse devices (FID). The adherence reported ranged from 30% to 95%, depending on timing of observation and definitions used. Although the majority of patients found FID comfortable, interference with sleep was quite widely reported (28% to 58%) among studies where patients were required to wear the devices continuously.

The study on FID which recruited only knee replacement patients reported patient comfort and adherence. Given a choice of options ranging from extremely uncomfortable to extremely comfortable, on average, patients found the foot wrap to be between “moderately comfortable” to “very comfortable” and the pumping action “slightly” comfortable.

One of these FID studies compared the acceptability of FID to subcutaneous LMWH injections. All patients received both prophylaxis methods, and were generally comfortable with them. Slightly more patients found LMWH painful (14.1% vs 11% in FID). However, significantly more patients would rather not have FIDs (37%) compared to LMWH (14.0%) or continue prophylaxis for 4 weeks (76.7% vs. 51.2%).

In another study, FID (n=120) were compared to intermittent pneumatic compression devices (IPCD) plus graduated compression stockings (GCS) (n=104). Significantly more patients were "comfortable" or had no complaints with FID (71% vs. 55%). Among 35 participants in the FID group who had used IPCD in a previous surgery, more (69%) preferred FID than IPCD (20%). The rest had no preference.

For patient views on specific interventions from all population subgroups (surgical and medical), are presented in section 6.6.
11.6 Summary of evidence

Table 11-70: Summary of evidence from network meta-analysis results for DVT, pulmonary embolism and major bleeding outcomes.

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DVT</td>
</tr>
<tr>
<td>Prophylaxis vs no prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID</td>
<td>no prophylaxis</td>
<td>IPCD/FID</td>
</tr>
<tr>
<td>Aspirin (high dose)</td>
<td>no prophylaxis</td>
<td>Not sig</td>
</tr>
<tr>
<td>VKA (adjusted dose)</td>
<td>no prophylaxis</td>
<td>VKA</td>
</tr>
<tr>
<td>UFH</td>
<td>no prophylaxis</td>
<td>UFH</td>
</tr>
<tr>
<td>LMWH</td>
<td>no prophylaxis</td>
<td>LMWH</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>no prophylaxis</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>no prophylaxis</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>no prophylaxis</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Asp (HD) + IPCD/FID</td>
<td>no prophylaxis</td>
<td>Asp (HD) + IPCD/FID</td>
</tr>
<tr>
<td>LMWH + IPCD/FID</td>
<td>no prophylaxis</td>
<td>LMWH + IPCD/FID</td>
</tr>
</tbody>
</table>

Cost-effectiveness

Dabigatran and fondaparinux were the most cost-effective strategies in the base case and in most of the deterministic sensitivity analyses. LMWH was the most cost-effective strategy when
* discounted drug costs were used or
* when population specific major bleeding relative risks or
* when the major bleeding risk for dabigatran was assumed the same as for LMWH. In TA170, the Committee concluded that, on balance, rivaroxaban, enoxaparin and dabigatran had very similar costs and benefits in the prevention of VTE. Rivaroxaban had a similar level of cost-effectiveness to LMWH, dabigatran and fondaparinux. A cost-effectiveness analysis of post discharge prophylaxis was not completed for this population.

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. ‘-‘ = not reported.

nil = no prophylaxis; GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; VKA – vitamin K antagonist; asp (HD) – high dose aspirin; high dose aspirin is >300mg MB = Major bleeding
11.7 Recommendations and link to evidence

**Recommendation**

Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing elective knee replacement surgery.

- Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors:
  - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of:
  - dabigatran etexilate, starting 1-4 hours after surgery *
  - fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established
  - LMWH, starting 6–12 hours after surgery
  - rivaroxaban, starting 6-10 hours after surgery
  - UFH (for patients with renal failure), starting 6–12 hours after surgery.

Continue pharmacological VTE prophylaxis for 10-14 days, according to the summary of product characteristics for the individual agent being used.

* Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157 (2008).\(^{476}\)

$ Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).\(^{479}\)

**Relative values of different**

The orthopaedic subgroup noted that although all cause
outcomes mortality is the most important outcome for this population the studies were not powered to detect a difference in mortality for any of the interventions under consideration. The next most important outcome was thought to be the risk of symptomatic venous thromboembolism balanced against the risk of major bleeding. The relative risk reduction for all DVT events was used as a surrogate for symptomatic VTE events as the orthopaedic subgroup accepted that there was a relationship between the risk reduction in DVT and PE.

Trade off between clinical benefit and harms The benefit of reducing VTE events was balanced with the potential harms of bleeding. The economic model includes consideration of long term sequelae such as the cost of reoperation due to bleeding, post thrombotic syndrome, chronic thromboembolic pulmonary hypertension and stroke.

Our decision model indicated that the QALYs lost due to major bleeding were outweighed by the QALYs gained from drug prophylaxis.

Economic considerations An economic model was developed for this population which found that fondaparinux, dabigatran, LMWH and rivaroxaban were the most cost-effective strategies.

AspirinHD_plus_IPCD-FID also came out as relatively cost-effective in the base case analysis but this was on the basis that aspirin does not increase the risk of major bleeding. When an increased risk of bleeding similar to LMWH was assumed then aspirin was no longer cost-effective. The GDG felt that the base case assumption was not plausible and therefore concluded that AspirinHD_plus_IPCD-FID was not sufficiently cost-effective.

Quality of evidence All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). The clinical evidence consisted of 23 RCTs in knee replacement surgery of which 18 were included in the network meta-analysis for DVT. The studies tended to be relatively large and only 17% (4/23) had less than 100 patients. Additionally they were relatively recent studies with only 9% (2/23) published before 1990 and 52% (11/23) published since 2000.

Other considerations Pharmacological prophylaxis: The orthopaedic subgroup were mindful of the increase in bleeding risk in the period immediately after knee surgery and agreed that prophylaxis should be started only after the immediate bleeding risk had reduced.

Only one RCT compared pre op start times with post-op start for LMWH and this showed no significant difference in major bleeding.

The summary of product characteristics states a postoperative
start time for dabigatran, rivaroxaban and fondaparinux, and a preoperative start time for most LMWHs although the actual start times vary depending on the specific LMWH. In this guideline it is recommended that LMWH is started postoperatively which is off-label because concerns about the risk of bleeding into the joint. Patients would be protected preoperatively against VTE by mechanical prophylaxis. Some of the LMWH studies included in our analyses also started LMWH postoperatively. Further information should be sought from the summary of product characteristics for each anticoagulant.

The LMWH dose used in the comparison of LMWH with rivaroxaban is higher than that recommended for use in the UK. This was taken into account when considering which pharmacological agents to use.

**Mechanical prophylaxis:**

There was no evidence in knee replacement patients for the use of stockings alone. Because there were no trials which used stockings they could not be included in the network meta-analysis for knee replacement patients, and were not included in the cost-effectiveness model. There was a discussion within the orthopaedic subgroup about the practicality of using anti-embolism stockings after knee replacement surgery. Patients are likely to have swollen legs after surgery and so it was felt important to ensure that patient’s legs are re-measured after surgery to ensure stockings remained correctly fitted correctly.

The evidence demonstrates that IPCD/FID devices were effective at reducing DVT and were a more practical solution in these patients. The orthopaedic subgroup therefore recommended that IPCD/FID were available as an alternative to anti-embolism stockings. The orthopaedic subgroup were aware of potential patient compliance issues with the use of IPCD and difficulty of their use when patients regained mobility but agreed that either anti-embolism stockings or IPCD devices should be continued until the patient was discharged or no longer had significantly reduced mobility.

Mechanical prophylaxis was felt to be particularly important in the period around the operation where patients were not protected by chemical prophylaxis. The orthopaedic subgroup agreed that by providing mechanical methods from admission the risk of developing DVT in the peri-operative period was reduced.

**Duration of prophylaxis:** The duration of pharmacological prophylaxis from the trials and on which the cost-effectiveness model was based was between 7-14 days. The orthopaedic subgroup noted that the length of stay for knee replacement patients is likely to be around 5-7 days. The orthopaedic subgroup decided that the duration of prophylaxis should be for 10-14 days (as per licensing conditions), in order to reflect
the evidence from trials. This may require prophylaxis outside the hospital period. If the patient is discharged with prophylaxis, their GP should be notified to ensure that appropriate after care is provided. A suitable regime might be LMWH whilst in hospital followed by oral agents once discharged home.

11.7.1 Other recommendations of relevance

The specific recommendations for patients having elective total knee replacement in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information including when patients are discharged with prophylaxis (Section 32.5)

11.8 Summary of recommendations

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing elective knee replacement surgery.

  - Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:
    - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

  - Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose one of the following:
    - dabigatran etexilate, starting 1–4 hours after surgery*
    - fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established
    - LMWH, starting 6–12 hours after surgery
- rivaroxaban, starting 6–10 hours after surgery
- UFH (for patients with renal failure), starting 6–12 hours after surgery.

Continue pharmacological VTE prophylaxis for 10–14 days, according to the summary of product characteristics for the individual agent being used.

* Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157(2008).476

$ Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).479
12 Hip fracture surgery

12.1 Introduction

Fractures of the proximal femur (commonly known as neck of femur or hip fractures) are very common in the elderly population and carry significant morbidity and mortality. They occur mainly as osteoporotic or fragility fractures but a small proportion may result from major trauma in a younger age group. The latter is covered under the section on major trauma (Section 22).

We have estimated from the incidence of RCTs that the risk of developing DVT, pulmonary embolism and major bleeding in patients with fractures of the proximal femur not receiving thromboprophylaxis is:

- DVT (symptomatic and asymptomatic) - 37% (95% CI: 35% to 40%)
- Symptomatic pulmonary embolism – 6% (95% CI: 4% to 7%)
- Major bleeding events – 2% (95% CI: 1% to 3%)

It is likely from the evidence available that the incidence of each is greater in this patient group with an additional impact mainly from cardiovascular, respiratory and cerebrovascular disease. Therefore, the risks of adding mechanical and pharmacological VTE prophylaxis have to be weighed very carefully against any potential adverse effects of this treatment. However, there is some evidence from the studies evaluated for this guideline that there is a reduction in VTE events if thromboprophylaxis is used. This effect is greater in proportion than the risk of adverse events, in particular, major bleeding.

12.2 Evidence of methods of prophylaxis

12.2.1 Summary of comparisons identified for any outcome

Thirty randomised controlled trials which reported at least one of the three main outcomes were identified[51,74,172,175-178,185,204,209,248,316,370,381,458,463-465,470,533,541,590,609,613,621,630,631,700,704,715]. Some of these investigated more than two methods of thromboprophylaxis. Most of RCTs had their data extracted from systematic reviews. Where applicable the study is cited in the evidence table for that review. Six systematic reviews included RCTs covering patients with hip fracture21,125,355,451,557,719.
Another two studies investigated thromboprophylaxis in a mixed population of both hip fracture and elective hip replacement patients\textsuperscript{122,459}.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++)..

![Figure 12-31: Number of studies which compared various types of prophylaxis methods.](image)

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg); Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis
### 12.2.2 Results from pairwise comparisons

#### Table 12-71: DVT – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proph vs no proph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID vs nil(185)</td>
<td>1</td>
<td>4/145</td>
<td>9/159</td>
<td>0.49</td>
<td>-0.03</td>
<td>ET: 24 FP: 4</td>
</tr>
<tr>
<td>LMWH vs nil(31,6,613)</td>
<td>2</td>
<td>33/102</td>
<td>78/116</td>
<td>0.48</td>
<td>-0.35</td>
<td>ET: 26 FP: 13</td>
</tr>
<tr>
<td>UFH vs nil(31,209,370,464,631,704)</td>
<td>6</td>
<td>63/236</td>
<td>115/228</td>
<td>0.56</td>
<td>-0.23</td>
<td>ET: 27 FP: 17</td>
</tr>
<tr>
<td>VKA vs nil(74,248,463,470,533)</td>
<td>5</td>
<td>57/245</td>
<td>132/240</td>
<td>0.44</td>
<td>-0.32</td>
<td>ET: 28 FP: 21</td>
</tr>
<tr>
<td>High dose asp vs nil(172,464,533,590,609,700,715)</td>
<td>7</td>
<td>117/385</td>
<td>116/338</td>
<td>0.85</td>
<td>-0.05</td>
<td>ET: 29 FP: 28</td>
</tr>
</tbody>
</table>

| **Single proph vs single** | | | | | | |
| Fon vs LMWH\(175\) | 1              | 49/624        | 117/623 | 0.42          | -0.11          | ET: 31 FP: 44                 |
| LMWH vs UFH\(381,458\) | 1              | 14/53         | 23/54   | 0.62          | -0.16          | ET: 32 FP: 48                 |
| VKA vs high dose asp\(533\) | 1              | 13/65         | 27/66   | 0.49          | -0.21          | ET: 35 FP: 60                 |

| **Double proph vs single** | | | | | | |
| UFH + GCS vs GCS\(465\) | 1              | 10/29         | 8/23    | 0.99          | -0.01          | ET: 27 FP: 142                |

| **Other prophylaxis strategies** | | | | | | |
| IPCD then LMWH vs LMWH\(177\) | 1              | 2/21          | 4/24    | 0.57          | -0.07          | ET: 51 FP: 209                |

| **Post discharge** | | | | | | |
| Fondaparinux\(176\) | 1              | 3/208         | 74/218  | 0.04          | -0.33          | ET: 57 FP: 221                |

* \(FP\) – forest plot number in Appendix E; \(ET\) – evidence table number in Appendix D

**Proph - prophylaxis**

(a) Significant statistical heterogeneity within the results \(I^2 = 54\%, p=0.03\)

(b) Significant statistical heterogeneity within the results \(I^2 = 60.3\%, p=0.02\)

#### Table 12-72: Pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proph vs no proph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID vs nil(185)</td>
<td>1</td>
<td>6/145</td>
<td>9/159</td>
<td>0.73</td>
<td>-0.01</td>
<td>ET: 24 FP: 5</td>
</tr>
<tr>
<td>UFH vs nil(204,464)</td>
<td>2</td>
<td>1/74</td>
<td>2/74</td>
<td>0.50</td>
<td>-0.01</td>
<td>ET: 27 FP: 18</td>
</tr>
<tr>
<td>VKA vs nil(4,178,463,470,533)</td>
<td>5</td>
<td>4/307</td>
<td>28/303</td>
<td>0.21</td>
<td>0.01</td>
<td>ET: 28 FP: 22</td>
</tr>
<tr>
<td>High dose asp vs nil(172,464,533,590,609,700,715)</td>
<td>7</td>
<td>12/385</td>
<td>26/338</td>
<td>0.44</td>
<td>-0.01</td>
<td>ET: 29 FP: 29</td>
</tr>
</tbody>
</table>

<p>| <strong>Single proph vs single</strong> | | | | | | |
| Fon vs LMWH(175) | 1              | 3/831         | 3/840   | 1.01          | -0.01          | ET: 31 FP: 45                 |</p>
<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH vs UFH(^{156})</td>
<td>1</td>
<td>6/46</td>
<td>0/42</td>
<td>11.89</td>
<td>(0.69, 204.91)</td>
<td>0.13</td>
</tr>
<tr>
<td>VKA vs high dose asp(^{533})</td>
<td>1</td>
<td>0/65</td>
<td>1/66</td>
<td>0.34</td>
<td>(0.01, 8.16)</td>
<td>-0.02</td>
</tr>
<tr>
<td><strong>Double proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH + GCS vs GCS(^{465})</td>
<td>1</td>
<td>2/29</td>
<td>1/23</td>
<td>1.59</td>
<td>(0.15, 16.42)</td>
<td>0.03</td>
</tr>
<tr>
<td>Aspirin + other prophylaxis vs other prophylaxis (b)(^{541})</td>
<td>1</td>
<td>46/6679</td>
<td>81/677</td>
<td>0.57</td>
<td>(0.40, 0.81)</td>
<td>-0.01</td>
</tr>
<tr>
<td><strong>Other prophylaxis strategies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD then LMWH vs LMWH(^{77})</td>
<td>1</td>
<td>1/21</td>
<td>0/24</td>
<td>3.41</td>
<td>(0.15, 79.47)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Extended duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux(^{176})</td>
<td>1</td>
<td>0/326</td>
<td>3/330</td>
<td>0.14</td>
<td>(0.01, 2.79)</td>
<td>-0.01</td>
</tr>
</tbody>
</table>

* FP – forest plot number in Appendix E; ET – evidence table number in Appendix D

Proph = prophylaxis

(a) Asymptomatic and symptomatic pulmonary embolism

---

### Table 12.73: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proph vs no proph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil(^{316})</td>
<td>1</td>
<td>0/41</td>
<td>0/41</td>
<td>not estimable</td>
<td></td>
<td>0.00</td>
</tr>
<tr>
<td>UFH vs nil(^{51,204,464,704})</td>
<td>4</td>
<td>4/129</td>
<td>6/123</td>
<td>0.69</td>
<td>(0.23, 2.13)</td>
<td>-0.01</td>
</tr>
<tr>
<td>VKA vs nil(^{74,178,248,463,533})</td>
<td>5</td>
<td>26/312</td>
<td>18/310</td>
<td>1.35</td>
<td>(0.70, 2.62)</td>
<td>0.02</td>
</tr>
<tr>
<td>High dose asp vs nil(^{72,464,533,590,609,700,715})</td>
<td>87</td>
<td>8/385</td>
<td>10/338</td>
<td>0.52</td>
<td>(0.14, 1.96)</td>
<td>-0.01</td>
</tr>
</tbody>
</table>

*FP – forest plot number in Appendix E; ET – evidence table number in Appendix D

Proph = prophylaxis

### Single proph vs single

**Double proph vs single**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fon vs LMWH(^{175})</td>
<td>1</td>
<td>18/831</td>
<td>19/842</td>
<td>0.96</td>
<td>(0.51, 1.82)</td>
<td>0.00</td>
</tr>
<tr>
<td>VKA vs high dose asp(^{533})</td>
<td>1</td>
<td>5/65</td>
<td>1/66</td>
<td>5.08</td>
<td>(0.61, 42.28)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Other prophylaxis strategies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Post discharge**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux(^{176})</td>
<td>1</td>
<td>8/327</td>
<td>2/329</td>
<td>4.02</td>
<td>(0.86, 18.81)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*FP – forest plot number in Appendix E; ET – evidence table number in Appendix D

Proph = prophylaxis
12.2.3 Additional information

12.2.3.1 All cause mortality

Table 12-74: Mortality – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil(^{316})</td>
<td>1</td>
<td>3/30</td>
<td>4/38</td>
<td>0.95</td>
<td>(-0.01, 0.14)</td>
<td>ET: 26 FP: 16</td>
</tr>
<tr>
<td>UFH vs nil(^{51,204,631})</td>
<td>3</td>
<td>20/193</td>
<td>20/187</td>
<td>0.96</td>
<td>(-0.01, 0.07)</td>
<td>ET: 27 FP: 20</td>
</tr>
<tr>
<td>VKA vs nil(^{74,178,248,463,470,533})</td>
<td>6</td>
<td>47/362</td>
<td>62/365</td>
<td>0.76</td>
<td>(-0.01, 0.03)</td>
<td>ET: 28 FP: 24</td>
</tr>
<tr>
<td>High dose asp vs nil(^{72,464,533,590,609,700,715})</td>
<td>7</td>
<td>23/385</td>
<td>25/338</td>
<td>0.75</td>
<td>(-0.04, 0.03)</td>
<td>ET: 29 FP: 31</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fon vs LMWH(^{175})</td>
<td>1</td>
<td>38/831</td>
<td>42/842</td>
<td>0.92</td>
<td>(-0.00, 0.02)</td>
<td>ET: 31 FP: 47</td>
</tr>
<tr>
<td>LMWH vs UFH(^{381,458})</td>
<td>2</td>
<td>6/99</td>
<td>5/98</td>
<td>1.17</td>
<td>(-0.05, 0.07)</td>
<td>ET: 32 FP: 51</td>
</tr>
<tr>
<td>VKA vs high dose asp(^{533})</td>
<td>1</td>
<td>2/65</td>
<td>3/66</td>
<td>0.68</td>
<td>(-0.08, 0.05)</td>
<td>ET: 35 FP: 63</td>
</tr>
<tr>
<td>Double proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH + GCS vs GCS(^{465})</td>
<td>1</td>
<td>0/29</td>
<td>3/23</td>
<td>0.11</td>
<td>(-0.13, 0.02)</td>
<td>ET: 27 FP: 145</td>
</tr>
<tr>
<td>Post discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux(^{176})</td>
<td>1</td>
<td>6/327</td>
<td>8/329</td>
<td>0.75</td>
<td>(-0.03, 0.02)</td>
<td>ET: 57 FP: 224</td>
</tr>
</tbody>
</table>

* FP – forest plot number in Appendix E; ET – evidence table number in Appendix D

Proph - prophylaxis

12.2.3.2 Additional outcomes

No RCTs or systematic reviews reported results for post thrombotic syndrome, chronic thromboembolic pulmonary hypertension, heparin induced thrombocytopenia, quality of life or length of stay as outcomes for this population.

12.2.3.3 Additional studies

Two RCTs investigated thromboprophylaxis in a mixed group of hip fracture and elective hip replacement patients. These have not been included in the above section and were not included in the economic model for either hip fracture or elective hip replacement:

- Cohen et al\(^{122}\) found there was no significant difference in DVT or pulmonary embolism when stockings for 35 days were added to fondaparinux for five to nine days. (Appendix D, Evidence table 40; Appendix E, Forest plots 170-172)

- Monreal et al\(^{459}\) found there was no significant difference in DVT or major bleeding when aspirin was added to UFH. (Appendix D, Evidence table 42; Appendix E, Forest plots 161, 163)
12.3 Network meta-analysis results

12.3.1 Introduction

A network meta-analysis was completed for DVT, major bleeding and all cause mortality. Details on the network meta-analysis methods can be found in section 3.10.

For patients undergoing surgery for fractures of the proximal femur the studies of standard duration prophylaxis (e.g. prophylaxis given for a maximum of 21 days) were analysed in the network meta-analysis. Prophylaxis extending beyond this period was analysed in a separate cost-effectiveness analysis.

12.3.2 Results

DVT results

There were 23 studies included in the network meta-analysis for DVT. One study compared three interventions.  

---

**Figure 12-32:** Network diagram for DVT. Numbers indicate the number of studies, which contributed results for each comparison.
Figure 12-33: DVT – network meta-analysis results of interventions compared to no prophylaxis

Table 12-75: DVT – network meta-analysis results

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux</td>
<td>0.11 (0.04, 0.31)</td>
</tr>
<tr>
<td>IPCD/FID then LMWH</td>
<td>0.14 (0.01, 0.82)</td>
</tr>
<tr>
<td>LMWH</td>
<td>0.29 (0.15, 0.50)</td>
</tr>
<tr>
<td>VKA (adjusted-dose)</td>
<td>0.33 (0.20, 0.51)</td>
</tr>
<tr>
<td>UFH</td>
<td>0.41 (0.25, 0.59)</td>
</tr>
<tr>
<td>IPCD / FID</td>
<td>0.58 (0.15, 1.37)</td>
</tr>
<tr>
<td>Asp (high dose)</td>
<td>0.79 (0.56, 1.07)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals.
The residual deviance was 56.0, which is quite close to the number of data points of 47, implying that the model fits the data well.

Pulmonary embolism results

There were not enough data to complete a network analysis for this outcome.

Major bleeding results

A network meta-analysis for major bleeding was conducted using studies across hip fracture surgery, hip replacement surgery, knee replacement surgery, general medical patients and general surgical patients.

One hundred and twenty eight (128) studies were included in the analysis of which:

- 10 studies were in medical patients
- 48 studies were in general surgery patients
- 28 studies were in elective hip replacement patients
- 9 studies were in patients undergoing hip fracture surgery

...
• 15 studies were in **elective knee replacement patients** 36,66,130,186,201,202,274,388,389,399,436,476,479.

• 7 studies were in **mixed orthopaedic surgery patients** 69,200,242,250,292,459,531.

• 11 studies were in **mixed surgery patients** 54,166,270,271,340,344,396,416,486,568,569,575,585,655.

Seven of these studies included three comparison arms 153,299,380,504,533,633,655.

---

**Figure 12-34: Network diagram for major bleeding.** Numbers indicate the number of studies which contributed results for each comparison.

Only the results for interventions included in the network meta-analysis for DVT were included in the results.
Table 12-76: Major bleeding – network meta-analysis results (pooled across all population subgroups)

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asp (high dose)</td>
<td>0.45 (0.18, 1.07)</td>
</tr>
<tr>
<td>VKA</td>
<td>1.24 (0.83, 1.85)</td>
</tr>
<tr>
<td>LMWH</td>
<td>1.26 (0.94, 1.71)</td>
</tr>
<tr>
<td>UFH</td>
<td>1.43 (1.08, 1.92)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.22 (1.30, 3.88)</td>
</tr>
<tr>
<td>Aspirin + UFH</td>
<td>2.69 (1.02, 6.91)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals.

The residual deviance was 291.5, which is quite close to the number of data points of 263, implying that the model fits the data quite well.

**Figure 12-35: Major bleeding – network meta-analysis results of interventions compared to no prophylaxis**

**All cause mortality**

There were 18 studies included in the network meta-analysis for all cause mortality51,74,172,175,178,204,248,316,380,458,463,470,533,590,609,631,700,715. One study compared three interventions533.
Figure 12-36: Network diagram for all cause mortality. Numbers indicate the number of studies which contributed results for each comparison

Table 12-77: All cause mortality – network meta-analysis results

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA</td>
<td>0.73 (0.44, 1.18)</td>
</tr>
<tr>
<td>Asp (high dose)</td>
<td>0.81 (0.42, 1.47)</td>
</tr>
<tr>
<td>UFH</td>
<td>0.88 (0.41, 1.68)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>0.93 (0.24, 2.85)</td>
</tr>
<tr>
<td>LMWH</td>
<td>1.00 (0.35, 2.55)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals.

The residual deviance was 33.5, which is quite close to the number of data points of 37, implying that the model fits the data well.

Figure 12-7: All cause mortality – network meta-analysis results of interventions compared to no prophylaxis

12.4 Cost-effectiveness evidence

12.4.1 Introduction

The general assumptions and methods for the cost-effectiveness model are described in chapter 4.

The results are driven by the network meta-analysis, above. Other data used for the cost-effectiveness analysis which are specific to hip fracture patients can be found in Table 12-76, Table 12-78 and Table 12-79.
Table 12-78: Baseline risk and other population specific parameters used in the economic model for hip fracture patients

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Source</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>Hospital Episode Statistics data 2005-6&lt;sup&gt;59&lt;/sup&gt;</td>
<td>82</td>
</tr>
<tr>
<td>% Male</td>
<td>Hospital Episode Statistics data 2005-6&lt;sup&gt;59&lt;/sup&gt;</td>
<td>23%</td>
</tr>
<tr>
<td>Standardised Mortality Ratio(a)</td>
<td>Seagroatt, 1994&lt;sup&gt;595&lt;/sup&gt;</td>
<td>461% (1 year)</td>
</tr>
<tr>
<td>Mean duration of prophylaxis</td>
<td>Systematic review of RCTs(b)</td>
<td>10 days</td>
</tr>
<tr>
<td>Proportion of DVTs that are symptomatic (Ratio of symptomatic DVTs to all DVTs)</td>
<td>Assumed to be the same as elective hip replacement.</td>
<td>21.0%</td>
</tr>
<tr>
<td>Major Bleed Fatality Rate (c)</td>
<td>Muntz (2004) systematic review of thromboprophylaxis RCTs&lt;sup&gt;467&lt;/sup&gt;</td>
<td>0.8% (5/632)</td>
</tr>
<tr>
<td>PE Fatality Rate (d)</td>
<td>Systematic review of RCTs (b)</td>
<td>31.0% (9/21)</td>
</tr>
<tr>
<td>DVT risk</td>
<td>Systematic review of RCTs (b)</td>
<td>39.8%</td>
</tr>
<tr>
<td>Symptomatic PE risk</td>
<td>Systematic review of RCTs (b)</td>
<td>7.9%</td>
</tr>
<tr>
<td>Major bleeding risk</td>
<td>Systematic review of RCTs (b)</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

a) Ratio of the death rate in the surgical group compared with the death rate in the general population, adjusting for age and sex
b) This refers to the systematic review of RCTs for the current guideline
c) Fatal major bleeds divided by all major bleeds
d) Fatal PEs divided by all symptomatic PEs

Table 12-79: Weights used for events in the base case analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Cost (£)</th>
<th>QALYs lost</th>
<th>Net loss&lt;sup&gt;*&lt;/sup&gt; (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT Asymptomatic</td>
<td>0</td>
<td>0.0000</td>
<td>0</td>
</tr>
<tr>
<td>DVT Symptomatic</td>
<td>576</td>
<td>0.0035</td>
<td>645</td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td>3,427</td>
<td>0.0801</td>
<td>5,030</td>
</tr>
<tr>
<td>Chronic pulmonary hypertension</td>
<td>69,123</td>
<td>0.9672</td>
<td>88,467</td>
</tr>
<tr>
<td>Pulmonary embolism - fatal</td>
<td>0</td>
<td>4.3044</td>
<td>86,089</td>
</tr>
<tr>
<td>Pulmonary embolism - symptomatic</td>
<td>2,521</td>
<td>0.0041</td>
<td>2,603</td>
</tr>
<tr>
<td>Major bleeding - No long-term sequelae</td>
<td>908</td>
<td>0.0267</td>
<td>1,441</td>
</tr>
<tr>
<td>Major bleeding - Stroke</td>
<td>23,877</td>
<td>2.2410</td>
<td>68,696</td>
</tr>
<tr>
<td>Major bleeding - fatal</td>
<td>0</td>
<td>4.3044</td>
<td>86,089</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopaenia</td>
<td>2,428</td>
<td>0.6395</td>
<td>15,219</td>
</tr>
</tbody>
</table>

QALY=quality-adjusted life-year

* Net loss is the sum of the resource cost plus the QALY loss:
  
  \[ \text{Net loss} = \text{cost} + (20,000 \times \text{QALYs lost}) \]

Event rates by strategy can be found in Appendix G.
12.4.2 Results: standard duration prophylaxis

12.4.2.1 Base case results

Table 12-80: Base case results – deterministic and probabilistic results

<table>
<thead>
<tr>
<th>Intervention (ordered by mean probabilistic INB)</th>
<th>Deterministic INB</th>
<th>Probabilistic INB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Mean</td>
<td>% of simulations where strategy was most cost-effective</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2151</td>
<td>2148</td>
</tr>
<tr>
<td>WarfarinAD</td>
<td>1835</td>
<td>1830</td>
</tr>
<tr>
<td>LMWH</td>
<td>1713</td>
<td>1711</td>
</tr>
<tr>
<td>UFH</td>
<td>1470</td>
<td>1465</td>
</tr>
<tr>
<td>IPCD-FID</td>
<td>979</td>
<td>999</td>
</tr>
<tr>
<td>AspirinHD</td>
<td>560</td>
<td>558</td>
</tr>
<tr>
<td>Nil</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost-effective overall.

Figure 12-7: Base case results of the cost-effectiveness analysis for hip fracture patients: standard duration prophylaxis

Fon = fondaparinux, Warf = warfarin, QALY=quality-adjusted life-year
12.4.3 Base case results – post discharge prophylaxis

Table 12-81: Results for study post discharge comparing LMWH with no prophylaxis

<table>
<thead>
<tr>
<th>Intervention (ordered by mean probabilistic INB)</th>
<th>Deterministic INB</th>
<th>Probabilistic INB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (%)</td>
<td>Mean (Mean)</td>
<td>% of simulations where strategy was most cost-effective</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>262</td>
<td>239</td>
</tr>
<tr>
<td>Nil</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost-effective overall.

Figure 12-7: Base case results of the cost-effectiveness analysis for hip fracture patients: post-discharge prophylaxis

Fon = fondaparinux

£1700 per QALY gained
### 12.4.4 Deterministic sensitivity analysis

**Table 12-82: Deterministic sensitivity analysis results**

<table>
<thead>
<tr>
<th>Factors changed within the Model</th>
<th>Most Cost-effective Strategy</th>
<th>Standard duration prophylaxis</th>
<th>Post Discharge (fondaparinux vs nil)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case</strong></td>
<td></td>
<td>Fondaparinux</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td><strong>Base case (probabilistic)</strong></td>
<td></td>
<td>Fondaparinux</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td><strong>Chronic Thromboembolic Pulmonary Hypertension and Post Thrombotic Syndrome</strong></td>
<td></td>
<td>Fondaparinux</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>0% Chronic Thromboembolic Pulmonary Hypertension</td>
<td></td>
<td>Fondaparinux</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>0.5% Chronic Thromboembolic Pulmonary Hypertension</td>
<td></td>
<td>Fondaparinux</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>1% Chronic Thromboembolic Pulmonary Hypertension</td>
<td></td>
<td>Fondaparinux</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>0% Chronic Thromboembolic Pulmonary Hypertension and 0% Post Thrombotic Syndrome</td>
<td></td>
<td>Fondaparinux</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>High Post Thrombotic Syndrome rate (e.g. 30% after symptomatic DVT and 21% after asymptomatic DVT)</td>
<td></td>
<td>Fondaparinux</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>Low Post Thrombotic Syndrome (e.g. 15% after symptomatic DVT and 8% after asymptomatic DVT)</td>
<td></td>
<td>Fondaparinux</td>
<td>Fondaparinux</td>
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<tr>
<td>Low cost for Post Thrombotic Syndrome</td>
<td></td>
<td>Fondaparinux</td>
<td>Fondaparinux</td>
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<tr>
<td>High cost for Post Thrombotic Syndrome</td>
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<td>Fondaparinux</td>
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<tr>
<td>High cost for Chronic Thromboembolic Pulmonary Hypertension</td>
<td></td>
<td>Fondaparinux</td>
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</table>

**Other Sensitivity Analyses**

- Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.5%, UFH=5%)
- Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.2%, UFH=2.6%)
- Using population specific major bleeding relative risks
- Low aspirin major bleeding relative risk from Network Meta-analysis (RR = 0.49)
- High aspirin major bleeding relative risk from aspirin vs. nil arms (RR = 1.3)
- Discounted LMWH cost = £1
- Fatality after PE = 10%
- Fatality after Major Bleeding = 5%
- Foot Impulse Device cost (consumable: £40, pump: £0)
- Increased NICE threshold (£30,000/QALY)

*QALY=quality-adjusted life-year*
Table 12-83: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: standard duration prophylaxis

<table>
<thead>
<tr>
<th>PE risk</th>
<th>0%</th>
<th>0.5%</th>
<th>1%</th>
<th>1.5%</th>
<th>2%</th>
<th>2.5%</th>
<th>3%</th>
<th>3.5%</th>
<th>4%</th>
<th>4.5%</th>
<th>5%</th>
<th>5.5%</th>
<th>6%</th>
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</table>

Fon=fondaparinux

Table 12-84: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: post-discharge

<table>
<thead>
<tr>
<th>PE risk</th>
<th>0%</th>
<th>0.5%</th>
<th>1%</th>
<th>1.5%</th>
<th>2%</th>
<th>2.5%</th>
<th>3%</th>
<th>3.5%</th>
<th>4%</th>
<th>4.5%</th>
<th>5%</th>
<th>5.5%</th>
<th>6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Nil</td>
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<td>Fon</td>
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<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
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</tr>
<tr>
<td>Fon</td>
<td>Fon</td>
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<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
<td>Fon</td>
</tr>
</tbody>
</table>

Fon=fondaparinux, Nil=no post-discharge prophylaxis

In a threshold sensitivity analysis, we found that post-discharge fondaparinux prophylaxis was no longer cost-effective if greater than 55% of patients require district nurse visits to deliver their prophylaxis.

12.4.5 Conclusion

For standard duration prophylaxis, fondaparinux was the most effective at increasing quality-adjusted life-years and the most cost-effective strategy.

For patients with a very low bleeding risk fondaparinux was the most cost-effective strategy. LMWH tended to be more cost-effective as the risk of major bleeding increased.
Fondaparinux was the most cost-effective strategy in all other deterministic sensitivity analyses conducted.

In the post discharge period fondaparinux was found to be cost-effective compared to no post-discharge prophylaxis. It remained the most cost-effective strategy in all of the deterministic sensitivity analyses conducted.

12.5 Patient views

No studies on patient views or adherence conducted specifically among patients undergoing hip fracture surgery were found.

For patient views from all patient groups (medical and surgical) about specific prophylaxis agents, see section 6.6 Error! Reference source not found. Error! Reference source not found. Error! Reference source not found.

12.6 Summary of evidence

Table 12-85: Summary of evidence from network meta-analysis results for DVT, symptomatic pulmonary embolism and major bleeding outcomes.

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DVT</td>
</tr>
<tr>
<td>Prophylaxis vs no prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID</td>
<td>no prophylaxis</td>
<td>Not sig</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>no prophylaxis</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>LMWH</td>
<td>no prophylaxis</td>
<td>LMWH</td>
</tr>
<tr>
<td>UFH</td>
<td>no prophylaxis</td>
<td>UFH</td>
</tr>
<tr>
<td>VKA (adjusted dose)</td>
<td>no prophylaxis</td>
<td>VKA</td>
</tr>
<tr>
<td>Aspirin (high-dose)</td>
<td>no prophylaxis</td>
<td>Not sig</td>
</tr>
<tr>
<td>IPCD then LMWH</td>
<td>no prophylaxis</td>
<td>IPCD then LMWH</td>
</tr>
<tr>
<td>Post Discharge (from direct evidence)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>No prophylaxis</td>
<td>Fondaparinux</td>
</tr>
</tbody>
</table>

Cost-effectiveness results

Fondaparinux was the most cost-effective strategy for standard duration prophylaxis except when major bleeding rate risk was high in which case LMWH was most cost-effective.

In the post discharge period fondaparinux was found to be cost-effective. No data were available for post-discharge use of LMWH in hip fracture patients.

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. No event = outcomes reported in study(ies) but no events were reported. ‘-’ = not reported. MB = Major bleeding
### 12.7 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing hip fracture surgery.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)</td>
</tr>
<tr>
<td></td>
<td>- foot impulse devices</td>
</tr>
<tr>
<td></td>
<td>- intermittent pneumatic compression devices (thigh or knee length).</td>
</tr>
<tr>
<td></td>
<td>Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.</td>
</tr>
<tr>
<td></td>
<td>- Provided there are no contraindications, add pharmacological VTE prophylaxis. Choose any one of:</td>
</tr>
<tr>
<td></td>
<td>- fondaparinux sodium, starting 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2)</td>
</tr>
<tr>
<td></td>
<td>- LMWH, starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.</td>
</tr>
<tr>
<td></td>
<td>- UFH (for patients with renal failure), starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.</td>
</tr>
<tr>
<td></td>
<td>Continue pharmacological VTE prophylaxis for 28–35 days, according to the summary of product characteristics for the individual agent being used.</td>
</tr>
</tbody>
</table>

| Recommendation | Fondaparinux sodium is not recommended for use preoperatively for patients undergoing hip fracture surgery. If it has been used preoperatively it should be stopped 24 hours before surgery and restarted 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2). |

<table>
<thead>
<tr>
<th>Box 2-Bleeding Risk Factors</th>
<th>Regard hospitalised patients as being at risk of bleeding if they have any of the following risk factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Active bleeding</td>
</tr>
<tr>
<td></td>
<td>- Acquired bleeding disorders (such as acute liver failure)</td>
</tr>
<tr>
<td></td>
<td>- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)</td>
</tr>
<tr>
<td></td>
<td>- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours</td>
</tr>
</tbody>
</table>
Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours

Acute stroke

Thrombocytopenia (platelets < 75 x 10⁹/l)

Uncontrolled systolic hypertension (230/120 mmHg or higher)

Untreated inherited bleeding disorders (such as haemophilia and von Willebrand’s disease).

**Relative values of different outcomes**

The orthopaedic subgroup noted that although all-cause mortality is the most important outcome for this population the studies were not powered to detect a difference in mortality for any of the interventions under consideration. The next most important outcome was thought to be the risk of symptomatic venous thromboembolism balanced against the risk of major bleeding. The relative risk reduction for all DVT events was used as a surrogate for symptomatic VTE events as the orthopaedic subgroup accepted that there was a relationship between the risk reduction in DVT and PE.

**Trade off between clinical benefit and harms**

The benefit of reducing VTE events is balanced with the potential harms of bleeding. The economic model includes consideration of long-term sequelae such as the cost of reoperation due to bleeding, post thrombotic syndrome, chronic thromboembolic pulmonary hypertension and stroke. Our decision model indicated that the QALYs lost due to major bleeding were outweighed by the QALYs gained from drug prophylaxis.

**Economic considerations**

An economic model was developed for this population. This model indicated that fondaparinux was the most effective and most cost-effective prophylaxis method for standard duration prophylaxis. LMWH was the next most-cost-effective strategy and became more cost-effective as the baseline risk of bleeding increases.

The economic model showed that extending prophylaxis with fondaparinux for 35 days post-surgery was cost-effective for this population. No data were available for determining the cost-effectiveness of extended LMWH prophylaxis used in this population, although results from elective hip replacement surgery indicated it was cost-effective for this population.

No evidence for combination prophylaxis in this population was included in the economic model. Evidence for the effectiveness of combination prophylaxis for fractures of the proximal femur is extrapolated from elective hip replacement evidence. As patients with fractures of the proximal femur have an increased DVT and PE risk compared with elective hip replacement surgery and that mechanical prophylaxis had no impact on the bleeding risk the orthopaedic subgroup felt that it was likely to be cost-effective in this population.
Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

The clinical evidence consisted of 30 RCTs of which 23 were included in the network meta-analysis for DVT. These studies tended to be small, 61% (14/23) and had less than 100 patients. In addition, 78% (18/23) were published before 1990. Some studies reported bleeding outcomes using different criteria. After a review of the techniques used for fixation of the fractures of the proximal femur used within individual studies it was noted that there was a wide variety of techniques including some which were no longer used in current practice. This may limit the applicability of the evidence.

Other considerations

Many patients undergoing surgery for fracture of the proximal femur are likely to be elderly and may have comorbidities that increase the risk of developing deep vein thrombosis and pulmonary emboli.

Initiation of prophylaxis: The orthopaedic subgroup noted that in this population, individual patient risk factors for VTE (e.g. advanced age and immobility) were likely to be present at admission. It was also noted that surgery for these cases might not occur immediately due to time taken to stabilise the patient or availability of surgical resources. The orthopaedic subgroup agreed that prophylaxis should be initiated at admission once the bleeding risks had been established and it had been confirmed that patients did not have contraindications. The orthopaedic subgroup were concerned about pre-operative bleeding and noted that if the bleeding risks were unknown at admission, mechanical prophylaxis should be initiated until the risk of bleeding had been established.

The summary of product characteristics states a postoperative start time for dabigatran, rivaroxaban and fondaparinux, and a preoperative start time for most LMWHs although the actual start times vary depending on the specific LMWH. In this guideline it is recommended that LMWH is started postoperatively which is off-label because concerns about the risk of bleeding into the joint. Patients would be protected preoperatively against VTE by mechanical prophylaxis. Some of the LMWH studies included in our analyses also started LMWH postoperatively.

Use of fondaparinux: Although the results of the economic model found fondaparinux to be cost-effective both for standard duration and post discharge prophylaxis, the orthopaedic subgroup were aware of the increased risk of bleeding using this agent. Therefore, an additional statement was added to indicate that this agent should only be used where there was not an increased bleeding risk.

In addition, the orthopaedic subgroup decided that due to the longer acting duration of fondaparinux and therefore the need to stop it up to 24 hours before surgery, it should not be given as the preferred thromboprophylactic agent on admission.

Use of warfarin: The orthopaedic subgroup decided that warfarin should not be recommended for this population. Warfarin was felt
to be an outdated modality, which was difficult to monitor. There were concerns with possible interactions between warfarin and other drugs and about lack of cost-effectiveness if continued after discharge.

**Use of UFH:** The Guideline Development Group felt that UFH should be considered as an option for patients with renal impairment.

**Timing of chemical prophylaxis around surgery:** The orthopaedic subgroup were mindful of the increase in bleeding risk in the period immediately after surgery. They suggested that prophylaxis with LMWH and UFH should be stopped 12 hours before surgery and recommenced once the immediate bleeding risk had reduced, 6-12 hours after the operation.

**Mechanical prophylaxis:** The orthopaedic subgroup noted that the use of anti-embolism stockings in patients with a fracture of the proximal femur after surgery was often painful and impractical but they felt that with care and following the recommendations relating to the use of stockings they could be used (section 6.7). The evidence demonstrates that IPCD/FID were cost-effective in this population compared with no prophylaxis and were likely to be a more practical solution than stockings in these patients.

Mechanical prophylaxis was felt to be particularly important in the period around the operation where patients were not protected by chemical prophylaxis. Likewise, if no pharmacological agents can be given for 24 hours then IPCD/FID should be provided at this time to ensure the patient has some protection from VTE events.

The orthopaedic subgroup were aware of patient compliance issues with the use of IPCD and anti-embolism stockings but agreed that they should be continued until the patient was discharged or no longer had significantly reduced mobility.

**Duration of prophylaxis:** The cost-effectiveness results support the provision of fondaparinux for prophylaxis outside hospital. There is no evidence for extending the duration of LMWH after hip fracture surgery and so the recommendation for LMWH up to 35 days has been extrapolated from the evidence relating to elective hip replacement.

### 12.7.1 Other recommendations of relevance

The specific recommendations for patients undergoing hip fracture surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information, including for post discharge prophylaxis (section 32.5)
12.8 Recommendations for research

Although not identified as a top 5 research recommendation (Chapter 2.3) the orthopaedic subgroup noted that the new oral anticoagulants (such as dabigatran and rivaroxaban) have not been trialed in patients undergoing hip fracture surgery. These drugs have the potential to make extended VTE prophylaxis much easier for patients with these patients as they are oral agents as opposed to requiring self injection (as LMWH does) and as such research in these patients would be beneficial.

12.9 Summary of recommendations

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing hip fracture surgery.

  - Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:
    - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

  - Provided there are no contraindications, add pharmacological VTE prophylaxis. Choose any one of the following:
    - fondaparinux sodium, starting 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2),
    - LMWH, starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.
    - UFH (for patients with renal failure), starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.

  Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used.

- Fondaparinux sodium is not recommended for use preoperatively for patients undergoing hip fracture surgery. If it has been used preoperatively it should be stopped 24 hours before surgery and restarted 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2).
Box 2. Bleeding Risk Factors

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10^9/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand’s disease)
13 Other orthopaedic surgery

13.1 Introduction

This section has been included to allow for a comprehensive review of the evidence available as it affects orthopaedic patients, mainly, in an elective setting. The populations covered are those undergoing upper limb surgery (including shoulders, elbows and hands), lower limb surgery (excluding elective total hip and knee replacement) and arthroscopy. There is some overlap with the section on lower limb plaster casts. Spinal surgery is not considered within this chapter (see section 14) It is difficult to be clear about the baseline risk of VTE as it affects these groups because of a lack of evidence but the incidence of DVT in the groups not receiving thromboprophylaxis of the RCTs identified for knee arthroscopy ranged between 4-15% and the effect may be magnified by the large number of patients involved.

The only available studies involve arthroscopy and, clearly, there are limitations in extrapolating from these data. However, the use of a risk assessment tool and a frank discussion with each patient at the pre-operative assessment clinic as part of the informed consent process about the pros and cons of prophylaxis is highly desirable. More complex procedures, for example, shoulder or elbow arthroplasty in a patient with rheumatoid arthritis, arthroscopically assisted ACL reconstruction or open ankle arthrodesis may be associated with a greater risk.

13.1.1 Spinal surgery

Spinal surgery can be completed by orthopaedic surgeons or neurosurgeons although there is a move to the same subspecialty practice in both specialties. Studies conducted in this population have often combined cranial and spinal surgery and it is difficult to separate the two. The evidence and recommendations for spinal surgery patients is presented in chapter 14 (Cranial and Spinal Surgery).

13.2 Evidence of methods of prophylaxis

13.2.1 Summary of comparisons identified for any outcome

The only population for which there was any evidence found was for knee arthroscopy, where 4 studies were identified. All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).
### 13.2.2 Results from pairwise comparisons

**Table 13-86: DVT – summary of results from RCTs**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>2</td>
<td>2/183</td>
<td>15/186</td>
<td>0.014</td>
<td>(-0.08, 0.04)</td>
<td>ET: 26 FP: 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.03, 0.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS vs LMWH</td>
<td>1</td>
<td>29/660</td>
<td>10/657</td>
<td>2.89</td>
<td>(0.03, 0.05)</td>
<td>ET: 37 FP: 81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.42, 5.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>1</td>
<td>2/72</td>
<td>28/68</td>
<td>0.07</td>
<td>(-0.38, -0.26)</td>
<td>ET: 58 FP: 225</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.02, 0.27)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

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**Figure 13-37: Number of studies which compared various types of prophylaxis methods.**

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicate areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) – low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis.
Proph - prophylaxis

### Table 13-87: Pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single proph vs single GCS vs LMWH 94</td>
<td>1</td>
<td>2/660</td>
<td>2/657</td>
<td>1.00 (0.14, 7.05)</td>
<td>0.00 (-0.01, 0.01)</td>
<td>Et: 37 FP: 81</td>
</tr>
<tr>
<td>Post discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH 425</td>
<td>1</td>
<td>0/87</td>
<td>0/88</td>
<td>N/A</td>
<td>0.00 (-0.02, 0.02)</td>
<td>Et: 58 FP: 226</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

### Table 13-88: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph LMWH vs nil 43,699</td>
<td>2</td>
<td>0/183</td>
<td>0/186</td>
<td>N/A</td>
<td>0.00 (-0.01, 0.01)</td>
<td>Et: 26 FP: 15</td>
</tr>
<tr>
<td>Single proph vs single GCS vs LMWH 94</td>
<td>1</td>
<td>1/660</td>
<td>2/657</td>
<td>0.50 (0.05, 5.48)</td>
<td>0.00 (-0.01, 0.00)</td>
<td>Et: 37 FP: 83</td>
</tr>
<tr>
<td>Post discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH 425</td>
<td>1</td>
<td>0/87</td>
<td>0/88</td>
<td>N/A</td>
<td>0.00 (-0.02, 0.02)</td>
<td>Et: 58 FP: 230</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

### 13.2.3 Additional information

#### 13.2.3.1 All cause mortality

None of the studies reported all cause mortality. Mortality is likely to be extremely rare after knee arthroscopy. In the elective knee replacement patients, estimating a mortality rate of 0.5% a power calculation estimated that 300,000 participants in each arm were required in order to detect a statistically significant difference between interventions (Chapter 1). As the mortality rate in knee arthroscopy patients is likely to be even lower than knee replacements, an even greater number of participants would be required to detect a difference.

#### 13.2.3.2 Additional outcomes

No RCTs or systematic reviews reported results for post thrombotic syndrome, chronic thromboembolic pulmonary hypertension, heparin induced thrombocytopenia, quality of life or length of stay as outcomes for this population.
13.3 **Network meta-analysis results**

No network meta-analysis was completed for this population.

13.4 **Cost-effectiveness evidence**

No cost effectiveness analysis was completed for this population.

13.5 **Patients view**

No patient views or adherence studies conducted specifically among the patient groups discussed in this chapter was identified. However, there are studies conducted in patients with hip replacement, knee replacement, lower limb plaster casts, and general surgery (Chapter 10 - 1, 21 and 9 respectively).

For patient views about specific prophylaxis agents, see section 6.6.

13.6 **Summary of evidence**

Table 13-4: Summary of evidence from direct evidence for DVT, symptomatic pulmonary embolism and major bleeding outcomes.

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DVT</td>
</tr>
<tr>
<td><strong>Prophylaxis vs no prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>No prophylaxis</td>
<td>LMWH</td>
</tr>
<tr>
<td><strong>Single prophylaxis vs. single</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>GCS</td>
<td>LMWH</td>
</tr>
<tr>
<td><strong>Post Discharge</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>No prophylaxis</td>
<td>LMWH</td>
</tr>
</tbody>
</table>

**Cost Effectiveness**

There is no relevant cost-effectiveness evidence specifically for this population subgroup.

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.

Not sig - not statistically significant difference; NR – not reported; no events – nobody in the study had the outcome. MB = Major bleeding.
13.7 Recommendations and link to evidence

**Recommendation**

Consider offering combined VTE prophylaxis with mechanical and pharmacological methods to patients having orthopaedic surgery (other than hip fracture, hip replacement, knee replacement) based on an assessment of risks (see section 5.9) and after discussion with the patient.

- Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:
  - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Start pharmacological VTE prophylaxis 6–12 hours after surgery. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

**Recommendation (From section 5.9)**

Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more of the risk factors shown in Box 1.

**Box 1 – VTE risk factor box**

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory
Venous Thromboembolism Prophylaxis

pathologies, acute infectious diseases or inflammatory conditions)

- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

Relative values of different outcomes

The main outcomes considered were venous thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

Trade off between clinical benefit and harms

The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.

Economic considerations

No cost-effectiveness analysis was conducted for this group of patients.

This is a potentially large population, and recommending prophylaxis may have significant impact on NHS costs. Patients in this population are relatively young compared to other groups, and any fatal VTE or fatal bleeding events, or long term events due to thrombosis or bleeding could result in a higher loss of quality adjusted life years than the populations where cost-effectiveness analysis has been conducted. However, the risk of pulmonary embolism is probably quite low compared with other groups, especially for patients having surgery on the upper limbs. Therefore it is unlikely that prophylaxis will be cost-effective unless patients have additional risk factors.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

The evidence for this population is weak, consisting of only 4 RCTs in knee arthroscopy patients. The incidence of DVT in the studies varied and the overall incidence of PE was very low, 0.3% in the trial comparing LMWH with GCS, and there was no evidence from this population that prophylaxis reduced the risk of these events.

Other considerations

Although the orthopaedic subgroup felt that many of the patients undergoing orthopaedic surgery in the upper limb, lower limb and arthroscopy other than elective hip replacement, elective knee
replacement and hip fracture surgery would not require prophylaxis, they did acknowledge that there may be a subgroup of these patients who were at increased risk of VTE and so should be offered the opportunity for prophylaxis. The factors that identify a patient at high risk are given in the recommendation for assessing VTE risk above. The orthopaedic subgroup felt that if any of these conditions were met then prophylaxis should be considered.

Although there is only evidence for prophylaxis with LMWH in knee arthroscopy patients, the orthopaedic subgroup felt that the evidence for fondaparinux from elective hip replacement, hip fracture and knee replacement surgery could be extrapolated for this population.

Similarly mechanical methods such as anti-embolism stockings or intermittent pneumatic compression devices can be used in conjunction or as an alternative to pharmacological prophylaxis.

13.7.1 Supporting recommendations based on Guideline Development Group consensus opinion

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Do not routinely offer VTE prophylaxis to patients undergoing upper limb surgery. If a patient is assessed to be at increased risk of VTE (section 5.9) refer to recommendation from other orthopaedic surgery (above in section 13.7).</th>
</tr>
</thead>
</table>

Trade off between clinical benefit and harms

The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.

Economic considerations

No cost-effectiveness analysis was conducted for this group of patients.

This is a potentially large population, and recommending prophylaxis may have significant impact on NHS costs. Patients in this population are relatively young compared to other groups, and any fatal VTE or fatal bleeding events, or long term events due to thrombosis or bleeding could result in a higher loss of quality adjusted life years than the populations where cost-effectiveness analysis has been conducted. However, the risk of pulmonary embolism is probably very low especially for patients having surgery on the upper limbs compared with other groups. Therefore it is unlikely that prophylaxis will be cost-effective unless patients have additional risk factors.

Other considerations

The feedback from stakeholder consultation indicated that the initial draft of the guideline did not make it clear that many patients undergoing upper limb surgery would not need VTE prophylaxis. Stakeholders raised the issue that no studies of prophylaxis had been completed in upper limb surgery and that the studies of incidence of VTE after this type of surgery
indicated that the risk was very small.

In order to make the recommendations clearer, the orthopaedic subgroup agreed that a separate recommendation should be included to clarify this. The orthopaedic subgroup agreed that although most patients undergoing upper limb surgery would not need VTE prophylaxis all patients should still be risk assessed as recommended in section 5.9 and if there were patients who were at an increased risk VTE prophylaxis should still be considered.

13.7.2 Other recommendations of relevance

The specific recommendations for patients undergoing orthopaedic surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)

13.8 Recommendations for research

Dabigatran and rivaroxaban are not licensed for this population but are oral anticoagulants that are licensed for hip and knee replacement patients. This might be an area for future research in this population, particularly where patients are identified to be at increased risk and have a lower limb plaster cast.

13.9 Summary of recommendations

- Consider offering combined VTE prophylaxis with mechanical and pharmacological methods to patients having orthopaedic surgery (other than hip fracture, hip replacement or knee replacement) based on an assessment of risks (see section 5.9) and after discussion with the patient.

- Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:
  - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Start pharmacological VTE prophylaxis 6–12 hours after surgery. Choose one of:
- LMWH
- UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

➢ Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more risk factors in Box 1.

Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

➢ Do not routinely offer VTE prophylaxis to patients undergoing upper limb surgery. If a patient is assessed to be at increased risk of VTE (section 5.9) refer to section 13.7.
14 Cranial or Spinal Surgery (Neurological Surgery)

14.1 Introduction

This section covers inpatients undergoing cranial or spinal surgery (commonly combined and called neurosurgery). Although the discussion for cranial and spinal surgery have been separated within this chapter, the evidence has been reviewed together as many of the papers combine cranial and spinal surgery patients and do not present the results separately. Neuroendovascular interventions are also covered by this section because such patients are generally admitted to neurosurgery wards.

Evidence and recommendations specific to spinal injury (including those with spinal cord involvement) are considered within chapter 20.

14.1.1 Cranial surgery

Cranial surgery is usually completed by neurosurgeons and includes a range of operations including craniotomies for brain tumours, subarachnoid haemorrhages and aneurysms. The majority of these procedures would be less than 6 hours duration but there are some that would last longer.

14.1.2 Spinal surgery

Spinal surgery is a subspecialty of both orthopaedic surgery and neurosurgery. It includes acute spinal injury surgery and elective spinal injury. In spinal surgery the catastrophic long term neurological consequences of extradural bleeding needs to be balanced against the risk to life of VTE disease. The patient process should involve the active recording of the clinical decision rather than a passive default position of no treatment.

Baseline risk

We have estimated from the incidence of RCTs that the risk of developing DVT, and major bleeding in neurosurgery patients (cranial and spinal surgery patients combined) not receiving thromboprophylaxis is:

- DVT - 20% (95% confidence intervals: 17% to 24%)
- Major bleeding - 2% (95% confidence intervals: 0% to 5%). The major bleeding events was in one patient who had a postoperative haematoma.
Population specific factors that may increase VTE or bleeding risk

- Severe head injury or spinal injury is invariably associated with altered conscious level and/or limb paralysis. The risk of VTE is increased because early ambulation is not possible and a prolonged period of recumbency is inevitable. Usually, there is no particular contraindication to the common methods of prophylaxis for these patients.

- An increased risk of VTE is associated with Brain (malignant or benign) tumours and cerebral haemorrhage.

- The risk of bleeding is a serious complication in patients requiring emergency neurosurgery. This is not confined to “major bleeding” which is often defined as a 2g drop in haemoglobin and/or clinically indicated transfusion. Very small volume bleeds within or compressing the brain or spinal cord can cause neurological injury which may be irreversible.

- The timing of when pharmacological prophylaxis is started is particularly important in patients with ruptured or unprotected vascular malformations or acute traumatic or untraumatic haemorrhage (because of an increased risk of bleeding).

- Many neurosurgical patients are on high doses of glucocorticoids which may alter the coagulation status of the patient.

- Some patients undergoing prolonged cranial surgery e.g meningiomas are at risk of developing disseminated intravascular coagulation.

14.2 Evidence of methods of prophylaxis

14.2.1 Summary of comparisons identified for any outcome

Sixteen randomised controlled trials which reported at least one of the three main outcomes were identified\textsuperscript{11,90,101,164,225,415,441,495,559,607,646,647,649,680,683,701}. Some of these investigated more than two methods of prophylaxis. Of the available literature, seven studies include only cranial surgery patients \textsuperscript{90,101,164,225,415,680,683} and two investigated spinal surgery patients only \textsuperscript{559,701}. Three studies included mixed cranial and spinal surgery populations but did not report results separately \textsuperscript{11,495,607}, three others contained mixed populations neurological and neurosurgical patients\textsuperscript{646,647,649} and one did not clarify the type of neurosurgery patients underwent\textsuperscript{441}. Some of the RCTs had their data extracted from systematic reviews. Where applicable the study is cited in the evidence table for that review. Three systematic reviews included RCTs covering patients having neurosurgery\textsuperscript{15,304,557}.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). The evidence tables for the included studies are in Appendix D presented by order of comparison.
VENOUS THROMBOEMBOLISM PROPHYLAXIS

14.2.2 Results from pairwise comparisons

Table 14-89: DVT – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS (a)</td>
<td>1</td>
<td>7/80</td>
<td>16/81</td>
<td>0.44</td>
<td>(-0.11, 0.19, 1.02)</td>
<td>ET: 23 FP: 1</td>
</tr>
<tr>
<td>IPCD/FID</td>
<td>5</td>
<td>13/251</td>
<td>52/247</td>
<td>0.30</td>
<td>(-0.16, 0.17, 0.53)</td>
<td>ET: 24 FP: 4</td>
</tr>
<tr>
<td>LMWH</td>
<td>1</td>
<td>10/64</td>
<td>14/58</td>
<td>0.65</td>
<td>(-0.09, 0.31, 1.34)</td>
<td>ET: 26 FP: 13</td>
</tr>
<tr>
<td>UFH vs nil101</td>
<td>1</td>
<td>3/50</td>
<td>17/50</td>
<td>0.18</td>
<td>(-0.28, 0.06, 0.56)</td>
<td>ET: 27 FP: 17</td>
</tr>
<tr>
<td>Double proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + GCS vs GCS      355,649,649,680</td>
<td>3</td>
<td>7/129</td>
<td>9/127</td>
<td>0.36</td>
<td>(-0.02, 0.02, 5.16)</td>
<td>ET: 39 FP: 117</td>
</tr>
<tr>
<td>LMWH + GCS vs GCS11,495</td>
<td>2</td>
<td>53/296</td>
<td>90/309</td>
<td>0.61</td>
<td>(-0.11, 0.45, 0.85)</td>
<td>ET: 26 FP: 134</td>
</tr>
</tbody>
</table>

* ET: Evidence tables. FP: Forest plots.
Table 14-90: Pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proph vs no proph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS vs nil</td>
<td>1</td>
<td>0/80</td>
<td>0/81</td>
<td>not estimable</td>
<td>0.00 (-0.02, 0.02)</td>
<td>ET: 23</td>
</tr>
<tr>
<td>ICD/FID vs nil</td>
<td>1</td>
<td>0/47</td>
<td>0/48</td>
<td>not estimable</td>
<td>0.00 (-0.04, 0.04)</td>
<td>ET: 24</td>
</tr>
<tr>
<td><strong>Double proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD + GCS vs GCS</td>
<td>1</td>
<td>0/18</td>
<td>0/5</td>
<td>not estimable</td>
<td>0.00 (-0.23, 0.23)</td>
<td>ET: 39</td>
</tr>
<tr>
<td>LMWH + GCS vs GCS</td>
<td>2</td>
<td>1/371</td>
<td>3/374</td>
<td>0.44 (0.06, 2.96)</td>
<td>-0.01 (-0.02, 0.01)</td>
<td>ET: 26</td>
</tr>
<tr>
<td><strong>Double proph vs double</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD + GCS vs LMWH + GCS</td>
<td>1</td>
<td>0/22</td>
<td>0/21</td>
<td>not estimable</td>
<td>0.00 (-0.09, 0.09)</td>
<td>ET: 49</td>
</tr>
<tr>
<td>LMWH + ICD vs ICD</td>
<td>1</td>
<td>0/51</td>
<td>0/49</td>
<td>not estimable</td>
<td>0.00 (-0.04, 0.04)</td>
<td>ET: 45</td>
</tr>
<tr>
<td><strong>Other strategies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD + GCS + LMWH vs GCS</td>
<td>1</td>
<td>0/23</td>
<td>0/21</td>
<td>not estimable</td>
<td>0.00 (-0.08, 0.08)</td>
<td>ET: 39</td>
</tr>
<tr>
<td>LMWH + ICD + GCS vs ICD + GCS</td>
<td>1</td>
<td>0/23</td>
<td>0/22</td>
<td>not estimable</td>
<td>0.00 (-0.08, 0.08)</td>
<td>ET: 26</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

(a) There was significant heterogeneity within the results (chi squared on 2 df =3.23, p=0.07, I^2 =69.1%) which appears to be attributable to one study with few patients.

Table 14-91: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proph vs no proph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>1</td>
<td>0/67</td>
<td>0/63</td>
<td>not estimable</td>
<td>0.00 (-0.03, 0.03)</td>
<td>ET: 26</td>
</tr>
<tr>
<td>UFH vs nil</td>
<td>1</td>
<td>2/50</td>
<td>1/50</td>
<td>2.00 (0.19, 21.36)</td>
<td>0.02 (-0.05, 0.09)</td>
<td>ET: 27</td>
</tr>
<tr>
<td><strong>Double proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH + GCS vs GCS</td>
<td>2</td>
<td>10/394</td>
<td>6/398</td>
<td>1.62 (0.55, 4.74)</td>
<td>0.01 (-0.01, 0.03)</td>
<td>ET: 26</td>
</tr>
</tbody>
</table>
14.2.3 Additional information

14.2.3.1 All cause mortality

Table 14-92: Mortality – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Interventions</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS vs nil†449</td>
<td>1</td>
<td>17/80</td>
<td>10/81</td>
<td>1.72</td>
<td>(0.84, 3.53)</td>
<td>0.00 (0.20)</td>
</tr>
<tr>
<td>IPCD/FID vs nil†07,647</td>
<td>2</td>
<td>9/129</td>
<td>8/127</td>
<td>1.12</td>
<td>(0.45, 2.75)</td>
<td>-0.01 (0.04)</td>
</tr>
<tr>
<td>LMWH vs nil†441</td>
<td>1</td>
<td>0/67</td>
<td>0/63</td>
<td>not estimable</td>
<td></td>
<td>0.00 (-0.03)</td>
</tr>
<tr>
<td>UFH vs nil†101</td>
<td>1</td>
<td>0/50</td>
<td>0/50</td>
<td>not estimable</td>
<td></td>
<td>0.00 (-0.04)</td>
</tr>
<tr>
<td>Double proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + GCS vs GCS†449</td>
<td>1</td>
<td>10/78</td>
<td>17/80</td>
<td>0.60</td>
<td>(0.29, 1.23)</td>
<td>-0.08 (0.03)</td>
</tr>
<tr>
<td>LMWH + GCS vs GCS†1,495</td>
<td>2</td>
<td>27/394</td>
<td>16/398</td>
<td>1.53</td>
<td>(0.60, 3.88)</td>
<td>-0.04 (0.08)</td>
</tr>
<tr>
<td>Double proph vs double</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + GCS vs LMWH + GCS†164</td>
<td>1</td>
<td>1/22</td>
<td>0/21</td>
<td>2.87</td>
<td>(0.12, 66.75)</td>
<td>0.05 (-0.16)</td>
</tr>
<tr>
<td>LMWH + IPCD vs UFH + IPCD†415</td>
<td>1</td>
<td>0/51</td>
<td>1/49</td>
<td>0.31</td>
<td>(0.01, 7.68)</td>
<td>-0.02 (-0.03)</td>
</tr>
<tr>
<td>Other strategies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + GCS + LMWH vs GCS + LMWH†164</td>
<td>1</td>
<td>1/23</td>
<td>0/21</td>
<td>2.75</td>
<td>(0.12, 64.04)</td>
<td>0.04 (-0.16)</td>
</tr>
<tr>
<td>LMWH + IPCD + GCS vs IPCD + GCS†164</td>
<td>1</td>
<td>1/23</td>
<td>1/22</td>
<td>0.96</td>
<td>(0.06, 14.37)</td>
<td>0.00 (-0.12)</td>
</tr>
<tr>
<td>LMWH + IPCD + GCS vs UFH + IPCD + GCS†225</td>
<td>1</td>
<td>0/75</td>
<td>0/75</td>
<td>not estimable</td>
<td></td>
<td>0.00 (-0.03)</td>
</tr>
</tbody>
</table>

* FP = forest plot number in appendix E; ET = evidence table number in appendix D
Proph - prophylaxis
Most of the studies had few deaths and a small overall sample size and showed no difference in mortality. However, two comparisons suggest prophylaxis may increase mortality.

Two studies reporting mortality compared LMWH plus GCS with GCS alone\textsuperscript{11,495}. Overall, there is no significant difference in mortality (RR = 1.53 (0.60, 3.88) but there is a suggestion of heterogeneity (I\textsuperscript{2} = 48.5\%). One of the studies shows significantly more patients using LMWH plus GCS died compared to patients using GCS alone\textsuperscript{495}. LMWH was started 18 to 24 hours postoperatively. There is no significant difference for major bleeding but, if minor bleeding is included too, the LMWH group had significantly more bleeding events overall (p=0.047). The study concludes that the deaths are not related to haemorrhage. No other reasons for the cause of mortality are explored in this study. None of the other heparin studies reported a similar mortality rate.

One study comparing GCS with no prophylaxis suggested an increase in mortality with GCS\textsuperscript{649}. At 3 months, 17 out of 80 patients who wore GCS had died compared to 10 out of 81 of the patients not receiving prophylaxis. In a third arm 10 out of 81 using IPCD plus GCS also died.

\subsection*{14.2.3.2 Other outcomes}

No studies reported chronic thromboembolic pulmonary hypertension, post thrombotic syndrome or heparin induced thrombocytopenia in the systematic reviews.

\subsection*{14.2.3.3 Additional studies}

One study not included in the above analysis compared IPCD plus stockings with foot pumps plus stockings\textsuperscript{701}. This comparison was addressed in the first version of the guideline\textsuperscript{473}. For economic model in this version of the guideline the effectiveness of IPCD devices and foot pumps were considered together. There was only one event DVT and one pulmonary embolism in the study, both occurring in the foot pumps arm. (Evidence table 30, Appendix D)

\subsection*{14.3 Network meta-analysis results}

Network meta-analysis was not conducted for this population.

\subsection*{14.4 Cost-effectiveness evidence}

No cost effectiveness analysis was completed for this population.

\subsection*{14.5 Patient views}

No patient views papers were found specific to this population.

For patient views about specific prophylaxis agents, see section 6.6.
### 14.6 Summary of evidence

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>DVT</td>
<td>PE</td>
</tr>
<tr>
<td><strong>Prophylaxis vs no prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td>no prophylaxis</td>
<td>not sig</td>
</tr>
<tr>
<td>IPCD/FID</td>
<td>no prophylaxis</td>
<td>IPCD/FID</td>
</tr>
<tr>
<td>LMWH</td>
<td>no prophylaxis</td>
<td>not sig</td>
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<tr>
<td>UFH</td>
<td>no prophylaxis</td>
<td>UFH</td>
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<td><strong>Single prophylaxis vs single</strong></td>
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<td></td>
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<td><strong>Double prophylaxis vs single</strong></td>
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<tr>
<td>IPCD + GCS</td>
<td>GCS</td>
<td>not sig</td>
</tr>
<tr>
<td>LMWH + GCS</td>
<td>GCS</td>
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</tr>
<tr>
<td>VKA + GCS</td>
<td>GCS</td>
<td>LMWH + GCS</td>
</tr>
<tr>
<td><strong>Double prophylaxis vs double</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + GCS</td>
<td>LMWH + GCS</td>
<td>not sig</td>
</tr>
<tr>
<td>LMWH + GCS</td>
<td>UFH + GCS</td>
<td>not sig</td>
</tr>
<tr>
<td><strong>Other strategies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + LMWH + GCS</td>
<td>LMWH + GCS</td>
<td>not sig</td>
</tr>
<tr>
<td>LMWH + IPCD + GCS</td>
<td>IPCD + GCS</td>
<td>not sig</td>
</tr>
<tr>
<td>LMWH + IPCD + GCS</td>
<td>UFH + IPCD + GCS</td>
<td>not sig</td>
</tr>
<tr>
<td><strong>Cost Effectiveness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cost effectiveness model was completed for this population</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.

*Not sig:* not statistically significant difference; *-* = not reported; *no events:* nobody in the study had the outcome

MB = Major bleeding

Overall, there is little evidence covering prophylaxis in patients undergoing cranial surgery. Most of the data available were in small studies. Giving prophylaxis does appear to reduce DVT but there are not enough data to show the level of reduction in pulmonary embolism and increase in major bleeding events (where applicable). There are no RCTs comparing single prophylaxis agents. LMWH plus GCS is better than GCS alone. There is less evidence covering prophylaxis in patients undergoing spinal surgery. Only two of the studies investigated prophylaxis in spinal surgery patients alone, neither of these compared prophylaxis to no prophylaxis.
## Recommendations and link to evidence

### Recommendation
Offer VTE prophylaxis to patients undergoing cranial or spinal surgery who are assessed to be at increased risk of VTE (see section 5.9).

- Start mechanical VTE prophylaxis from admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
  - LMWH
  - UFH (for patients with renal failure)

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5–7 days).

### Recommendation - from section 5.9
Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more of the risk factors shown in Box 1.

### Box 1 – VTE Risk factor box
- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory
Venous Thromboembolism Prophylaxis

pathologies, acute infectious diseases or inflammatory conditions
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

Relative values of different outcomes
The outcomes considered were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

Trade off between clinical benefit and harms
The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. The timing of when pharmacological prophylaxis is started is particularly important in patients who have suffered a spontaneous or traumatic haemorrhage. The risk of bleeding is a serious complication in patients requiring emergency cranial or spinal surgery. In spinal surgery the catastrophic long term neurological consequences of extradural bleeding need to be balanced against the risk to life of VTE disease.

Economic considerations
No economic model was run specifically for cranial or spinal surgery patients. The economic model for general surgical patients indicated that a combination of pharmacological and mechanical prophylaxis was cost effective for this broader population as long as the risk of major bleeding is less than 1%. Given the high risk of VTE in neurosurgery patients, it is quite likely that prophylaxis is cost-effective. However, given that these patients seem to have a very high baseline risk of major bleeding and the consequences of surgical site bleeding are likely to be very serious for this group, drug prophylaxis is likely only to be cost-effective if the risk of intracranial bleeding or bleeding into the spinal column is minimised.

Quality of evidence
All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

Seven studies investigated prophylaxis in patients undergoing cranial surgery, with an additional 7 providing information from mixed populations of cranial and spinal surgery, or other...
neurological patients.

There were only 2 studies that investigated spinal surgery patients alone, a further 7 studies combined spinal surgery patients with patients undergoing cranial surgery and/or other neurology patients

Where available, most the evidence was in small studies.

**Other considerations**

Severe head injury and spinal injury are associated with altered conscious level and/or limb paralysis. The risk of VTE is increased because early ambulation is not possible and a prolonged period of recumbency is inevitable. There is, however, no particular contraindication to any of the methods of prophylaxis for these patients.

An increased risk of VTE is associated with Brain (malignant or benign) tumours and cerebral haemorrhage.

Many neurosurgical patients are on high doses of glucocorticoids which may alter the coagulation status of the patient.

Some patients undergoing prolonged cranial surgery e.g Meningiomas are at risk of developing disseminated intravascular coagulation.

The average duration of VTE prophylaxis for ‘general surgery’ patients in the trials was 7 days. This concurs with the licensing conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. It is known in many cases surgical patients are discharged within 5 days of their operation. The guideline development group felt that the risk of VTE may still persist beyond this time period and prophylaxis may be effective after discharge. No economic analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given.

There are other considerations for each agent when choosing pharmacological prophylaxis. UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH.

14.7.1 Supporting recommendations based on Guideline Development Group consensus opinion
### Recommendation

| Recommendation | Do not offer pharmacological VTE prophylaxis to patients with ruptured cranial or spinal vascular malformations (for example, brain aneurysms) or acute traumatic or non-traumatic haemorrhage until until the lesion has been secured or the condition is stable. |

**Trade off between clinical benefit and harms**

The timing of when pharmacological prophylaxis is started is particularly important in patients who have suffered a spontaneous or traumatic haemorrhage. The risk of bleeding is a serious complication in patients requiring emergency cranial or spinal surgery.

**Economic considerations**

None

**Other considerations**

None

#### 14.7.2 Other recommendations of relevance

The specific recommendations for neurosurgery patients in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- recommendations about patients with spinal injury (Section 20.7)
- recommendations about metastatic spinal injury from the NICE guidelines

#### 14.8 Summary of recommendations

- Offer VTE prophylaxis to patients undergoing cranial or spinal surgery who are assessed to be at increased risk of VTE (see section 5.9).
  - Start mechanical VTE prophylaxis from admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)
  - Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility
Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:

- LMWH
- UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

- Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
  - acute surgical admission with inflammatory or intra-abdominal condition
  - expected significant reduction in mobility
  - have one or more risk factors shown in Box 1.

Do not offer pharmacological VTE prophylaxis to patients with ruptured cranial or spinal vascular malformations (for example, brain aneurysms) or acute traumatic or non-traumatic haemorrhage until until the lesion has been secured or the condition is stable.

**Box 1. Risk factors for VTE**

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).
15 Cardiac surgery

15.1 Introduction

This section covers patients undergoing cardiac surgery.

We have estimated, from the incidence in the RCTs (chapter 5), that the risk of developing DVT in cardiac surgery patients not receiving thromboprophylaxis:

- 14% (95% confidence intervals: 7% to 24%), although its ranking in amongst other surgeries in our HES data would suggest that the risk could be higher.

- we do not have data from the RCTs to estimate the risk of pulmonary embolism or bleeding

Factors that may alter the risk of VTE.

- Pacing wires and implantable cardioverter-defibrillator devices may lead to an increase in upper limb deep vein thrombosis

Factors that increase the risk of bleeding or hazard associated with it

- Many patients will be receiving antiplatelet medication, heparin or warfarin and will therefore have an increased risk of bleeding.

Other special factors that would affect the choice of, and use of, specific methods of prophylaxis

- Several procedures in cardiac surgery involve the use of anticoagulation or antiplatelet therapy:
  - Full heparin anticoagulation is used during cardiopulmonary bypass which is typically one to two hours of a two to five hour surgery.
  - Surgeries performed "off pump" (surgeries performed without the use of heart lung machines) are also covered by heparin anticoagulation.
  - Most patients with coronary artery disease are given antiplatelet therapy up to shortly prior to surgery and it is recommenced soon after.
  - Many patients with valve disease have warfarin anticoagulation.
Patients in atrial fibrillation will generally have warfarin anticoagulation.

- Many cardiac surgery patients have leg veins removed for use as grafts. This would preclude the use of both GCS and IPCD during the surgery but they could be used afterwards.

### 15.2 Evidence of methods of prophylaxis

#### 15.2.1 Summary of comparisons identified for any outcome

Five randomised controlled trials which reported at least one of the three main outcomes were identified\(^{38,41,226,345,544}\). One of the RCTs\(^ {41} \) data were extracted from a systematic review\(^ {125} \).

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

![Figure 15-39: Number of studies which compared various types of prophylaxis methods.](image)

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicate areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) – low dose aspirin (< 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis
15.2.2 Results from pairwise comparisons

Table 15-93: DVT – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH vs no prophylaxis</td>
<td>1</td>
<td>3/24</td>
<td>8/25</td>
<td>0.39 (0.12, 1.30)</td>
<td>-0.20 (-0.42, 0.03)</td>
<td>ET: 27 FP: 17</td>
</tr>
<tr>
<td>UFH + IPCD vs no prophylaxis</td>
<td>1</td>
<td>1/50</td>
<td>2/40</td>
<td>0.40 (0.04, 4.25)</td>
<td>-0.03 (-0.11, 0.05)</td>
<td>ET: 27 FP: 34</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH</td>
<td>1</td>
<td>0/20</td>
<td>0/19</td>
<td>not estimable</td>
<td>0.00 (-0.09, 0.09)</td>
<td>ET: 32 FP: 48</td>
</tr>
<tr>
<td>Other prophylaxis strategies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + GCS + asp vs GCS + asp</td>
<td>1</td>
<td>31/164</td>
<td>36/166</td>
<td>0.87 (0.57, 1.34)</td>
<td>-0.03 (-0.11, 0.06)</td>
<td>ET: 39 FP: 127</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

Table 15-94: Pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + UFH vs UFH</td>
<td>1</td>
<td>21/1355</td>
<td>48/119</td>
<td>0.39 (0.23, 0.64)</td>
<td>-0.02 (-0.04, -0.01)</td>
<td>ET: 39 FP: 121</td>
</tr>
<tr>
<td>Other prophylaxis strategies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + GCS + asp vs GCS + asp</td>
<td>1</td>
<td>1/164</td>
<td>1/166</td>
<td>1.01 (0.06, 16.05)</td>
<td>0.00 (-0.02, 0.02)</td>
<td>ET: 39 FP: 128</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

Table 15-95: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH vs no prophylaxis</td>
<td>1</td>
<td>8/24</td>
<td>1/25</td>
<td>8.33 (1.13, 61.70)</td>
<td>0.29 (0.09, 0.50)</td>
<td>ET: 27 FP: 19</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

15.2.3 Additional information

There is no additional information to add for this population.

15.3 Network meta-analysis results

Network meta-analysis was not completed for this population.

15.4 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.
### 15.5 Patient views

No patient views papers were found specific to this population.

For patient views about specific prophylaxis agents, see section 6.6.

### 15.6 Summary of evidence

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DVT</td>
</tr>
<tr>
<td>Prophylaxis vs no prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>no prophylaxis</td>
<td>not sig</td>
</tr>
<tr>
<td>UFH + IPCD</td>
<td>no prophylaxis</td>
<td>not sig</td>
</tr>
<tr>
<td>Single prophylaxis vs single</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>UFH</td>
<td>no events</td>
</tr>
<tr>
<td>Double prophylaxis vs single</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + UFH</td>
<td>UFH</td>
<td>-</td>
</tr>
<tr>
<td>Other strategies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + GCS + asp</td>
<td>GCS + asp</td>
<td>not sig</td>
</tr>
<tr>
<td>Cost Effectiveness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>There is no relevant cost-effectiveness evidence specifically for this population subgroup.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.

Not sig - not statistically significant difference; ‘-’ = not reported; no events – nobody in the study had the outcome. MB = Major bleeding

Overall, there is little RCT evidence covering prophylaxis in patients undergoing cardiac surgery.
### 15.7 Recommendations and link to evidence

<table>
<thead>
<tr>
<th><strong>Recommendation</strong></th>
<th><strong>Offer VTE prophylaxis to patients undergoing cardiac surgery who are not having other anticoagulation therapy and are assessed to be at increased risk of VTE (see section 5.9)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Start mechanical VTE prophylaxis at admission. Choose any one of:</td>
</tr>
<tr>
<td></td>
<td>- anti-embolism stockings (thigh or knee length)</td>
</tr>
<tr>
<td></td>
<td>- foot impulse devices</td>
</tr>
<tr>
<td></td>
<td>- intermittent pneumatic compression devices (thigh or knee length).</td>
</tr>
<tr>
<td></td>
<td>Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.</td>
</tr>
<tr>
<td></td>
<td>- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:</td>
</tr>
<tr>
<td></td>
<td>- LMWH</td>
</tr>
<tr>
<td></td>
<td>- UFH (for patients with renal failure).</td>
</tr>
<tr>
<td></td>
<td>Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Recommendation from section 5.9</strong></th>
<th><strong>Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb</td>
</tr>
<tr>
<td></td>
<td>- acute surgical admission with inflammatory or intra-abdominal condition</td>
</tr>
<tr>
<td></td>
<td>- expected significant reduction in mobility</td>
</tr>
<tr>
<td></td>
<td>- have one or more of the risk factors shown in Box 1.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Box 1 – VTE Risk factor box</strong></th>
<th><strong>Active cancer or cancer treatment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Age over 60 years</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Critical care admission</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Dehydration</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Known thrombophilias</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Obesity (BMI over 30 kg/m²)</strong></td>
</tr>
</tbody>
</table>
|                                 | **One or more significant medical comorbidities (such**


as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)

- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

Relative values of different outcomes

The outcomes considered were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome)

Trade off between clinical benefit and harms

The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. Patients already receiving antiplatelet medication will have an increased risk of bleeding.

Economic considerations

There is no relevant cost-effectiveness evidence specifically for this population subgroup. However, a combination of drug and mechanical prophylaxis was found to be cost-effective for general surgery patients where the risk of major bleeding is less than 1% (Chapter 9). It seems likely that combination prophylaxis will also be cost-effective for cardiac surgery patients who are at elevated risk of VTE.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

There is little RCT evidence covering cardiac surgery. Evidence was extrapolated from general surgery patients.

Other considerations

Several procedures in cardiac surgery involve the use of anticoagulation or antiplatelet therapy:

Many cardiac surgery patients have leg veins removed for use as grafts. This would preclude the use of both GCS and IPCD during the surgery but they could be used after.

The average duration of VTE prophylaxis for ‘general surgery’ patients in the trials was 7 days. This concurs with the licensing
conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. It is known in many cases surgical patients are discharged within 5 days of their operation. The guideline development group felt that the risk of VTE may still persist beyond this time period and prophylaxis may be effective after discharge. No economic analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given.

There are other considerations for each agent when choosing pharmacological prophylaxis. UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH.

15.7.1 Other recommendations of relevance

The specific recommendations for patients undergoing cardiac surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- patients using anticoagulants or antiplatelets for reasons other than VTE prophylaxis (Chapter 1)

15.8 Summary of recommendations

- Offer VTE prophylaxis to patients undergoing cardiac surgery who are not having other anticoagulation therapy and are assessed to be at increased risk of VTE (see section 5.9)

  - Start mechanical VTE prophylaxis at admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.
• Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

• surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
• acute surgical admission with inflammatory or intra-abdominal condition
• expected significant reduction in mobility
• have one or more risk factors shown in Box 1.

**Box 1. Risk factors for VTE**

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).
16 Vascular surgery

16.1 Introduction

This section covers inpatients undergoing vascular surgery. Vascular surgery encompasses two distinct patient populations: surgery for peripheral arterial disease (PAD) including carotid, aorto-iliac and limb arterial surgery; and patients with venous disease (superficial or deep venous reflux and varicose veins). A significant proportion of surgery for uncomplicated primary varicose veins is undertaken as day-case procedures.

We did not have enough data, from the incidence in the RCTs (chapter 5), to enable us to estimate the risk of developing deep vein thrombosis in vascular surgery patients not receiving thromboprophylaxis, according to our HES data, its ranking in amongst other surgery would suggest that the risk is relatively high.

Factors that may alter the risk of VTE

- Arterial surgery patients are often elderly and immobile.
- Many arterial surgery patients will already be receiving antiplatelet therapy and some will be on warfarin.
- Systemic heparin is frequently administered during surgery for arterial disease.
- Surgery for varicose veins is mostly in women, oral contraceptive use and hormone replacement therapy are therefore more commonly associated with varicose veins surgery.

Factors that increase the risk of bleeding or hazard associated with it

- Patients using anticoagulation or antiplatelet therapy not related to surgery will have an increased risk of bleeding.

Other factors that may alter the choice of prophylaxis

- The use of intermittent compression devices is contraindicated in patients with peripheral arterial disease.
- The use of intermittent compression devices and anti-embolism / graduated compression stockings will usually be inappropriate on the operated leg for a patient undergoing lower limb arterial surgery.
- Anti-embolism / graduated compression stockings will be contraindicated for patients with lower limb arterial disease.

### 16.2 Evidence of methods of prophylaxis

#### 16.2.1 Summary of comparisons identified for any outcome

Three randomised controlled trials which reported at least one of the three main outcomes were identified\(^{181,383,615}\). One of the RCTs\(^{615}\) data were extracted from a systematic review\(^{125}\).

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

![Figure 16-40: Number of studies which compared various types of prophylaxis methods.](image)

**Table:** Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicate areas where no studies were identified.

- **GCS** – anti-embolism / graduated compression stockings; **IPCD/FID** – intermittent pneumatic compression devices or foot impulse devices; **LMWH** – low molecular weight heparin; **UFH** – unfractionated heparin; **Asp (HD)** – high dose aspirin (>300mg); **Asp (LD)** – low dose aspirin (≤300mg); **Mech + pharm** – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); **pharm** – pharmacological prophylaxis
### 16.2.2 Results from pairwise comparisons

#### Table 16-96: DVT – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk (95% CI)</th>
<th>Absolute effect (95% CI)</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH vs nil</td>
<td>1</td>
<td>3/24</td>
<td>2/19</td>
<td>1.19 (0.22, 6.40)</td>
<td>0.02 (-0.17, 0.21)</td>
<td>ET: 27 FP: 17</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH</td>
<td>1</td>
<td>4/41</td>
<td>4/34</td>
<td>0.83 (0.22, 3.07)</td>
<td>-0.02 (-0.16, 0.12)</td>
<td>ET: 32 FP: 48</td>
</tr>
<tr>
<td>Double proph vs double</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH + introperative UFH vs UFH</td>
<td>1</td>
<td>10/122</td>
<td>4/111</td>
<td>2.27 (0.73, 7.05)</td>
<td>0.05 (-0.01, 0.11)</td>
<td>ET: 45 FP: 188</td>
</tr>
<tr>
<td>LMWH + introperative UFH + introperative UFH</td>
<td>1</td>
<td>0/122</td>
<td>0/111</td>
<td>not estimable</td>
<td>0.00 (0.02, 0.02)</td>
<td>ET: 45 FP: 189</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

#### Table 16-97: Pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk (95% CI)</th>
<th>Absolute effect (95% CI)</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH vs nil</td>
<td>1</td>
<td>1/24</td>
<td>0/19</td>
<td>1.19 (0.22, 6.40)</td>
<td>0.02 (-0.17, 0.21)</td>
<td>ET: 27 FP: 18</td>
</tr>
<tr>
<td>Double proph vs double</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH + introperative UFH vs UFH</td>
<td>1</td>
<td>0/122</td>
<td>0/111</td>
<td>not estimable</td>
<td>0.00 (0.02, 0.02)</td>
<td>ET: 45 FP: 189</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

#### Table 16-98: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk (95% CI)</th>
<th>Absolute effect (95% CI)</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH vs nil</td>
<td>1</td>
<td>0/24</td>
<td>0/19</td>
<td>not estimable</td>
<td>0.00 (-0.05, 0.05)</td>
<td>ET: 27 FP: 19</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH</td>
<td>1</td>
<td>0/41</td>
<td>0/34</td>
<td>not estimable</td>
<td>0.00 (-0.09, 0.09)</td>
<td>ET: 32 FP: 50</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

### 16.2.3 Additional information

There is no additional information for this population.
16.3 Network meta-analysis results

Network meta-analysis was not completed for this population.

16.4 Cost-effectiveness evidence

No cost-effectiveness evidence was identified and no model produced for this population.

16.5 Patient views

No patient views papers were found specific to this population.

For patient views about specific prophylaxis agents, see section 6.6.

16.6 Summary of evidence

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DVT</td>
</tr>
<tr>
<td>Prophylaxis vs no prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>no prophylaxis</td>
<td>not sig</td>
</tr>
<tr>
<td>Single prophylaxis vs single</td>
<td>UFH</td>
<td>not sig</td>
</tr>
<tr>
<td>LMWH</td>
<td>UFH</td>
<td>not sig</td>
</tr>
<tr>
<td>Double prophylaxis vs double</td>
<td>UFH + introperative UFH</td>
<td>not sig</td>
</tr>
</tbody>
</table>

Cost Effectiveness

No cost effectiveness model was completed for this population.

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.

Not sig - not statistically significant difference; '-' = not reported; no events – nobody in the study had the outcome. MB = Major bleeding

Overall, there is little RCT evidence covering prophylaxis in patients undergoing vascular surgery.
16.7 Recommendations and link to evidence

**Recommendation**
Offer VTE prophylaxis to patients undergoing vascular surgery who are not having other anticoagulant therapy and are assessed to be at increased risk of VTE (see section 2.2.1). If peripheral arterial disease is present, seek expert opinion before fitting anti-embolism stockings

- Start mechanical VTE prophylaxis at admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis for patients who have a low risk of bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
  - LMWH
  - UFH for patients with renal failure

  Continue pharmacological VTE prophylaxis until the patients no longer has significantly reduced mobility (generally 5-7 days).

**Recommendation from section 5.9**
Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more of the risk factors shown in Box 1.

**Box 1 – VTE Risk factor box**
- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
### Relative values of different outcomes

The outcomes considered were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

### Trade off between clinical benefit and harms

The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.

### Economic considerations

There is no cost-effectiveness evidence for vascular surgery patients. An economic model was developed for general surgical patients. The model concluded that a combination of drug and mechanical prophylaxis was cost effective for general surgery patients where the risk of major bleeding is less than 1%.

There is little trial evidence for vascular surgery patients but we believe the relative effects of prophylaxis will be similar. We consider it likely that combination prophylaxis is cost-effective for vascular patients with moderate risk of major bleeding, given their high baseline risk of VTE.

### Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

There is little RCT evidence covering vascular surgery. Evidence was extrapolated from general surgery patients.
Other considerations

Arterial surgery patients are often elderly and immobile. Many arterial surgery patients will already be receiving antiplatelet therapy and some will be on warfarin. In addition, systemic heparin is frequently administered during surgery for arterial disease.

Surgery for varicose veins is mostly in women, oral contraceptive use and hormone replacement therapy are therefore more commonly associated with varicose veins surgery.

Patients using anticoagulation or antiplatelet therapy not related to surgery will have an increased risk of bleeding.

The use of intermittent compression devices and antiembolism / graduated compression stockings will usually be inappropriate on the operated leg for a patient undergoing lower limb arterial surgery.

Antiembolism / graduated compression stockings and intermittent pneumatic compression devices will be contraindicated for patients with peripheral arterial disease.

The average duration of VTE prophylaxis for 'general surgery' patients in the trials was 7 days. This concurs with the licensing conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. It is known in many cases surgical patients are discharged within 5 days of their operation. The guideline development group felt that the risk of VTE may still persist beyond this time period and prophylaxis may be effective after discharge. No economic analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given.

There are other considerations for each agent when choosing pharmacological prophylaxis. UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH.

16.7.1 Other recommendations of relevance

The specific recommendations for patients undergoing vascular surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- the use of, and contraindications to, mechanical prophylaxis (Section 6.7)
the use of pharmacological prophylaxis (Section 6.8)

- risk assessment for VTE and major bleeding (Section 5.9)

- the provision of patient information (Section 32.5)

- patients using anticoagulants or antiplatelets for reasons other than VTE prophylaxis (Chapter 1).

16.8 Summary of recommendations

➢ Offer VTE prophylaxis to patients undergoing vascular surgery who are not having other anticoagulation therapy and are assessed to be at increased risk of VTE (see section 5.9)

- Start mechanical VTE prophylaxis at admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more risk factors shown in Box 1.
Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).
17 Day-case surgery

17.1 Introduction
This section covers patients undergoing procedures as a day-case. It will cover a wide range of procedures across many of the specialities. For the purpose of this guideline, patients are considered as day-cases their procedures meet one of the following three criteria described by the British Association of Day Surgery84:

- Procedure room – operation that may be performed in a suitable clean environment outside of theatres
- Day-case – “traditional day surgery”
- 23 hour stay – patients admitted and discharged within 24 hours

Special considerations for VTE

- day-case patients are likely to be more mobile and on average, younger than patients admitted for an in-patient stay.

There are no special considerations for bleeding in this group

17.2 Evidence of methods of prophylaxis
No studies were identified that investigating VTE prophylaxis in day-case surgery patients.

17.3 Network meta-analysis results
Network meta-analysis was not completed for this population

17.4 Cost-effectiveness evidence
No cost effectiveness analysis was completed for this population.

17.5 Patient views
No patient views papers were found specific to this population.

For patient views about specific prophylaxis agents, see section 6.6.
## 17.6 Summary of evidence

There is no RCT evidence covering prophylaxis in patients having day-case surgery.

## 17.7 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Offer VTE prophylaxis to patients undergoing day surgery who are assessed to be at increased risk of VTE (see section 5.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Start mechanical VTE prophylaxis at admission. Choose any one of:</td>
</tr>
<tr>
<td></td>
<td>- anti-embolism stockings (thigh or knee length)</td>
</tr>
<tr>
<td></td>
<td>- foot impulse devices</td>
</tr>
<tr>
<td></td>
<td>- intermittent pneumatic compression devices (thigh or knee length)</td>
</tr>
<tr>
<td></td>
<td>Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.</td>
</tr>
<tr>
<td></td>
<td>• Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account patient factors and according to clinical judgement. Choose one of:</td>
</tr>
<tr>
<td></td>
<td>- fondaparinux</td>
</tr>
<tr>
<td></td>
<td>- LMWH</td>
</tr>
<tr>
<td></td>
<td>- UFH (for patients with renal failure).</td>
</tr>
<tr>
<td></td>
<td>If the patient is expected to have significantly reduced mobility after discharge, continue pharmacological VTE prophylaxis for generally 5-7 days.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation from section 5.9</th>
<th>Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb</td>
</tr>
<tr>
<td></td>
<td>• acute surgical admission with inflammatory or intra-abdominal condition</td>
</tr>
<tr>
<td></td>
<td>• expected significant reduction in mobility</td>
</tr>
<tr>
<td></td>
<td>• have one or more of the risk factors shown in Box 1.</td>
</tr>
</tbody>
</table>

| Box 1 – VTE Risk factor box     | • Active cancer or cancer treatment |
|----------------------------------| • Age over 60 years |
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m\(^2\))
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

<table>
<thead>
<tr>
<th>Relative values of different outcomes</th>
<th>The outcomes considered for the review were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade off between clinical benefit and harms</td>
<td>The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. These trade offs were considered to be similar to those for patients admitted to hospital for surgery. Should an individual risk factor exist then the patient would still be considered at risk of developing VTE.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>There is no relevant cost-effectiveness evidence specifically for this population subgroup. However, a combination of drug and mechanical prophylaxis was found to be cost-effective for general surgery patients where the risk of major bleeding is less than 1%. It seems likely that combination prophylaxis will also be cost-effective for day-case surgery patients who are at elevated risk of VTE and who have a moderate risk of major bleeding.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>No evidence was identified specifically in this population.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>The GDG discussed the use of prophylaxis in this population. Although they acknowledged that some day case patients may be younger and more mobile than patients undergoing the same type of surgery as an inpatient, this is not necessarily the case. They felt that the increase in the number of day case procedures completed may result in more complex surgery</td>
</tr>
</tbody>
</table>
being completed on a day case basis and that there was the potential for patients to be discharged from hospital only for them to have an extended periods of significantly reduced mobility at home. They agreed that the principle of risk assessment for all patients VTE was key.

The average duration of VTE prophylaxis for 'general surgery' patients in the trials was 7 days. This concurs with the licensing conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. The guideline development group felt that the risk of VTE may still persist beyond discharge and post-discharge prophylaxis may be effective in some cases. No economic analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given.

There are other considerations for each agent when choosing pharmacological prophylaxis. UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH.

17.7.1 Other recommendations of relevance

The specific recommendations for patients undergoing day-case surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- The use of local anaesthesia by local infiltration with no reduction in mobility (Section 19.4)
- risk assessment for VTE and major bleeding (Section 5.9)
- the use of VTE prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)

17.8 Summary of recommendations

- Offer VTE prophylaxis to patients undergoing day surgery who are assessed to be at increased risk of VTE (see section 5.9)
- Start mechanical VTE prophylaxis at admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
- foot impulse devices
- intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account patient factors and according to clinical judgement. Choose one of:
  - fondaparinux
  - LMWH
  - UFH (for patients with renal failure).

If the patient is expected to have significantly reduced mobility after discharge, continue pharmacological VTE prophylaxis for 5-7 days.

➢ Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
  - acute surgical admission with inflammatory or intra-abdominal condition
  - expected significant reduction in mobility
  - have one or more risk factors shown in Box 1.
Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).
18 Other surgery

18.1 Introduction

This section covers patients undergoing surgery not mentioned elsewhere in the document (chapters 9 to 17) including plastic surgery, ear nose and throat surgery, and oral and maxillofacial surgery. It is not possible to mention all fields of surgery and all procedures but prophylaxis should be considered as for the closest comparable patient group.

The risk of VTE in this patient group may vary. Hospital Episode Statistic data presented in section 5.3.2 for gives the following values for the symptomatic VTE, although the limitations of this data have been discussed previously (section 5.3.2):

- Plastic surgery - 0.8%
- Breast surgery – 0.03%
- Ear, nose and throat surgery (ENT) – 0.02%
- Head and neck surgery – 0.02%
- Max facial dental surgery – 0.02%
- Eye surgery – 0.02%

Factors that might alter the risk of VTE

- These may be more mobile than other patients and therefore at less of a risk of VTE. This will depend on the type of surgery.

With the wide range of surgery types covered within this chapter it is important that the general factors that may increase the risk of bleeding, the hazard associated with it or other general factors that would affect the choice of specific methods of prophylaxis are considered for each individual surgery specialty.
18.2 Evidence of methods of prophylaxis

No studies were identified that investigated prophylaxis in these patients which is in essence why they are in this “other” group.

18.3 Network meta-analysis results

Network meta-analysis was not completed for this population

18.4 Cost-effectiveness evidence

Network meta-analysis was not conducted for this population.

18.5 Patient views

No patient views papers were found specific to this population.

For patient views about specific prophylaxis agents, see section 6.6.

18.6 Summary of evidence

There is no RCT evidence covering prophylaxis in patients undergoing surgery not mentioned in the other surgery chapters.
### 18.7 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Offer VTE prophylaxis to patients undergoing surgery other than that covered in chapters 9 to 17, who are assessed to be at increased risk of VTE (see section 5.9).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Start mechanical VTE prophylaxis at admission. Choose any one of:</td>
</tr>
<tr>
<td></td>
<td>– anti-embolism stockings (thigh or knee length)</td>
</tr>
<tr>
<td></td>
<td>– foot impulse devices</td>
</tr>
<tr>
<td></td>
<td>– intermittent pneumatic compression devices (thigh or knee length).</td>
</tr>
<tr>
<td></td>
<td>Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.</td>
</tr>
<tr>
<td></td>
<td>• Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account patient factors and according to clinical judgement. Choose one of:</td>
</tr>
<tr>
<td></td>
<td>- LMWH</td>
</tr>
<tr>
<td></td>
<td>- UFH (for patients with renal failure).</td>
</tr>
<tr>
<td></td>
<td>Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation from section 5.9</th>
<th>Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb</td>
</tr>
<tr>
<td></td>
<td>• acute surgical admission with inflammatory or intra-abdominal condition</td>
</tr>
<tr>
<td></td>
<td>• expected significant reduction in mobility</td>
</tr>
<tr>
<td></td>
<td>• have one or more of the risk factors shown in Box 1.</td>
</tr>
</tbody>
</table>

| Box 1 – VTE Risk factor box     | • Active cancer or cancer treatment                                                                                                                                                              |
|                                 | • Age over 60 years                                                                                                                                                                             |
|                                 | • Critical care admission                                                                                                                                                                          |
|                                 | • Dehydration                                                                                                                                                                                        |
|                                 | • Known thrombophilias                                                                                                                                                                             |
|                                 | • Obesity (BMI over 30 kg/m²)                                                                                                                                                                       |
|                                 | • One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or...)                                               |
### Relative values of different outcomes

The outcomes considered for the review were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

### Trade off between clinical benefit and harms

The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.

### Economic considerations

There is no relevant cost-effectiveness evidence specifically for this population subgroup. However, a combination of drug and mechanical prophylaxis was found to be cost-effective for general surgery patients where the risk of major bleeding is less than 1%. It seems likely that combination prophylaxis will also be cost-effective for other surgery patients who are at increased risk of VTE.

### Quality of evidence

No evidence specific to these other groups was identified. Evidence is extrapolated from the section relating to gastrointestinal, gynaecological, urological and thoracic surgery to make recommendations.

### Other considerations

The average duration of VTE prophylaxis for ‘general surgery’ patients in the trials was 7 days. This concurs with the licensing conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. It is known in many cases surgical patients are discharged within 5 days of their operation. The guideline development group felt that the risk of VTE may still persist beyond this time period and prophylaxis may be effective after discharge. No economic analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given. There are other considerations for each agent when choosing pharmacological prophylaxis. UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH.

---

<table>
<thead>
<tr>
<th><strong>inflammatory conditions)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Personal history or a first degree relative with a history of VTE</td>
</tr>
<tr>
<td>• Use of hormone replacement therapy</td>
</tr>
<tr>
<td>• Use of oestrogen-containing contraceptive therapy</td>
</tr>
<tr>
<td>• Varicose veins with phlebitis.</td>
</tr>
</tbody>
</table>

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).
18.7.1 **Other recommendations of relevance**

The specific recommendations for patients undergoing surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- patients using anticoagulants or antiplatelets for reasons other than VTE prophylaxis (Chapter 1)

18.8 **Summary of recommendations**

- Offer VTE prophylaxis to patients undergoing surgery other than that covered in chapters 9 to 17, who are assessed to be at increased risk of VTE (see section 5.9).
  - Start mechanical VTE prophylaxis at admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)
  - Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).
  - Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

- Regard **surgical patients and patients with trauma** as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
  - acute surgical admission with inflammatory or intra-abdominal condition
  - expected significant reduction in mobility
  - have one or more risk factors shown in **Box 1**.
Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).
19 Anaesthesia

19.1 Introduction

Anaesthesia is required for most operations and many investigations and other procedures. A general anaesthetic results in a patient losing consciousness. A regional anaesthetic technique involves injecting local anaesthetic into the epidural space (an epidural anaesthetic) or the subarachnoid space (a spinal anaesthetic) to achieve a sensory and/or motor block of the required area. Other drugs such as opioids may be added to the local anaesthetic agents or used as sole agents. Spinal injections are usually given as a single dose with a limited duration of action. Epidural anaesthesia may be continued for hours or days by placing additional medication through a catheter left in the epidural space. Regional techniques may be combined with sedation or a general anaesthetic. Certain procedures such as caesarean section, some urological operations or orthopaedic procedures on the lower limbs, are well suited to the use of regional techniques. Other procedures such as intracranial neurosurgery are not suitable.

The use of regional anaesthesia is rare in cardiac surgery but may be used for thoracic and vascular operations.

A concern with regional anaesthesia is that when neuroaxial blockades are used, thromboprophylaxis agents will increase the risk of spinal haematoma. Therefore, the timing of the use drugs that affect haemostasis or platelet function should be carefully planned.

19.2 Clinical evidence on anaesthesia

19.2.1 Regional vs. general anaesthesia

We identified one systematic review of 11 RCTs of regional vs general anaesthesia\(^5\) and four additional RCTs giving a total of 15 studies with 1115 participants (Evidence Table 64, Appendix D). Twelve studies were in elective orthopaedic surgery patients, two urological and one in general surgery patients. Eleven studies used an epidural regional anaesthetic and four administered a spinal anaesthetic. Eight of the 11 studies using epidural anaesthesia continued the anaesthetic into the post-operative period for pain relief (in the remaining three studies the duration of the epidural anaesthetic was either unclear or not reported). In seven studies patients were given no prophylaxis for VTE, patients wore stockings in three studies, and received a pharmacological method of prophylaxis in five studies.

Nine studies were conducted in the 1980s and six in the 1990s, with the most recent trial published in 1996. It should be noted that general anaesthetic techniques and other aspects of perioperative management have changed considerably over this period.
All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

**Effect on DVT:** A significant risk reduction for DVT was found in patients receiving regional compared with general anaesthesia (38%) (RR=0.62, 95% CI: 0.53 to 0.73, 15 studies) (Forest Plot 242, Appendix E).

**Effect on pulmonary embolism:** Regional anaesthesia was significantly more effective in reducing risk of pulmonary embolism than general anaesthesia, with an overall reduction of 43% (RR=0.57, 95% CI: 0.35 to 0.91) (Forest Plot 243, Appendix E).

**Effect on major bleeding:** Seven studies measured major bleeding events. Only one study reported an event, (RR=0.10, 95% CI: 0.01 to 1.71). The difference was not significant (Forest Plot 245, Appendix E).

### 19.2.2 Subgroup analysis of epidural vs spinal anaesthesia

We found no RCTs comparing spinal and epidural anaesthesia with regard to the development of post-operative VTE. A subgroup analysis of the regional vs general anaesthesia RCTs was carried out to look for a difference in the magnitude of effect based on whether spinal or epidural regional anaesthesia was used. Eleven studies used epidural and four studies used spinal regional anaesthesia.

For deep vein thrombosis, a random effects meta-analysis was used, due to the heterogeneity within the results. Subgroup analyses were not possible for proximal DVT and major bleeding as there were no studies using spinal anaesthesia that assessed these variables.

**Effect on DVT:** A significantly reduced risk of DVT was found with both epidural compared with general anaesthesia (RR=0.62, 95% CI: 0.51 to 0.75, 11 studies) and spinal compared with general anaesthesia (RR=0.63, 95% CI: 0.48 to 0.83, 4 studies). No significant difference in the magnitude of effect between epidural and spinal anaesthesia was found (Chi-square on 1 df = 0.03, p=0.86) (Forest Plot 246, Appendix E).

**Effect on pulmonary embolism:** We found a significantly reduced risk with epidural compared to general anaesthesia (RR=0.61, 95% CI: 0.38 to 0.99, 5 studies). There was a significant difference in risk of developing pulmonary embolism in a comparison of spinal vs general anaesthesia (RR=0.47, 95% CI: 0.23 to 0.96). There was no significant difference in the magnitude of effect between epidural and spinal anaesthesia Chi-square on 1 df = 0.42, p=0.52) (Forest Plot 247, Appendix E).

### 19.2.3 Regional and general anaesthesia vs general anaesthesia only

One study in the systematic review mentioned above and one further study compared the combined use of regional anaesthesia and general anaesthesia with general anaesthesia alone (Evidence Table 65, Appendix D). One study was in elective hip surgery patients. All patients received vitamin K antagonists for VTE prophylaxis. Patients receiving regional anaesthesia had an epidural for the duration of surgery only. The study was small, with only 37 patients. The second study was of general surgery (elective gall bladder) patients. No VTE prophylaxis was given to patients in the study. For regional anaesthesia patients, the epidural was prolonged into
the post-operative period for pain relief. The studies did not report major bleeds or pulmonary embolism. One study\textsuperscript{145} reported the site of deep vein thrombosis. No patient had a DVT that was situated above the knee and therefore the relative risk of proximal DVT was not estimable.

**Effect on DVT:** No significant difference was found (RR=0.69, 95% CI: 0.26 to 1.82, two studies) (Forest Plot 248, Appendix E).

### 19.2.4 Risk of haematoma in anticoagulated patients receiving a regional anaesthetic

Risk of haematoma at the injection site is increased with the concomitant use of pharmacological prophylaxis agents. Removal of epidural catheter in the anticoagulated patient has also been associated with the development of spinal haematoma. The consequences of an epidural haematoma may be permanent paralysis below the level of the haematoma. The diagnosis is difficult as patients may have weakness or block because of the effects of the epidural. It would be extremely difficult to determine the true incidence as a randomised study would require very large numbers of patients due to the rarity of the event, however it has been estimated to be about 1 in 150,000 epidural blocks and 1 in 220,000 spinal anaesthetics\textsuperscript{87}.

### 19.3 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.

### 19.4 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Consider regional anaesthesia for individual patients, in addition to other methods of VTE prophylaxis, as it carries a lower risk of VTE than general anaesthesia. Take into account the patients' preferences, their suitability for regional anaesthesia and any other planned method of VTE prophylaxis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative values of different outcomes</td>
<td>The outcomes considered were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).</td>
</tr>
<tr>
<td>Trade off between clinical benefit and harms</td>
<td>The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. The timing of when pharmacological prophylaxis is started is particularly important because of the risk from bleeding.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>We found no evidence on the cost-effectiveness of regional anaesthesia compared with general anaesthesia in the context of VTE prophylaxis. However, there is a small body of literature that shows regional anaesthesia to be associated with faster recovery time and reduced cost for some types of surgery\textsuperscript{447,679}. This would suggest that, when it can be performed safely, regional anaesthesia is likely to be a highly</td>
</tr>
</tbody>
</table>
cost-effective form of VTE prophylaxis.

**Quality of evidence**

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). Evidence from RCTs shows that regional anaesthesia compared with general anaesthesia reduces the risk of developing postoperative VTE. There was not enough evidence to determine differences in effect for major bleeding.

**Other considerations**

The evidence is limited to certain surgical procedures and there are other considerations involved when selecting an anaesthetic technique. Patient preferences are also an important consideration.

Regional anaesthesia alone should not be considered a suitable method of VTE prophylaxis. There are effective alternative techniques to prevent these complications and other matters to be taken into account when deciding on the most appropriate anaesthetic for a patient. In the absence of data on bleeding and the practical implications for different surgical procedures the guideline development group decided to recommend that its use be considered where practical in addition to other methods of prophylaxis.

Neuroaxial blockade should be avoided in those patients with significant bleeding disorders or receiving certain drugs that affect haemostasis or platelet function. The summary of product characteristics for each agent should be consulted for the latest guidance.

### 19.4.1 Supporting recommendation based on Guideline Development Group consensus opinion

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>If regional anaesthesia is used, plan the timing of pharmacological VTE prophylaxis to minimise the risk of epidural haematoma. If antiplatelet or anticoagulant agents are being used, or their use is planned, refer to the summary of product characteristics for guidance about the safety and timing of these in relation to the use of regional anaesthesia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade off between clinical benefit and harms</td>
<td>The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. An additional concern is the risk of developing an epidural haematoma as a result of the regional anaesthetic technique. Consequently, the Guideline Development Group recommends</td>
</tr>
</tbody>
</table>
that the timing of pharmacological prophylaxis should be carefully planned to minimise the risk of spinal haematoma if a regional anaesthetic technique is used. Patients using antiplatelets or anticoagulant agents may be at increased risk of bleeding.

**Economic considerations**
We found no evidence on the cost-effectiveness of the timing of regional anaesthesia. However, it seems logical that the careful consideration of timing will improve the cost-effectiveness of regional anaesthesia.

**Other considerations**
The type of anticoagulant used may affect the timing of insertion and removal of the catheter. Such procedures should be delayed until the anticoagulant effect of the agent is minimal. For example, this may involve removing the catheter just before the next dose of thromboprophylaxis and delaying any further thromboprophylaxis for 2 hours after epidural catheter removal.

The requirements for each antiplatelet agent or anticoagulant will be different. The guideline development group recommends that clinicians refer to information within the summary of product characteristics for each agent and seek advice from experienced anaesthetists if uncertainty remains.

The balance of risks and benefits should be individualised for each patient and will depend on the type of regional anaesthesia, patient risk factors (including bleeding risks), and the type and dose of anticoagulant or use of other drugs affecting haemostasis or platelet function. An additional concern is the risk of developing an epidural haematoma as a result of a regional anaesthetic technique.

<table>
<thead>
<tr>
<th><strong>Recommendation</strong></th>
<th>Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients undergoing a surgical procedure with local anaesthesia by local infiltration with no limitation of mobility.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade off between clinical benefit and harms</strong></td>
<td>The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.</td>
</tr>
<tr>
<td><strong>Economic considerations</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Other considerations</strong></td>
<td>The guideline development group decided that although a risk assessment for VTE should still be required upon admission to hospital (section 5.9), patients undergoing minor procedures under local anaesthesia without reduced mobility were likely to be at a low risk of VTE and as such routine prophylaxis was</td>
</tr>
</tbody>
</table>
not likely to be beneficial.

19.5 Summary of recommendations

- Consider regional anaesthesia for individual patients, in addition to other methods of VTE prophylaxis, as it carries a lower risk of VTE than general anaesthesia. Take into account the patients' preferences, their suitability for regional anaesthesia and any other planned method of VTE prophylaxis.

- If regional anaesthesia is used, plan the timing of pharmacological VTE prophylaxis to minimise the risk of epidural haematoma. If antiplatelet or anticoagulant agents are being used or their use is planned, healthcare professionals should refer to the summary of product characteristics for guidance about the safety and timing of these in relation to the use of regional anaesthesia.

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients undergoing a surgical procedure with local anaesthesia by local infiltration with no limitation of mobility.
20 Spinal injury

20.1 Introduction

Spinal injury and, in particular, spinal cord injury is a significant cause of morbidity and mortality with younger age groups frequently affected. Spinal injury can occur without injury to the spinal cord and when nerve injury occurs at the level below the dorsal/lumbar junction (where the injury will be to the cauda equine and not the spinal cord). Even without injury to the spinal cord or nerve injury, patients with spinal injury may be at increased risk of VTE for reasons of prolonged immobility.

Most patients with spinal injury are treated conservatively but a not insignificant proportion will require spinal stabilisation. Most patients recover to a greater degree but a not insubstantial number will have a permanent neurological deficit and require assessment, at least initially, in a Regional Spinal Injury Centre.

Non-traumatic causes of spinal cord compression are covered elsewhere, for example, in the NICE Metastatic Spinal Cord Compression guideline. However, further evidence is evaluated in the Palliative care (Chapter 28) and Critical care (Chapter 29) sections of this document. The evidence for patients undergoing spinal surgery is presented in Chapter 14.

The major concern is the constantly changing balance between the initial risk of bleeding (a potential disaster within the enclosed space of the spinal column) and the subsequent increased risk of thrombotic events, particularly, with prolonged immobilisation. The small number of trials completed in this population recorded the baseline risk of DVT at between 40-50% in the absence of thromboprophylaxis. A risk assessment tool should be utilised as soon after admission as is practicable with constant clinical evaluation and re-evaluation depending on patient progress.

20.2 Evidence of methods of prophylaxis

20.2.1 Summary of comparisons identified for any outcome

Four randomised controlled trials which reported at least one of the three main outcomes were identified.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).
Venous Thromboembolism Prophylaxis

### Figure 20-41: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

**GCS** – anti-embolism / graduated compression stockings; **IPCD/FID** – intermittent pneumatic compression devices or foot impulse devices; **LMWH** – low molecular weight heparin; **UFH** – unfractionated heparin; **Asp (HD)** – high dose aspirin (>300mg); **Asp (LD)** – low dose aspirin (<300mg); **mech** – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); **pharm** – pharmacological prophylaxis

#### 20.2.2 Results from pairwise comparisons

**Table 20-99: DVT – summary of results from RCTs**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proph vs no proph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asp (high dose) +/- other antiplatelets vs nil 234</td>
<td>1</td>
<td>3/13</td>
<td>6/15</td>
<td>0.58 (0.18, 1.86)</td>
<td>-0.17</td>
<td>ET: 29; FP: 28</td>
</tr>
<tr>
<td>UFH vs nil 442</td>
<td>1</td>
<td>8/16</td>
<td>8/17</td>
<td>1.06 (0.53, 2.15)</td>
<td>0.03 (0.31, 0.37)</td>
<td>ET: 27; FP: 17</td>
</tr>
<tr>
<td><strong>Single proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH 233</td>
<td>1</td>
<td>0/20</td>
<td>3/21</td>
<td>0.15 (0.01, 2.73)</td>
<td>-0.14 (0.31, 0.02)</td>
<td>ET: 32; FP: 48</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis
Table 20-100: Symptomatic pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asp (high dose) +/- other antiplatelets vs nil</td>
<td>234</td>
<td>0/13</td>
<td>0/15</td>
<td>Not estimatable</td>
<td>0 (-0.13, 0.13)</td>
<td>ET: 29 FP: 29</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis

Table 20-101: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + UFH vs LMWH</td>
<td>616</td>
<td>13/246</td>
<td>6/230</td>
<td>2.03 (0.78, 5.24)</td>
<td>0.03 (-0.01, 0.06)</td>
<td>ET: 43 FP: 219</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis

20.2.3 Additional information

20.2.3.1 All cause mortality

Table 20-102: All cause mortality summary from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asp (high dose) +/- other antiplatelets vs nil</td>
<td>234</td>
<td>0/13</td>
<td>0/15</td>
<td>Not estimatable</td>
<td>0.00 (-0.13, 0.13)</td>
<td>ET: 29 FP: 31</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH</td>
<td>233</td>
<td>0/20</td>
<td>2/21</td>
<td>0.21 (0.01, 4.11)</td>
<td>-0.10 (-0.24, 0.05)</td>
<td>ET: 32 FP: 51</td>
</tr>
<tr>
<td>Double proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + UFH vs LMWH</td>
<td>616</td>
<td>2/246</td>
<td>2/230</td>
<td>0.93 (0.13, 6.58)</td>
<td>0.00 (-0.02, 0.02)</td>
<td>ET: 43 FP: 220</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis

20.2.3.2 Additional studies

The DVT and pulmonary embolism outcomes of a study which compared the safety and efficacy of a combination of UFH plus IPCD against LMWH had been excluded from the main analysis of DVT and PE because only 107/456 (23.5%) of patients were able to be evaluated for these outcomes. Major bleeding events were reported on an intention to treat basis and are presented in Table 1-3.

This study was followed with a rehabilitative phase study where patients were enrolled from week 2 for 6 additional weeks and were given UFH or LMWH prophylaxis. The study was excluded as the reported patient inclusion was unclear. The study did not find any significant difference in all cause mortality, DVT, symptomatic PE and major bleeding rates.

20.2.3.3 Additional outcomes

No studies reported heparin induced thrombocytopenia, post thrombotic syndrome or chronic thromboembolic pulmonary hypertension.
20.3 Network meta-analysis results

No network meta-analysis was completed for this population.

20.4 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.

20.5 Patient views

Only two patient view or adherence to treatment studies were found in this population, and both were conducted as RCTs.

In a United States study, patients received more than 99% of the prescribed LMWH doses, for both once or twice daily regimens (Evidence Table 62, Appendix D). Most patients did not think getting the injections a “hassle” (compared to taking pills 3 times a day) or painful.

The other study compared FID vs IPCD among adults undergoing major thoracolumbar reconstructive spinal procedures (Evidence Table 61, Appendix D). All participants also wore thigh-length stockings and the devices were started postoperatively and worn when in bed until discharge. There was a wide range of responses in both groups ranging from extremely comfortable to extremely uncomfortable. There was no difference in visual analogue scores for comfort between the FID and the IPCD groups.

For more information patient views and adherence on specific prophylaxis methods, see section 6.6, where information from different populations are presented.

20.6 Summary of evidence

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DVT</td>
</tr>
<tr>
<td>Prophylaxis vs no prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>Nil</td>
<td>Not sig</td>
</tr>
<tr>
<td>Asp(HD) +/- antiplatelets</td>
<td>Nil</td>
<td>Not sig</td>
</tr>
<tr>
<td>Single prophylaxis vs single</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>LMWH</td>
<td>Not sig</td>
</tr>
<tr>
<td>Double prophylaxis vs single</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD + UFH</td>
<td>LMWH</td>
<td>-</td>
</tr>
</tbody>
</table>

Cost Effectiveness

There is no relevant cost-effectiveness evidence specifically for this population subgroup.

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.

Not sig - not statistically significant difference; ‘-’= not reported; no events – nobody in the study had the outcome. MB = Major bleeding

Very few RCTs had been conducted in patients with spinal injury. The studies were mostly very small, and therefore may be unable to detect any difference in the effectiveness of different strategies, even if there was one.
### 20.7 Recommendations and link to evidence

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td><strong>Recommendation</strong></td>
</tr>
<tr>
<td></td>
<td>- Start mechanical VTE prophylaxis at admission or as early as clinically possible. Choose any one of:</td>
</tr>
<tr>
<td></td>
<td>- anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)</td>
</tr>
<tr>
<td></td>
<td>- foot impulse devices</td>
</tr>
<tr>
<td></td>
<td>- intermittent pneumatic compression devices (thigh or knee length).</td>
</tr>
<tr>
<td></td>
<td>Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.</td>
</tr>
<tr>
<td></td>
<td><strong>Recommendation</strong></td>
</tr>
<tr>
<td></td>
<td>- If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see Box 2) and the bleeding risk has been established as low, add pharmacological VTE prophylaxis. Choose one of:</td>
</tr>
<tr>
<td></td>
<td>- LMWH</td>
</tr>
<tr>
<td></td>
<td>- UFH (for patients with renal failure).</td>
</tr>
<tr>
<td></td>
<td>Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Box 2. Bleeding Risk Factors</strong></th>
<th>Regard hospitalised patients as being at risk of bleeding if they have any of the following risk factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Active bleeding</td>
</tr>
<tr>
<td></td>
<td>- Acquired bleeding disorders (such as acute liver failure)</td>
</tr>
<tr>
<td></td>
<td>- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalised ration [INR] higher than 2)</td>
</tr>
<tr>
<td></td>
<td>- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours</td>
</tr>
<tr>
<td></td>
<td>- Lumbar puncture/epidural/spinal analgesia within the previous 4 hours</td>
</tr>
<tr>
<td></td>
<td>- Acute stroke</td>
</tr>
<tr>
<td></td>
<td>- Thrombocytopenia (platelets &lt; 75 x 10⁹/l)</td>
</tr>
<tr>
<td></td>
<td>- Uncontrolled systolic hypertension (≥ 230/120 mmHg)</td>
</tr>
<tr>
<td></td>
<td>- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand’s disease).</td>
</tr>
</tbody>
</table>

| **Relative values of different** | The main outcomes considered were venous thromboembolic |
outcomes

The outcomes considered were venous thromboembolism events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

Trade off between clinical benefit and harms

The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.

Economic considerations

There is no relevant cost-effectiveness evidence specifically for this population subgroup.

The implications for spinal injury patients developing VTE are similar to other groups of patients and the risk of VTE in this population is likely to be very high (40-47% in no prophylaxis arms of included RCTs). The results of our economic model for the general medical and surgical patients (Chapters 23 and 9) could therefore be extrapolated for this subgroup.

The model result suggests that LMWH is the most cost-effective for general medical patients. This was followed by unfractionated heparin. The model for general surgical patients suggests that a combination of mechanical prophylaxis and either unfractionated heparin or LMWH are most cost-effective where the risk of major bleeding is less than 1%.

It is likely that any major bleeding events have more severe consequences for this group of patients than for general medical or surgical patients from which the data have been extrapolated; especially if the bleeding occurs in the spinal cord. The importance of establishing bleeding risk before providing pharmacological prophylaxis is therefore very important.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

There was very little evidence available for this group of patients. All three studies where venous thromboembolism outcomes were included had small sample sizes (mean = 34, range 28 to 41), and would not have been powered to detect significant differences in VTE events or bleeding risks.

Therefore, the quality of evidence is disadvantaged from lack of precision in the results. Moreover, only two of the studies masked patients and VTE investigators to the treatment.

Other considerations

Despite a lack of evidence which is specific to this group, it had been noted that the incidence of VTE is very high (40-47% in no prophylaxis arms of included RCTs). Based on evidence in
other groups, prophylaxis should be offered, unless outweighed by the risk of bleeding. The Guideline Development Group recognised that it is difficult to determine a time point where the risk of bleeding would be significantly reduced based on the literature. This would need to be assessed individually for each patient.

There is little evidence available in terms of patients' views. The study which was found in this population found LMWH could be administered without adherence problems in the hospital setting, and most patients did not find it a painful or an inconvenience ("hassle").

20.7.1 Other recommendations of relevance

The specific recommendations for patients with spinal injury in this chapter should be read in conjunction with other relevant recommendations in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- recommendations about patients undergoing spinal surgery (Section 14.7)
- recommendations about patients in critical care (Section 29.7)
- recommendations about patients receiving palliative care (Section 28.7)
- recommendations about metastatic spinal injury from the NICE guidelines

20.8 Recommendations for research

Although not identified as a top priority research recommendation the Guideline Development Group identified that information about prophylaxis in this group is sparse, particularly around the duration of prophylaxis and suggested that further research in this area would be helpful.

20.9 Summary of recommendations

- Offer combined VTE prophylaxis with mechanical and pharmacological methods for patients with spinal injury. Regularly reassess the patient’s risks of VTE and bleeding.
- Start mechanical VTE prophylaxis at admission or as early as clinically possible.
  - Choose any one of:
    - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
    - foot impulse device
- intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see Box 2) and the bleeding risk has been established as low, add pharmacological VTE prophylaxis. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

**Box 2. Bleeding Risk Factors**

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalised ratio [INR] higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10⁹/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand’s disease)
21 Lower limb plaster casts

21.1 Introduction

The use of lower limb plaster casts in trauma and elective orthopaedic surgery affects a significant number of patients. The populations involved include trauma patients who do not require surgery, trauma patients who have had operative fixation and elective cases usually involving the knee, foot and ankle. A cast may be used for three months or more following the intervention.

Although the DVT risk (symptomatic or asymptomatic) in patients with lower limb plaster casts was reported as between 4-40% in the arms of the trials which did not receive any thromboprophylaxis, the risk of symptomatic pulmonary embolism is considerably lower (0.5%). However, the large volume of potential patients affected is a concern. In addition certain groups may be at greater risk, for example, those undergoing conservative or operative treatment on the Achilles tendon, more complex procedures with longer immobilisation, and those returning from abroad with their affected injured limb in a cast.

21.2 Evidence of methods of prophylaxis

21.2.1 Summary of comparisons identified for any outcome

Six studies were indentified in patients with lower limb plaster casts. All these compared low molecular weight heparin (LMWH) prophylaxis against no prophylaxis.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

In these studies, patients were given prophylaxis until the removal of plaster cast. This was 2-3 weeks in two, and 5 to 6 weeks in the other three studies.

One additional paper which investigated the impact of extended duration prophylaxis was found. In this study, all patients received LMWH prophylaxis for 7 days after ankle surgery before being randomised to 6 weeks (or until plaster cast removal) of LMWH prophylaxis or no prophylaxis. The results of a subgroup of patients who used plaster casts is included in this section.
Venous Thromboembolism Prophylaxis

21.2.2 Results from pairwise comparisons

Table 21-103: DVT – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td>5</td>
<td>51/633</td>
<td>100/631</td>
<td>0.52</td>
<td>-0.07</td>
<td>ET: 26 FP: 13</td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>317,356,367,374,377</td>
<td>33/86</td>
<td>55/120</td>
<td>0.55</td>
<td>-0.17</td>
<td>ET: 58 FP: 225</td>
</tr>
</tbody>
</table>

* FP = forest plot number in appendix E; ET = evidence table number in appendix D. Proph - prophylaxis
(a) There is substantial statistical heterogeneity between studies for this population ($I^2 = 54.5\%$, $\chi^2$ on 4 df = 8.80, $p = 0.07$).
Table 21-104: Symptomatic pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>3</td>
<td>0/368</td>
<td>2/380</td>
<td>0.20</td>
<td>0.00</td>
<td>(-0.02, 0.01) ET: 26 FP: 14</td>
</tr>
<tr>
<td>Post discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>1</td>
<td>0/114</td>
<td>0/108</td>
<td>Not estimable</td>
<td>0.00</td>
<td>(-0.02, 0.02) ET: 58 FP: 226</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Table 21-105: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>3</td>
<td>2/445</td>
<td>1/437</td>
<td>2.04</td>
<td>0.00</td>
<td>(-0.01, 0.01) ET: 26 FP: 15</td>
</tr>
<tr>
<td>Post discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>1</td>
<td>0/114</td>
<td>0/108</td>
<td>Not estimable</td>
<td>0.00</td>
<td>(-0.02, 0.02) ET: 58 FP: 227</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

21.2.3 Additional information

Table 21-106: All cause mortality – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>2</td>
<td>0/269</td>
<td>0/274</td>
<td>Not estimable</td>
<td>0.00</td>
<td>(-0.01, 0.01) ET: 26 FP: 16</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

21.3 Network meta-analysis results

No network meta-analysis was completed for this population.

21.4 Cost-effectiveness evidence

No cost-effectiveness analysis was completed for this population.

21.5 Patient views

One open label RCT compared subcutaneous self-injection of LMWH at the abdominal wall using disposable needles against no prophylaxis until the removal of the below knee plaster cast. In this study, 12% of the 148 participants discontinued because of discomfort with self injection, approximately 60% had “no difficulties” and some patients had difficulties remembering the injections. 87% of patients in this study were male, and their average age was 49 years old.

For patient views about specific prophylaxis agents, see section 6.6.
21.6 Summary of evidence

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DVT</td>
</tr>
<tr>
<td>Prophylaxis vs no prophylaxis</td>
<td>Nil</td>
<td>LMWH</td>
</tr>
<tr>
<td>Post discharge</td>
<td>Nil</td>
<td>LMWH</td>
</tr>
</tbody>
</table>

Cost Effectiveness

No cost-effectiveness analysis was conducted for this group.

The prophylaxis strategy which is significantly more effective in reducing DVT or PE, or resulting in significantly less major bleeding is stated in bold.

Not sig - not statistically significant difference; no events – nobody in the study had the outcome. MB = Major bleeding

21.7 Recommendations and link to evidence

**Recommendation**

Consider offering pharmacological VTE prophylaxis to patients with lower limb plaster casts after evaluating the risks (see section 5.9) and benefits based on clinical discussion with the patient. Offer LMWH (or UFH for patients with renal failure) until lower limb plaster cast removal.

**Recommendation from section 5.9**

Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more of the risk factors shown in Box 1.

**Box 1 – VTE Risk factors**

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m2)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
### Relative values of different outcomes

The main outcomes considered were venous thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

### Trade off between clinical benefit and harms

The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.

We cannot say definitively that the benefits outweigh the harms since the mortality rate is too low to make a conclusion about all-cause mortality. The data on pulmonary embolism and major bleeding were very sparse. The only significant outcome was a 50% reduction in all DVT events with LMWH compared with no prophylaxis.

### Economic considerations

No cost-effectiveness analysis was completed for this group of patients.

This is a potentially large population, and recommending prophylaxis may have significant impact on NHS costs, especially as prophylaxis is continued until the cast is removed. Patients in this population are relatively young compared to other groups, and any fatal VTE or fatal bleeding events, or long term events due to thrombosis or bleeding could result in a higher loss of quality adjusted life years than the populations where cost-effectiveness analysis had been conducted. However, the risk of pulmonary embolism seems low compared with some other groups and therefore it is unlikely that prophylaxis will be cost-effective unless patients have additional risk factors.

### Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

All studies in this population compared LMWH administered until plaster cast removal against no prophylaxis or shorter term prophylaxis. The studies included specific groups of patients, and some extrapolation is required to cover plaster cast patients not included. Some of the studies which compared LMWH vs nil were
not masked.

When considering adherence data observed from RCTs, it is important to note that patients in RCTs are a selected group, and as a result of the study protocol, patients are likely to receive more intense care and support than a patient in usual practice. This may produce adherence results which are more optimistic than usual practice.

Other considerations

The orthopaedic subgroup discussed this group in detail. Although they acknowledged the reduction in DVT, they noted the very low incidence of PE in these patients. They discussed whether the patients who developed pulmonary embolism would have developed it irrespective of whether they had been given prophylaxis. Although it is by no means certain the use of a robust risk assessment tool might help to “pick out” these individuals. They decided that VTE prophylaxis should be considered and offered only after a discussion of the risks and benefits with the patient.

There is a range of procedures and injuries which require the application of lower limb plaster casts. The length of the plaster cast and the location of injury within the leg may also differ. Most patients are expected to remain mobile (although not weight bearing on the affected limb), while others may remain immobile, generally. These are the factors which may put patients at different levels of risks. Among the RCTs reviewed, risk of DVT in the arm which did not receive prophylaxis ranged from 4.3% in a study among patients with injuries not requiring surgery to 40.4% in a study where all patients had Achilles tendon rupture and received surgery.

The practicality and adherence of self-administering subcutaneous LMWH injection and other mechanical prophylaxis methods was also considered. Although the result from a RCT showed that most people could self-administer LMWH without problems, there are still some patients who were not comfortable with it, and who reported problems remembering the injection.

Dabigatran and rivaroxaban are new oral anticoagulants which are licensed for use after hip and knee replacement. They are not licensed in this population. The orthopaedic subgroup felt that as no evidence had been gained in this population it was not appropriate to recommend them for lower limb plaster cast patients, although more research into these agents may make them suitable for use in this population in the future. Fondaparinux has not been evaluated in this group of patients and is therefore not recommended.
21.7.1 Other recommendations of relevance

The specific recommendations for patients with lower limb plaster casts in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)

21.8 Recommendations for research

21.8.1 Thromoprophylaxis for patients with lower limb plaster casts

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of pharmacological prophylaxis for reducing the risk of VTE in patients with lower limb plaster casts?

Why this is important

A number of randomised controlled trials have been published reporting the use of VTE prophylaxis in patients with lower limb plaster casts. However, within these trials there has been a range of patients including patients with soft tissue injuries and no operation, those with operated and unoperated fractures and patients having elective procedures. The incidence of VTE in the published trials that did not use VTE prophylaxis ranges from 4%–40%. The implications of providing pharmacological prophylaxis for all patients with lower limb plaster casts are potentially considerable with respect to cost. Trials stratifying patients by reason for plaster cast would be useful to determine which patients should be recommended for prophylaxis.

Recommended design: RCT

(More details in Appendix F).

21.9 Summary of recommendations

- Consider offering pharmacological VTE prophylaxis to patients with lower limb plaster casts after evaluating the risks (see section 5.9) and benefits based on clinical discussion with the patient. Offer LMWH (or UFH for patients with renal failure) until lower limb plaster cast removal.

- Regard **surgical patients and patients with trauma** as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb or
  - acute surgical admission with inflammatory or intra-abdominal condition or
  - expected significant reduction in mobility or
  - have one or more risk factors in **Box 1**.
Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory diseases)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).
22 Major trauma

22.1 Introduction

The majority of patients suffering significant trauma require assessment and management by the orthopaedic service. There may be associated injury to the head, chest or abdomen, in those with multiple trauma, most frequently in road traffic collisions. However, major pelvic and spinal injury and multiple long bone fractures in isolation constitute significant orthopaedic trauma. A proportion will require management in a critical care setting, in either an Intensive Care or High Dependency Unit, for which additional guidance can be found in Chapter 29.

There is no evidence for the use of pharmacological or mechanical VTE prophylaxis for patients with minor injuries such as simple fractures requiring an upper limb plaster cast who are mobile and have no other risk factors for VTE. However, further guidance for patients with these types of injuries and significant reduction in mobility or an increased risk for VTE (Section 5.9) can be found in the guidance for general medical patients (Chapter 23). Guidance for patients undergoing upper limb surgery can be found in the section for ‘other orthopaedic surgery’ (Chapter 13).

For major trauma patients, the main concern is the constantly changing balance between the initial risk of bleeding and the subsequent increased risk of thrombotic events. Trauma patients have been identified to be at increased risk of venous thromboembolism as although none of the RCTs identified had a "no prophylaxis" arm, the incidence of DVT even when thromboprophylaxis was provided was reported as up to 37%.

The safe management of these patients should include a risk assessment tool for VTE with continuous clinical monitoring of the potential initial bleeding risk and the subsequent increased thrombotic tendency.

22.2 Evidence of methods of prophylaxis

A total of 5 studies were identified. Two of these studies compared low molecular weight heparin (LMWH) against mechanical methods (e.g. anti-embolism stockings, intermittent pneumatic compression devices or foot impulse devices). Another study compared LMWH immediate initiation against initiation after using 'pulsatile foot pumps' only for the first 5 days.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).
### 22.2.1 Summary of comparisons identified for any outcome

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No prophylaxis</td>
<td>Post-discharge</td>
<td>GCS</td>
<td>Dabigatran</td>
<td>Fondaparinux</td>
<td>LMWH</td>
<td>UFH</td>
<td>VKA</td>
<td>High dose aspirin</td>
<td>Low dose aspirin</td>
<td>GCS + IPCD/FID</td>
<td>Mech + pharm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Figure 22-43: Number of studies which compared various types of prophylaxis methods.**

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

### Table 22-107: Types of injury in included study

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohn et al, 1999124</td>
<td>LMWH vs UFH</td>
<td>“moderately injured” – mixed population</td>
</tr>
<tr>
<td>Knudson et al, 1996154</td>
<td>IPCD+GCS or FID vs LMWH</td>
<td>Mixed trauma population</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– ISS &gt;10: 53%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Fractures: Lower extremity:16.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Head injury (GCS ≤ 8): 7%</td>
</tr>
<tr>
<td>Ginzburg et al, 2003222</td>
<td>IPCD or FID vs LMWH</td>
<td>ISS ≥9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Injuries: Chest: 37.3%; head: 22.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Fractures: Leg or pelvis: 35.1%</td>
</tr>
<tr>
<td>Geerts et al, 1996218</td>
<td>LMWH vs UFH</td>
<td>ISS ≥9, 67.5% motor vehicle accident</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Spinal cord injury: 8.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Fractures: Pelvic/femur :38.1%; tibial:17.8%</td>
</tr>
</tbody>
</table>
### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stannard et al, 2006</td>
<td>FID + delayed LMWH</td>
<td>Severe blunt skeletal trauma, AIS ≥ 3, with single or multiple long bone fracture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— 52% of patients had injury at the acetabulum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— The following is the % of a certain type of injury out of total injuries reported: 25% hip, 16 % pelvis, 20% long bones</td>
</tr>
</tbody>
</table>

### 22.2.2 Results from pairwise comparisons

#### Table 22-108: DVT – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH ≤2,218</td>
<td>2</td>
<td>40/163</td>
<td>62/168</td>
<td>0.69</td>
<td>(-0.18, -0.01)</td>
<td>ET: 32 FP: 48, E: 32 FP: 48, E: 32 FP: 48</td>
</tr>
<tr>
<td>IPCD/FID vs LMWH 222</td>
<td>1</td>
<td>6/224</td>
<td>1/218</td>
<td>5.84</td>
<td>(0.71, 48.10)</td>
<td>ET: 37 FP: 87, E: 37 FP: 87, E: 37 FP: 87</td>
</tr>
<tr>
<td>Other prophylaxis strategies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(IPCD + GCS) or FID vs LMWH 354</td>
<td>1</td>
<td>2/82</td>
<td>1/120</td>
<td>2.93</td>
<td>(0.27, 31.75)</td>
<td>ET: 37 FP: 101, E: 37 FP: 101, E: 37 FP: 101</td>
</tr>
<tr>
<td>FID + delayed LMWH vs LMWH 620</td>
<td>1</td>
<td>9/103</td>
<td>13/97</td>
<td>0.65</td>
<td>(-0.13, 0.04)</td>
<td>ET: 52 FP: 211, E: 52 FP: 211, E: 52 FP: 211</td>
</tr>
</tbody>
</table>

*FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

#### Table 22-109: Symptomatic pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH ≤2,218</td>
<td>2</td>
<td>1/182</td>
<td>0/187</td>
<td>3.16</td>
<td>(0.13, 76.91)</td>
<td>ET: 32 FP: 49, E: 32 FP: 49, E: 32 FP: 49</td>
</tr>
<tr>
<td>IPCD/FID vs LMWH 222</td>
<td>1</td>
<td>1/224</td>
<td>1/218</td>
<td>0.97</td>
<td>(0.06, 15.46)</td>
<td>ET: 37 FP: 88, E: 37 FP: 88, E: 37 FP: 88</td>
</tr>
<tr>
<td>Other prophylaxis strategies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(IPCD + GCS) or FID vs LMWH 354</td>
<td>1</td>
<td>0/82</td>
<td>0/120</td>
<td>Not estimatable</td>
<td>0.00</td>
<td>ET: 37 FP: 102, E: 37 FP: 102, E: 37 FP: 102</td>
</tr>
<tr>
<td>FID + delayed LMWH vs LMWH 620</td>
<td>1</td>
<td>0/103</td>
<td>2/97</td>
<td>0.19</td>
<td>(0.01, 3.88)</td>
<td>ET: 52 FP: 212, E: 52 FP: 212, E: 52 FP: 212</td>
</tr>
</tbody>
</table>

*FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

#### Table 22-110: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH 218</td>
<td>1</td>
<td>5/171</td>
<td>1/173</td>
<td>5.06</td>
<td>(0.60, 42.85)</td>
<td>ET: 32 FP: 50, E: 32 FP: 50, E: 32 FP: 50</td>
</tr>
<tr>
<td>IPCD/FID vs LMWH 222</td>
<td>1</td>
<td>4/224</td>
<td>4/218</td>
<td>0.97</td>
<td>(0.25, 3.84)</td>
<td>ET: 37 FP: 89, E: 37 FP: 89, E: 37 FP: 89</td>
</tr>
<tr>
<td>Other prophylaxis strategies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(IPCD + GCS) or FID vs LMWH 354</td>
<td>1</td>
<td>0/82</td>
<td>0/120</td>
<td>Not estimatable</td>
<td>0.00</td>
<td>ET: 37 FP: 89, E: 37 FP: 89, E: 37 FP: 89</td>
</tr>
</tbody>
</table>

*FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*
22.2.3 Additional information

Table 22-111: All cause mortality – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single proph vs single LMWH vs UFH</td>
<td>1</td>
<td>2/171</td>
<td>0/173</td>
<td>5.06 (0.24, 104.59)</td>
<td>0.01 (-0.01, 0.03)</td>
<td>ET: 32 FP: 51</td>
</tr>
<tr>
<td>IPCD/FID vs LMWH</td>
<td>1</td>
<td>0/224</td>
<td>0/218</td>
<td>Not estimatable</td>
<td>0.00 (-0.01, 0.01)</td>
<td>ET: 37 FP:</td>
</tr>
<tr>
<td>Other prophylaxis strategies</td>
<td>1</td>
<td>0/82</td>
<td>0/120</td>
<td>Not estimatable</td>
<td>0.00 (-0.02, 0.02)</td>
<td>ET: 37</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis

22.3 Network meta-analysis results

No network meta-analysis was completed for this population.

22.4 Cost-effectiveness evidence

An original cost-effectiveness analysis was not completed for this population. One study was identified in the published literature. This study was based on one of the randomised trials included in our review Geerts et al, 1996 (Table 22-107). This found that LMWH was dominated by UFH (that is patients receiving UFH had longer life expectancy and incurred less cost) due to increased bleeding from LMWH. However, they did not include the impact of prophylaxis on post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension and therefore they will have under-estimated the health gain and over-estimated the cost associated with LMWH. Furthermore, the results of this study are only partially applicable to this guideline trauma population as costs were assessed from a Canadian (rather than as UK NHS perspective) and quality adjusted life years (QALYs) were not estimated.

22.5 Patient views

One of the RCTs reported adherence to recommended duration of FID use. In this study, patients were advised to use FID for at least 12 hours per day. Most patients were compliant and the mean duration of use was 13.3 hours (range of 1 to 23 hours per day). A few patients did not wear the pump for the recommended period, especially when patients began to walk.

No other patient view or adherence studies conducted in major trauma patients were identified. For patient views about specific prophylaxis agents, see section 6.6.
22.6 Summary of evidence

Table 22-112: Summary of evidence from direct results for DVT, pulmonary embolism and major bleeding outcomes.

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DVT</td>
</tr>
<tr>
<td>LMWH</td>
<td>UFH</td>
<td>LMWH</td>
</tr>
<tr>
<td>IPCD or FID</td>
<td>LMWH</td>
<td>Not sig</td>
</tr>
</tbody>
</table>

Other strategies

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td>FID + delayed LMWH</td>
<td>LMWH</td>
<td>Not sig</td>
</tr>
<tr>
<td>IPCD + GCS or FID</td>
<td>LMWH</td>
<td>Not sig</td>
</tr>
</tbody>
</table>

Cost effectiveness Results

No cost-effectiveness analysis was conducted in this population

One economic study was identified which suggested UFH was cost effective for major trauma patients but is subject to a number of limitation as described in section 1.4

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.

Not sig - not statistically significant difference; ‘-‘= not reported, no events – nobody in the study had the outcome. MB = Major bleeding
### 22.7 Recommendations and link to evidence

**Recommendation**

Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients with major trauma. Regularly reassess the patient’s risks of VTE and bleeding.

- Start mechanical VTE prophylaxis at admission or as early as clinically possible. Choose any one of:
  - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see Box 2) and when the bleeding risk has been established as low, add pharmacological VTE prophylaxis. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

**Recommendation—from section 5.9**

Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more of the risk factors shown in Box 1.

**Box 1 –Risk Factors for VTE**

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory
conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

**Recommendation—from section 5.9**

Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.

*Consult the summary of product characteristics for the pharmacological VTE prophylaxis being used or planned for further details.

**Box 2-Risk Factors for bleeding**

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalised ratio [INR] higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than $75 \times 10^9/l$)
- Uncontrolled systolic hypertension ($230/120 \text{ mmHg}$ or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand’s disease)

**Relative values of different outcomes**
The main outcomes considered were venous thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

**Trade off between clinical benefit and harms**
The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. In this group, patients are at an increased risk of both VTE and bleeding.
Economic considerations

Although no cost-effectiveness model was developed for this population, the implications for trauma patients developing VTE are similar to other groups of patients, and the risk of developing VTE in this group is likely to be high. The cost-effectiveness of thromboprophylaxis is robust in many medical and surgical patients. However, this is a group where the risk of major bleeding (and fatal bleeding is potentially high). It is assumed that providing mechanical prophylaxis for major trauma patients is cost-effective and that pharmacological prophylaxis is cost-effective as long as the risk of bleeding has subsided.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

The generalisability of evidence from studies to individual patients should be considered. The RCTs included moderate to severe trauma patients with a variety of injuries, with the more severe patients usually managed in specialised trauma centres. There is a range of risks for VTE and bleeding, depending on the type, location and severity of the injuries.

The orthopaedic subgroup noted that orthopaedic trauma methods have changed over the last decade and so some of the evidence published may not represent the methods and techniques currently used. This may have had an impact on the incidence of DVT in these studies. No statistical heterogeneity was found in the results.

Other considerations

When fractures are stabilised, bleeding risk generally decreases, but this might be accompanied by increasing thrombosis risk. It is difficult to determine the time point where the risk of thromboembolism exceeds the risk of bleeding in an individual patient based on the literature. This would require each individual to be assessed and monitored closely.

Although there are no studies with a nil prophylaxis arm it was noted that the incidence of VTE is very high in this group (risk of DVT was up to 37% even when VTE prophylaxis was used). Based on evidence in other groups, prophylaxis should be offered, unless outweighed by the risk of bleeding.

The orthopaedic subgroup felt that in some situations where a trauma patient is at increased risk of VTE but pharmacological prophylaxis is contraindicated due to bleeding risks and mechanical prophylaxis is contraindicated due to lower limb injury, the use of temporary inferior vena caval filters could be considered (Chapter 8).

There is little evidence available in terms of patients’ views.
22.7.1 Other recommendations of relevance

The specific recommendations for patients with major trauma in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- patients being managed in a critical care setting (Section 29.7)

22.8 Summary of recommendations

➢ Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients with major trauma. Regularly reassess the patient's risks of VTE and bleeding:

- Start mechanical VTE prophylaxis at admission or as early as clinically possible. Choose any one of:
  - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see Box 2) and when the bleeding risk has been established as low, add pharmacological VTE prophylaxis. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

➢ Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb or
- acute surgical admission with inflammatory or intra-abdominal condition or
- expected significant reduction in mobility or
- have one or more risk factors shown in Box 1.
Box 1 Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and 6 weeks post partum)
• Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in BOX 2, unless the risk of VTE outweighs the risk of bleeding.

*Prescribers should consult the summary of product characteristics for the pharmacological VTE prophylaxis being used or planned for further details.

**Box 2 Risk factors for bleeding**

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalised ratio(INR) higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10^9/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand’s disease)
23 General medical patients

23.1 Introduction

Although VTE is most often associated with surgery, 70-80% of hospital-acquired fatal pulmonary embolisms (PEs) occur in medical patients. Apart from being an older cohort, 40% of medical patients have more than one risk factor for VTE, including previous VTE, cancer, stroke, heart failure, chronic obstructive airways disease, sepsis and bed rest. The baseline risk of VTE is estimated to be around 15% for those who are acutely unwell in medical beds, with risks rising to about 50-60% having been reported after severe stroke.

The risk of bleeding is different from surgical patients as medical patients by definition do not have the same open wounds however they are at similar risks of gastrointestinal haemorrhage. The use of thromboprophylaxis in medical patients provides an opportunity to greatly reduce the morbidity due to VTE, however the uptake of thromboprophylaxis in medical patients is poor and some studies report that the majority of patients are left unprotected.

23.2 Evidence of methods of prophylaxis

Eleven (11) randomised controlled trials which reported at least one of the three main outcomes (DVT, PE and major bleeding) were identified.

Another two studies did not report DVT, PE or major bleeding but reported all cause mortality and other outcomes.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).
### 23.2.1 Summary of comparisons identified for any main outcomes

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proph vs no proph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs Nil¹⁴¹,¹⁹¹,³⁷⁹</td>
<td>3</td>
<td>29/488</td>
<td>63/479</td>
<td>0.46</td>
<td>-0.06</td>
<td>ET: 26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.31, 0.70)</td>
<td>(-0.10, -0.03)</td>
<td>FP: 13</td>
</tr>
<tr>
<td>Fondaparinux vs Nil¹²¹</td>
<td>1</td>
<td>18/321</td>
<td>29/323</td>
<td>0.62</td>
<td>-0.03</td>
<td>ET: 25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.35, 1.10)</td>
<td>(-0.07, 0.01)</td>
<td>FP: 9</td>
</tr>
<tr>
<td><strong>Single proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH⁴⁵,²⁵⁶,³⁸⁷</td>
<td>3</td>
<td>11/738</td>
<td>15/742</td>
<td>0.79</td>
<td>-0.01</td>
<td>ET: 32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.36, 1.73)</td>
<td>(-0.02, 0.00)</td>
<td>FP: 48</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

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**Figure 23-44: Number of studies which compared various types of prophylaxis methods.**

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis
Table 23-114: Symptomatic pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil [390,395,379]</td>
<td>3</td>
<td>8/2027</td>
<td>13/1986</td>
<td>0.61</td>
<td>(0.25, 1.50)</td>
<td>0.00</td>
</tr>
<tr>
<td>Fondaparinux vs Nil [21]</td>
<td>1</td>
<td>4/425</td>
<td>11/414</td>
<td>0.35</td>
<td>(0.11, 1.10)</td>
<td>-0.02</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH [5,257,350,387]</td>
<td>4</td>
<td>4/1698</td>
<td>7/1651</td>
<td>0.72</td>
<td>(0.16, 3.25)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

Table 23-115: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil [391,390,395,579]</td>
<td>4</td>
<td>29/2367</td>
<td>18/2355</td>
<td>1.61</td>
<td>(0.79, 3.26)</td>
<td>0.00</td>
</tr>
<tr>
<td>Fondaparinux vs Nil [21]</td>
<td>1</td>
<td>1/425</td>
<td>1/414</td>
<td>0.97</td>
<td>(0.06, 15.52)</td>
<td>0.00</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH [5,256,257,350,387]</td>
<td>5</td>
<td>9/1924</td>
<td>15/1901</td>
<td>0.64</td>
<td>(0.27, 1.49)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

23.2.3 Additional information

23.2.3.1 All cause mortality

Table 23-116: All cause mortality summary from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH vs nil [212]</td>
<td>1</td>
<td>304/5776</td>
<td>333/5917</td>
<td>0.94</td>
<td>(0.80, 1.09)</td>
<td>0.00</td>
</tr>
<tr>
<td>LMWH vs nil [141,191,390,395,418,577]</td>
<td>6</td>
<td>171/3819</td>
<td>179/3825</td>
<td>0.97</td>
<td>(0.79, 1.18)</td>
<td>0.00</td>
</tr>
<tr>
<td>Fondaparinux vs Nil [121]</td>
<td>1</td>
<td>14/425</td>
<td>25/414</td>
<td>0.55</td>
<td>(0.29, 1.03)</td>
<td>-0.03</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH [5,256,257,350,387]</td>
<td>5</td>
<td>49/1924</td>
<td>42/1901</td>
<td>1.12</td>
<td>(0.54, 2.35)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D.

Proph - prophylaxis

23.2.3.2 Composite venous thromboembolism outcomes

Composite venous thromboembolism was reported as the primary outcome in five studies [45,121,350,395,579]. The results obtained using composite VTE outcomes were consistent with...
the PE and DVT data reported separately and did not change the conclusions of the study.

23.2.3.3 Other outcomes

No studies reported chronic thromboembolic pulmonary hypertension or post thrombotic syndrome. One study reported on the incidence of heparin induced thrombocytopenia but found no significant difference between the group receiving LMWH and the group receiving UFH (1/233 and 0/216 respectively).

23.3 Network meta-analysis results

23.3.1 Introduction

A network meta-analysis was completed for DVT, symptomatic pulmonary embolism and major bleeding. Details on the network meta-analysis methods can be found in section 3.10.

23.3.2 Results

DVT results

There were 7 studies included in the network meta-analysis for DVT.

Figure 23-45: Network diagram for DVT. Numbers indicate the number of studies which contributed results for each comparison
Table 23-117: DVT – network meta-analysis results

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH</td>
<td>0.40 (0.17, 0.89)</td>
</tr>
<tr>
<td>UFH</td>
<td>0.52 (0.14, 1.96)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>0.63 (0.16, 2.10)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals.
The residual deviance was 12.7, which is quite close to the number of data points of 14, suggesting that the model fits the data well.

Symptomatic PE results

There were 8 studies included in the network meta-analysis for symptomatic PE.45,121,257,350,387,390,394,579.

![Network diagram for symptomatic pulmonary embolism](image)

Figure 23-46: DVT – network meta-analysis results of interventions compared to no prophylaxis

Figure 23-47: Network diagram for symptomatic pulmonary embolism. Numbers indicate the number of studies which contributed results for each comparison.
Table 23-118: Symptomatic pulmonary embolism – network meta-analysis results

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux</td>
<td>0.33 (0.03, 3.08)</td>
</tr>
<tr>
<td>LMWH</td>
<td>0.56 (0.11, 2.13)</td>
</tr>
<tr>
<td>UFH</td>
<td>1.55 (0.19, 13.80)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals. The residual deviance was 16.3, which is quite close to the number of data points of 16, suggesting that the model fits the data well.

Figure 23-48: Symptomatic pulmonary embolism – network meta-analysis results of interventions compared to no prophylaxis

**Major bleeding results**

A network meta-analysis for major bleeding was conducted using studies across hip fracture surgery, hip replacement surgery, knee replacement surgery, general medical patients and general surgical patients.

One hundred and twenty eight (128) studies were included in the analysis of which:

- 10 studies were in **medical patients**45,121,191,256,257,350,387,390,394,579,

- 48 studies were in **general surgery patients**10,14,29,40,50,52,72,75,76,92,113,199,210,227,230,238,262,266,267,269,280,283,321,324,329,358,366,385,439,469,499,503,504,516,517,552,553,570,573,575,588,589,633,639,641,645,657,667,703,711,713,

- 28 studies were in **elective hip replacement patients**126,129,151,153,174,188,195,201,202,243,260,293,299,377,380,400,409,421,465,527,573,574,635,651,659,684,

- 9 studies were in patients undergoing **hip fracture surgery**175,178,204,248,463,533,609,704,715

- 15 studies were in **elective knee replacement patients**36,66,130,186,201,202,274,388,399,436,476,479,

- 7 studies were in **mixed orthopaedic surgery patients**69,200,242,250,292,459,531

- 11 studies were in **mixed surgery patients**54,166,270,271,340,344,396,416,486,568,569,575,585,655

Seven of these studies included three comparison arms153,299,380,504,533,633,655.
Figure 23-49: Network diagram for major bleeding. Numbers indicate the number of studies which contributed results for each comparison.

Table 23-119: Major bleeding – network meta-analysis results (pooled across all population subgroups) *

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH</td>
<td>1.57 (1.16, 2.16)</td>
</tr>
<tr>
<td>UFH</td>
<td>1.79 (1.34, 2.43)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.85 (1.62, 5.22)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals. The residual deviance was 291.5, which is quite close to the number of data points of 263, suggesting that the model fits the data well.

* Only the results for interventions included in the network meta-analysis for DVT were shown included in Figure 23-50 and
Table 23-119.

**All cause mortality**

Twelve studies were included in the analysis of all cause mortality\(^{45,121,191,212,256,257,387,390,394,418,579}\).

![Network diagram for all cause mortality](image)

**Figure 23-51**: Network diagram for all cause mortality. Numbers indicate the number of studies which contributed results for each comparison.

<table>
<thead>
<tr>
<th>Intervention (compared with no prophylaxis)</th>
<th>Relative Risk (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux</td>
<td>0.54 (0.24, 1.14)</td>
</tr>
<tr>
<td>UFH</td>
<td>0.87 (0.58, 1.16)</td>
</tr>
<tr>
<td>LMWH</td>
<td>0.99 (0.78, 1.24)</td>
</tr>
</tbody>
</table>

Credible intervals are the Bayesian equivalent of confidence intervals. The residual deviance was 22.5, which is quite close to the number of data points of 24, suggesting that the model fits the data well.

**Figure 23-52**: All cause mortality – network meta-analysis results of interventions compared to no prophylaxis.
23.4 Cost-effectiveness evidence

23.4.1 Introduction

General assumptions and methods for model are described in chapter 4.

Data used for the cost-effectiveness analysis which were specific to medical patients can be found in Table 23-121 and Table 23-122.

Table 23-121: Baseline risk and other population specific parameters used in the economic model for general medical patients

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Source</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>Systematic review of RCTs (a) (weighted mean)</td>
<td>74</td>
</tr>
<tr>
<td>% Male</td>
<td>Systematic review of RCTs (a)</td>
<td>47%</td>
</tr>
<tr>
<td>Standardised Mortality Ratio (b)</td>
<td>Mortality rate = 15.3%</td>
<td>357% (1 year)</td>
</tr>
<tr>
<td>Mean duration of prophylaxis</td>
<td>Systematic review of RCTs (a)</td>
<td>10 days</td>
</tr>
<tr>
<td>Proportion of DVTs that are symptomatic (Ratio of symptomatic DVTs to all DVTs)</td>
<td>Systematic review of RCTs (a)</td>
<td>6.2% (40/644)</td>
</tr>
<tr>
<td>Major Bleed Fatality Rate (d)</td>
<td>Systematic review of RCTs (a)</td>
<td>14.3% (8/56)</td>
</tr>
<tr>
<td>PE Fatality Rate (e)</td>
<td>Systematic review of RCTs (a)</td>
<td>44.7% (17/38)</td>
</tr>
<tr>
<td>DVT risk</td>
<td>No prophylaxis/placebo arms</td>
<td>13.4%</td>
</tr>
<tr>
<td>Symptomatic PE risk</td>
<td>of RCTs from systematic review (a)</td>
<td>0.9%</td>
</tr>
<tr>
<td>Major bleeding risk</td>
<td></td>
<td>0.4%</td>
</tr>
</tbody>
</table>

(a) This refers to the systematic review of RCTs for the current guideline
(b) Ratio of the death rate in the surgical group compared with the death rate in the general population, adjusting for age and sex
(c) Rate calculated from the mortality rate for general medical patients at 1 year (Herrman Lingen (2001)) divided by death rate in the general population matched for age and gender. (Office of National statistics (2005)).
(d) Fatal major bleeds divided by all major bleeds
(e) Fatal PEs divided by all symptomatic PE

Table 23-122: Weights used for events in the base case analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Cost (£)</th>
<th>QALYs lost (a)</th>
<th>Net loss (£) (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT Asymptomatic</td>
<td>0</td>
<td>0.0000</td>
<td>0</td>
</tr>
<tr>
<td>DVT Symptomatic</td>
<td>576</td>
<td>0.0035</td>
<td>645</td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td>5,818</td>
<td>0.1492</td>
<td>8,803</td>
</tr>
<tr>
<td>Chronic pulmonary hypertension</td>
<td>69,123</td>
<td>3.9706</td>
<td>148,536</td>
</tr>
<tr>
<td>Pulmonary embolism - fatal</td>
<td>0</td>
<td>7.3079</td>
<td>146,157</td>
</tr>
<tr>
<td>Pulmonary embolism - symptomatic</td>
<td>2,521</td>
<td>0.0041</td>
<td>2,603</td>
</tr>
<tr>
<td>Major bleeding - No long-term sequelae</td>
<td>722</td>
<td>0.0267</td>
<td>1,255</td>
</tr>
<tr>
<td>Major bleeding - Stroke</td>
<td>23,691</td>
<td>5.2444</td>
<td>128,579</td>
</tr>
<tr>
<td>Major bleeding - fatal</td>
<td>0</td>
<td>7.3079</td>
<td>146,157</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia (sensitivity analysis only)</td>
<td>2,512</td>
<td>1.0891</td>
<td>24,294</td>
</tr>
</tbody>
</table>

(a) Net loss is the sum of the resource cost plus the QALY loss:
Net loss=cost+ (20,000 x QALYs lost)
23.4.2 Results: standard duration prophylaxis

23.4.2.1 Base case results

Event rates by strategy can be found in Appendix G.

Table 23-123: Base case results – deterministic and probabilistic results

<table>
<thead>
<tr>
<th>Intervention (ordered by mean probabilistic INB)</th>
<th>Deterministic INB</th>
<th>Probabilistic INB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td>LMWH</td>
<td>329</td>
<td>328</td>
</tr>
<tr>
<td>UFH</td>
<td>118</td>
<td>116</td>
</tr>
<tr>
<td>Nil</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>-61</td>
<td>-58</td>
</tr>
</tbody>
</table>

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost effective overall.

Figure 23-53: Base case results of the cost effectiveness analysis for medical patients (probabilistic analysis)

Fon = fondaparinux; UFH = Unfractionated Heparin, LMWH = Low molecular weight heparin
23.4.2.2 Deterministic sensitivity analysis

**Table 23-124: Deterministic sensitivity analysis results**

<table>
<thead>
<tr>
<th>Factors changed within the Model</th>
<th>Most Cost Effective Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>LMWH</td>
</tr>
<tr>
<td>Base case (probabilistic)</td>
<td>LMWH</td>
</tr>
<tr>
<td><strong>Chronic Thromboembolic Pulmonary Hypertension and Post Thrombotic Syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>0% Chronic Thromboembolic Pulmonary Hypertension</td>
<td>LMWH</td>
</tr>
<tr>
<td>0.5% Chronic Thromboembolic Pulmonary Hypertension</td>
<td>LMWH</td>
</tr>
<tr>
<td>1% Chronic Thromboembolic Pulmonary Hypertension</td>
<td>LMWH</td>
</tr>
<tr>
<td>0% Chronic Thromboembolic Pulmonary Hypertension and 0% Post Thrombotic Syndrome</td>
<td>LMWH</td>
</tr>
<tr>
<td>High Post Thrombotic Syndrome rate (e.g. 30% after symptomatic DVT and 21% after asymptomatic DVT)</td>
<td>LMWH</td>
</tr>
<tr>
<td>Low Post Thrombotic Syndrome (e.g. 1.5% after symptomatic DVT and 8% after asymptomatic DVT)</td>
<td>LMWH</td>
</tr>
<tr>
<td>Low cost for Post Thrombotic Syndrome</td>
<td>LMWH</td>
</tr>
<tr>
<td>High cost for Post Thrombotic Syndrome</td>
<td>LMWH</td>
</tr>
<tr>
<td>High cost for Chronic Thromboembolic Pulmonary Hypertension</td>
<td>LMWH</td>
</tr>
<tr>
<td><strong>Other Sensitivity Analyses</strong></td>
<td></td>
</tr>
<tr>
<td>Include Heparin Induced Thrombocytopenia (LMWH=0.8%, UFH=0.8%)</td>
<td>LMWH</td>
</tr>
<tr>
<td>Reduced incidence of Heparin Induced Thrombocytopenia (LMWH=0.2%, UFH=2.6%)</td>
<td>LMWH</td>
</tr>
<tr>
<td>Using PE relative risk for symptomatic PE and not DVT relative risk</td>
<td>LMWH</td>
</tr>
<tr>
<td>Using population specific major bleeding relative risks</td>
<td>LMWH</td>
</tr>
<tr>
<td>Discounted LMWH cost = £1</td>
<td>LMWH</td>
</tr>
<tr>
<td>Fatality after PE = 10%</td>
<td>LMWH</td>
</tr>
<tr>
<td>Fatality after Major Bleeding = 5%</td>
<td>LMWH</td>
</tr>
<tr>
<td>Increased NICE threshold (£30,000/QALY)</td>
<td>LMWH</td>
</tr>
</tbody>
</table>

**Table 23-125: Deterministic results, by baseline risk of pulmonary embolism and major bleeding**

<table>
<thead>
<tr>
<th>Major bleeding risk</th>
<th>0%</th>
<th>0.5%</th>
<th>1%</th>
<th>1.5%</th>
<th>2%</th>
<th>2.5%</th>
<th>3%</th>
<th>3.5%</th>
<th>4%</th>
<th>4.5%</th>
<th>5%</th>
<th>5.5%</th>
<th>6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>LMWH</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>0.5%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
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<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>1%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>1.5%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>2%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>2.5%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>3%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>3.5%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>Nil</td>
</tr>
<tr>
<td>4%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
</tr>
<tr>
<td>4.5%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
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<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
</tr>
<tr>
<td>5%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
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<tr>
<td>5.5%</td>
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<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
</tr>
<tr>
<td>6%</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
<td>LMWH</td>
</tr>
</tbody>
</table>

We considered in a threshold sensitivity analysis what would happen if patients discharged early received their prophylaxis at home. We found that even if every patient required district nurse visits to deliver their prophylaxis, LMWH was still cost-effective.
23.4.3 Conclusion of cost-effectiveness analysis

The cost effective analysis for general medical patients indicates that LMWH is the most effective and most cost effective strategy followed by unfractionated heparin. Fondaparinux was less effective than no prophylaxis in the base case, due to the increase in major bleeding.

LMWH remained the most cost effective in all of the deterministic sensitivity analyses completed.

23.5 Patient views

There is a lack of patient views evidence from medically ill patients about thromboprophylaxis. Therefore, patient views of thromboprophylaxis in this group could only be inferred from other populations. A recent qualitative study conducted in the United Kingdom among cancer patients receiving palliative care showed acceptability of thromboprophylaxis. This study found that patients were aware of the purpose of subcutaneous LMWH thromboprophylaxis. They balanced the potential benefit of venous thromboembolism reduction against potential side effects (bruising was quoted) and found it acceptable. 492.

For patient views about specific prophylaxis agents, see section 6.6 Patient views.

23.6 Summary of evidence

Table 23-126: Summary of evidence from network meta-analysis results for DVT, symptomatic pulmonary embolism and major bleeding outcomes.

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DVT</td>
</tr>
<tr>
<td>Prophylaxis vs no prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>No prophylaxis</td>
<td>Not sig</td>
</tr>
<tr>
<td>LMWH</td>
<td>No prophylaxis</td>
<td>LMWH</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>No prophylaxis</td>
<td>Not sig</td>
</tr>
</tbody>
</table>

Cost-effectiveness

In the base case cost effectiveness analysis using probabilistic analysis, LMWH is the most cost-effective strategy, followed by unfractionated heparin.

LMWH remained the most cost effective in all of the deterministic sensitivity analyses.

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.

Not sig - not statistically significant difference; no events = nobody in the study had the outcome. MB = Major bleeding
23.7 Recommendations and link to evidence

| Recommendation | Offer pharmacological VTE prophylaxis to general medical patients assessed to be at increased risk of VTE. Choose any one of:
|                | - fondaparinux sodium
|                | - LMWH*
|                | - UFH (for patients with renal failure).
|                | Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.
|                | *At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for of label use should be obtained and documented.

| Recommendation –from section 5.9 | Regard medical patients as being at increased risk of VTE if they:
|                                | - have had or are expected to have significantly reduced mobility for 3 days or more, or
|                                | - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1. |
Box 1 – Risk Factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (for example: heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant for have given birth within the previous 6 weeks please refer to recommendations in Chapter 30 (Pregnancy and up to 6 weeks post partum)

Relative values of different outcomes

The outcomes included in the economic model were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome). Each of these events had a cost and loss of quality adjusted life year associated with it, the details of which are provided in the methods of cost effectiveness chapter (chapter 4).

Trade off between clinical benefit and harms

The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding in the economic model.

Our decision model indicated that the QALYs lost due to major bleeding were outweighed by the QALYs gained from drug prophylaxis.

Economic considerations

An original cost-effectiveness analysis was conducted for medical patients. The cost effectiveness analysis for general medical patients indicates that LMWH is the most effective and most cost effective strategy followed by unfractionated heparin.

Lower risk patients are often not included in trials. It was felt by the Guideline Development Group that for those medical
patients who are soon mobile and do not have predisposing risk factors, the risk of VTE was too low for prophylaxis to be cost-effective.

**Quality of evidence**

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++ ) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

Only LMWH was demonstrated to be statistically significant in reducing the risk of DVT compared to no prophylaxis among general medical patients. The efficacy of UFH and fondaparinux were not statistically significant. It is unclear whether the sample sizes were powered to demonstrate a difference. However, there was a trend that these prophylactic methods reduce the risk of DVT and PE compared to no prophylaxis. Their efficacy could be also be inferred from studies conducted in surgical patients.

Directness of evidence obtained was a concern due to the strict inclusion criteria used in many of the clinical trials. There are only a small number of trials identified in medical patients and generally the inclusion criteria was narrow, including only patients with acute medical illness with a hospital stay of at least 3 days and often with severely limited mobility. Many studies excluded patients with an increased risk of bleeding.

**Other considerations**

Alternative thromboprophylaxis options were listed so that individual patient factors could be taken into account when selecting an appropriate prophylaxis agent. For example, some patients may have concerns about using a product of animal origin. If this is a concern, a synthetic product such as fondaparinux may be appropriate.

Although UFH is seldom used, it will be a useful alternative for patients with renal failure.

There is a lack of information about patient views on the acceptability or preference of thromboprophylaxis agents in this population. It is also unclear how thromboprophylaxis strategies impact on patient’s quality of life. A qualitative study which had been conducted in UK among palliative care patients showed that patients found LMWH acceptable and a component of care.

Despite the recognition of specific risk factors it is impossible to predict exactly within a group at risk, which individual will have a VTE. Therefore in the view of the Guideline Development Group, the standard approach should be to administer thromboprophylaxis to all those at increased risk.
**Recommendation**

Consider offering mechanical VTE prophylaxis to medical patients in whom pharmacological prophylaxis is contraindicated. Choose any one of:

- anti-embolism stockings (thigh or knee length)
- foot impulse devices
- intermittent pneumatic compression devices (thigh or knee length)

**Relative values of different outcomes**

The Guideline Development Group considered that it was a priority to reduce the risk of death from PE and to prevent long term morbidity from DVT such as post thrombotic syndrome. The main consideration for this recommendation is ensuring some measure of thromboprophylaxis is provided for patients at increased risk of VTE but who are also at an increased risk of bleeding.

**Trade off between clinical benefit and harms**

For mechanical methods (IPCD, FID and anti-embolism stockings) it is unclear whether the benefits outweigh the risks in general medical patients because RCT evidence in this group is lacking.

For anti-embolism stockings, there is even greater uncertainty about the benefit vs risk trade off than IPCDs and FIDs. Although shown to be effective in surgical patients (Chapter 9), it was shown to be ineffective in stroke patients and associated with cutaneous adverse reactions (Chapter 24). Although evidence from stroke patients cannot be directly applied to medical patients, neither can it be ignored.

The benefits are more likely to outweigh the harms in patients that aren’t receiving other forms of prophylaxis.

**Economic considerations**

Mechanical methods of prophylaxis were not considered in the economic model because there were no suitable trials in medical patients. Such methods are highly cost-effective for general surgery patients when compared with no prophylaxis and are not associated with increased bleeding (Chapter 9). However anti-embolism stockings have been shown to be ineffective and harmful in stroke patients (Chapter 24). We think it possible that they would be cost-effective in medical patients who are at elevated risk of VTE (in the absence of drug prophylaxis).
Quality of evidence

No studies which investigated anti-embolism stockings, intermittent pneumatic compression devices or foot impulse devices in general medical patients were found.

Randomised controlled trials in surgical populations showed that these methods are effective at reducing venous thromboembolism without an associated increase in bleeding.

The following are the evidence available in non-surgical patients:

*Foot impulse devices and intermittent pneumatic pump devices:*

- Stroke patients: a very small RCT with total of 26 patient, and two RCTs in patients who also used GCS all showed no significant difference.

*Anti-embolism stockings:*

- Acute coronary syndrome: One RCT (n=160) showed no significant difference in DVT risk reduction.

- Stroke: Two RCTs were found and both showed no significant difference in effectiveness. One of these, a large multi-centred RCT with 2518 participants, showed increased risks of cutaneous adverse events.

Other considerations

Because there was uncertainty about the trade off between risk and benefits in these methods, the GDG deliberated at great length whether a recommendation should be made about mechanical prophylaxis in medical patients.

However, the GDG considered that the absence of any recommendations for medical patients at increased risk of VTE but contraindicated to pharmacological prophylaxis may result in variations of practice and may result in some high risk patients going without thromboprophylaxis. Therefore, a decision was made to make a cautious recommendation that clinicians should consider one of the three forms of mechanical prophylaxis (including anti-embolism stockings) in medical patients contraindicated to pharmacological prophylaxis. The decision was not unanimous but it was the majority decision of the GDG.

The GDG were unanimous that this is an area where research is needed.

23.7.1 Other recommendations of relevance

The specific recommendations for general medical admissions in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
23.8 Recommendations for research

23.8.1 Pharmacological and mechanical prophylaxis in a broader population of medical patients:

The Guideline Development Group recommended the following research question:

- What is the clinical and cost effectiveness of pharmacological prophylaxis, mechanical prophylaxis and combined pharmacological and mechanical prophylaxis for reducing the risk of VTE in medical patients?

Why this is important

Only a small number of trials with medical patients were identified and generally the inclusion criteria were narrow, for example, patients with an acute medical illness, with a hospital stay of more than 5 days, and often with severely limited mobility. Further research into less severely ill patient groups would be beneficial.

The evidence concerning mechanical prophylaxis in medical patients is sparse. There have been a few small trials of patients with coronary syndrome but the only large, randomised controlled trial was of patients with stroke. This trial showed that routine care plus thigh-length anti-embolism stockings did not confer significantly more protection against VTE than routine care alone and was associated with significantly more harm. All of these trials included large proportions of patients who were taking aspirin, which may have influenced the results.

New trial(s) should investigate the benefits of reducing the risk of VTE balanced against the risk of bleeding. The trial(s) should compare pharmacological prophylaxis alone, mechanical prophylaxis alone, and combined mechanical and pharmacological prophylaxis. The benefit of extended-duration prophylaxis in medical patient groups may also be investigated.

Recommended design: RCT

Further details are provided in Appendix F
23.9 Summary of recommendations

- Offer pharmacological VTE prophylaxis to general medical patients assessed to be at increased risk of VTE (see Section 5.9). Choose any one of:
  - fondaparinux sodium
  - LMWH*
  - UFH (for patients with renal failure)

  Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

* At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off label use should be obtained and documented.

- Regard medical patients as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more or
  - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.

### Box 1 Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).
Consider offering mechanical VTE prophylaxis to medical patients in whom pharmacological prophylaxis is contraindicated. Choose any one of:

- anti-embolism stockings (thigh or knee length)
- foot impulse devices
- intermittent pneumatic compression devices (thigh or knee length)
24 Stroke patients

24.1 Introduction

Recent stroke has been associated with an increased developing venous thromboembolism (VTE)\(^{217}\). Reasons for this increased risk of VTE is thought to be due to the alteration in blood flow as a results of the weakness in the affected limb, possibly leading to vessel wall injury, and a resulting hypercoagulable state related to changes in the blood after stroke\(^{236}\). A wide range of VTE incidence has been reported for stroke patients with estimates of between 15-60%\(^\text{18,120}\). Diagnosing DVT after stroke may be difficult as symptoms may be similar to those related to the stroke such as leg swelling\(^{236}\). One study\(^\text{149}\) reviewed stroke patients 6 months after onset and found that patients who developed a DVT after stroke had a statistically significant poorer outcome, using a modified Rankin score, compared to those who did not develop DVT.

Stroke is divided into two main types; ischaemic stroke caused by blood clots preventing blood flow to the brain and haemorrhagic stroke caused by bleeding into/of the brain. Both types of stroke are associated with an increased risk of VTE\(^{236}\). NICE published guidelines in 2008 for the diagnosis and acute management of stroke and transient ischaemic attacks\(^{477}\).

24.2 Evidence of methods of prophylaxis

24.2.1 Summary of comparisons identified for any outcome

Seventeen (17) studies were identified that considered the interventions under consideration for stroke patients\(^\text{35,157,158,165,167,240,278,369,434,435,466,509,520,538,540,581,598}\). Of these, 2 studies were three arm trials\(^\text{509,520}\). Only studies using prophylactic-doses were included.

Only three of these studies included haemorrhagic stoke patients\(^\text{158,434,435}\) all other patients were ischaemic stroke patients.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

Although it is likely that many patients within a large RCT of thigh length anti-embolism stockings vs no stockings\(^\text{158}\) were treated with aspirin, the authors have not provided this information in the paper published for the study. For this reason the results of the
study have been reported as ‘GCS vs. no prophylaxis’ rather than ‘GCS + aspirin vs. aspirin’.

<table>
<thead>
<tr>
<th>Proph vs no proph</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS vs nil</td>
<td>1</td>
<td>205/125</td>
<td>224/126</td>
<td>0.92 (0.77, 1.09)</td>
<td>-0.01 (-0.04, 0.02)</td>
<td>ET: 23 FP: 1</td>
</tr>
<tr>
<td>IPCD/FID vs nil</td>
<td>1</td>
<td>6/13</td>
<td>6/13</td>
<td>1.00 (0.44, 2.29)</td>
<td>0.00 (-0.38, 0.38)</td>
<td>ET: 24 FP: 4</td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>3</td>
<td>23/89</td>
<td>36/110</td>
<td>0.74 (0.40, 1.35)</td>
<td>-0.08 (-0.25, 0.08)</td>
<td>ET: 26 FP: 13</td>
</tr>
<tr>
<td>UFH vs nil</td>
<td>4</td>
<td>41/238</td>
<td>146/243</td>
<td>0.31 (0.23, 0.41)</td>
<td>-0.35 (-0.61, -0.09)</td>
<td>ET: 27 FP: 17</td>
</tr>
<tr>
<td>Asp (high dose) vs nil</td>
<td>2</td>
<td>9/54</td>
<td>21/54</td>
<td>0.43 (0.22, 0.85)</td>
<td>-0.22 (-0.38, -0.06)</td>
<td>ET: 29 FP: 28</td>
</tr>
</tbody>
</table>

24.2.2 Results from pairwise comparisons

Table 24-127: DVT – summary of results from RCTs
### Venous Thromboembolism Prophylaxis

#### Comparison

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharm vs pharm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH 278</td>
<td>1</td>
<td>14/76</td>
<td>24/72</td>
<td>0.55 (0.31, 0.98)</td>
<td>-0.15 (-0.29, -0.01)</td>
<td>ET: 32 FP: 48</td>
</tr>
<tr>
<td>Asp (high dose) vs UFH 520</td>
<td>1</td>
<td>6/35</td>
<td>7/40</td>
<td>0.98 (0.36, 2.64)</td>
<td>0.00 (-0.18, 0.17)</td>
<td>ET: 36 FP: 64</td>
</tr>
<tr>
<td><strong>Double proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS + aspirin vs aspirin 466</td>
<td>1</td>
<td>7/65</td>
<td>7/32</td>
<td>0.49 (0.19, 1.28)</td>
<td>-0.11 (-0.25, 0.05)</td>
<td>ET: 38 FP: 114</td>
</tr>
<tr>
<td>IPCD/FID + GCS vs GCS 365,509</td>
<td>2</td>
<td>11/181</td>
<td>17/184</td>
<td>0.65 (0.15, 2.81)</td>
<td>-0.04 (-0.17, 0.09)</td>
<td>ET: 39 FP: 117</td>
</tr>
<tr>
<td>UFH + GCS vs GCS 509</td>
<td>1</td>
<td>5/120</td>
<td>6/115</td>
<td>0.80 (0.25, 2.54)</td>
<td>-0.01 (-0.06, 0.04)</td>
<td>ET: 27 FP: 142</td>
</tr>
<tr>
<td><strong>Other strategies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH + Asp vs UFH + Asp 165,598</td>
<td>1</td>
<td>67/666</td>
<td>118/669</td>
<td>0.57 (0.43, 0.75)</td>
<td>-0.08 (-0.11, -0.04)</td>
<td>ET: 45 FP: 184</td>
</tr>
<tr>
<td>IPCD/FID + GCS vs UFH + GCS 509</td>
<td>1</td>
<td>8/117</td>
<td>5/120</td>
<td>1.64 (0.55, 4.87)</td>
<td>0.03 (-0.03, 0.08)</td>
<td>ET: 50 FP: 200</td>
</tr>
</tbody>
</table>

*FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis

a) There is substantial statistical heterogeneity between studies for this population ($I^2 = 70.3\%$, $\chi^2$ on 1 df = 3.37, $p = 0.07$)

### Table 24-128: Pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proph vs no proph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS vs nil 138</td>
<td>1</td>
<td>13/1256</td>
<td>20/1262</td>
<td>0.65 (0.33, 1.31)</td>
<td>-0.01 (-0.01, 0.00)</td>
<td>ET: 23 FP: 2</td>
</tr>
<tr>
<td>Asp (high dose) vs nil 520</td>
<td>1</td>
<td>1/40</td>
<td>0/40</td>
<td>3.00 (0.13, 71.5)</td>
<td>-0.03 (-0.04, 0.09)</td>
<td>ET: 29 FP: 29</td>
</tr>
<tr>
<td><strong>Pharm vs pharm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs UFH 278</td>
<td>1</td>
<td>2/106</td>
<td>4/106</td>
<td>0.50 (0.09, 2.67)</td>
<td>-0.02 (-0.06, 0.03)</td>
<td>ET: 32 FP: 49</td>
</tr>
<tr>
<td>LMWH vs Asp (low dose) 35</td>
<td>1</td>
<td>4/507</td>
<td>4/491</td>
<td>0.97 (0.24, 3.85)</td>
<td>0.00 (-0.01, 0.01)</td>
<td>ET: 36 FP: 52</td>
</tr>
<tr>
<td><strong>Double proph vs single</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS + aspirin vs aspirin 466</td>
<td>1</td>
<td>0/65</td>
<td>0/32</td>
<td>Not estimable</td>
<td>0.00 (-0.05, 0.05)</td>
<td>ET: 38 FP: 115</td>
</tr>
<tr>
<td>IPCD/FID + GCS vs GCS 369</td>
<td>1</td>
<td>0/64</td>
<td>0/69</td>
<td>Not estimable</td>
<td>0.00 (-0.03, 0.03)</td>
<td>ET: 39 FP: 118</td>
</tr>
<tr>
<td><strong>Other strategies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH + Asp vs UFH + Asp 165,598</td>
<td>2</td>
<td>1/938</td>
<td>7/942</td>
<td>0.21 (0.04, 1.21)</td>
<td>-0.01 (-0.01, 0.00)</td>
<td>ET: 45 FP: 185</td>
</tr>
</tbody>
</table>

*FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis
Table 24-129: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>2</td>
<td>8/74</td>
<td>4/77</td>
<td>2.21(a) (0.69, 7.00)</td>
<td>0.06 (-0.08, 0.20)</td>
<td>ET: 26 FP: 15</td>
</tr>
<tr>
<td>UFH vs nil</td>
<td>1</td>
<td>0/35</td>
<td>0/30</td>
<td>Not Estimable</td>
<td>0.00 (-0.06, 0.06)</td>
<td>ET: 27 FP: 19</td>
</tr>
</tbody>
</table>

| Pharm vs pharm | | | | | | |
| LMWH vs UFH   | 1 | 1/106 | 0/106 | 3.00 (0.12,72.82) | 0.01 (-0.02, 0.04) | ET: 32 FP: 50 |

| Other strategies | | | | | | |
| LMWH + Asp vs UFH + Asp | 2 | 14/1149 | 11/1145 | 1.18 (a) (0.41, 3.41) | 0.00 (-0.01, 0.01) | ET: 45 FP: 186 |

* FP – forest plot number in appendix E; ET – evidence table number in appendix D
  a) There is some evidence of statistical heterogeneity ($I^2=36.3\%$, $\chi^2$ on 1 df = 1.57, $p = 0.21$)

24.2.3 Additional information

24.2.3.1 All cause mortality

Table 24-5: All cause mortality – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS vs nil</td>
<td>1</td>
<td>122/1256</td>
<td>110/1262</td>
<td>1.11 (0.87, 1.42)</td>
<td>0.01 (-0.01, 0.03)</td>
<td>ET: 23 FP: 3</td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>3</td>
<td>15/102</td>
<td>5/111</td>
<td>2.75 (1.11, 6.83)</td>
<td>0.08 (0.01, 0.14)</td>
<td>ET: 26 FP: 16</td>
</tr>
<tr>
<td>UFH vs nil</td>
<td>4</td>
<td>44/235</td>
<td>64/247</td>
<td>0.83 (0.44, 1.55)</td>
<td>-0.04 (-0.14, 0.06)</td>
<td>ET: 27 FP: 20</td>
</tr>
<tr>
<td>Asp (high dose) vs nil</td>
<td>2</td>
<td>7/40</td>
<td>5/40</td>
<td>1.40 (0.48, 4.04)</td>
<td>0.05 (-0.11, 0.21)</td>
<td>ET: 29 FP: 31</td>
</tr>
</tbody>
</table>

| Pharm vs pharm | | | | | | |
| LMWH vs UFH   | 1 | 9/106 | 8/106 | 1.13 (0.45, 2.80) | 0.01 (-0.06, 0.08) | ET: 32 FP: 51 |
| Asp (high dose) vs UFH | 1 | 7/40 | 10/40 | 0.70 (0.30, 1.66) | -0.08 (-0.25, 0.10) | ET: 36 FP: 67 |

| Double proph vs single | | | | | | |
| GCD + aspirin vs aspirin | 1 | 9/65 | 4/32 | 1.11 (0.37, 3.32) | 0.01 (-0.13, 0.16) | ET: 38 FP: 116 |
| IPCD/FID + GCS vs GCS | 2 | 15/191 | 24/192 | 0.65 (0.37, 1.14) | -0.05 (-0.41, 0.30) | ET: 39 FP: 119 |
| UFH + GCS vs GCS      | 1 | 0/120 | 0/115 | Not Estimable | 0.00 (-0.02, 0.02) | ET: 27 FP: 145 |

| Other strategies | | | | | | |
| LMWH + Asp vs UFH + Asp | 2 | 69/1149 | 60/1145 | 1.15 (0.82, 1.61) | 0.01 (-0.01, 0.03) | ET: 45 FP: 187 |
| IPCD/FID + GCS vs UFH + GCS | 1 | 0/114 | 0/120 | Not Estimable | 0.00 (-0.02, 0.02) | ET: 50 FP: 201 |

* FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis
24.2.3.2 Additional outcomes

None of the included studies reported chronic thromboembolic pulmonary hypertension, heparin induced thrombocytopenia or post thrombotic syndrome as outcomes.

One study\textsuperscript{158} reported cutaneous adverse events related to the use of GCS, i.e. skin breaks, ulcers, blisters or skin necrosis. The event rate in the GCS arm was 64/1256 vs 16/1262 in the control arm without GCS (RR 4.02, 95% CI 2.31 to 6.91, $p<0.001$). Lower limb ischaemia or amputation was 7/1249 in the GCS arm and 2/1262 in the control arm (RR 3.54 95% CI 0.74 to 16.99, $p=0.108$).

24.3 Network meta-analysis results

No network meta-analysis was completed for this population.

24.4 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.

24.5 Patient views

No studies investigating the experience of prophylaxis in stroke patients were found. Section 6.6 contains more information on patient views on specific prophylaxis agents.

24.6 Summary of evidence

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DVT</td>
</tr>
<tr>
<td>Prophylaxis vs no prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCD/FID</td>
<td>No prophylaxis</td>
<td>Not sig</td>
</tr>
<tr>
<td>GCS</td>
<td>No prophylaxis</td>
<td>Not sig</td>
</tr>
<tr>
<td>Aspirin (high dose)</td>
<td>No prophylaxis</td>
<td>Asp (HD)</td>
</tr>
<tr>
<td>UFH</td>
<td>No prophylaxis</td>
<td>UFH</td>
</tr>
<tr>
<td>LMWH</td>
<td>No prophylaxis</td>
<td>Not sig</td>
</tr>
<tr>
<td>Single prophylaxis vs single</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>UFH</td>
<td>LMWH</td>
</tr>
<tr>
<td>Aspirin (High dose)</td>
<td>UFH</td>
<td>Not sig</td>
</tr>
<tr>
<td>Double prophylaxis vs single</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS + aspirin</td>
<td>aspirin</td>
<td>Not sig</td>
</tr>
<tr>
<td>IPCD/FID + GCS</td>
<td>GCS</td>
<td>Not sig</td>
</tr>
<tr>
<td>UFH + GCS</td>
<td>GCS</td>
<td>Not sig</td>
</tr>
<tr>
<td>Other Strategies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH + Asp</td>
<td>UFH + Asp</td>
<td>LMWH + Asp</td>
</tr>
<tr>
<td>IPCD/FID + GCS</td>
<td>UFH + GCS</td>
<td>Not sig</td>
</tr>
</tbody>
</table>

Cost Effectiveness

No cost effectiveness model was completed for this population.
The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold. Not sig - not statistically significant difference; ‘-’ = not reported; no events – nobody in the study had the outcome. MB = Major bleeding

24.7 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Do not offer anti-embolism stockings for VTE prophylaxis to patients who are admitted for stroke.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative values of different outcomes</td>
<td>The outcomes identified as important by the Guideline Development Group were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).</td>
</tr>
<tr>
<td>Trade off between clinical benefit and harms</td>
<td>Unlike pharmacological prophylaxis, mechanical methods do not increase the risk of bleeding. However, anti-embolism stockings have been shown to be ineffective in reducing the risk of VTE in stroke patients and were associated with an increased risk of cutaneous adverse reactions.</td>
</tr>
<tr>
<td>Economic considerations</td>
<td>No economic model was run specifically for stroke patients. Anti-embolism stockings were found to be ineffective in reducing VTE in stroke patients and had cutaneous side effects; this is therefore not a cost-effective intervention for this population.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). One large multicentred RCT with more than 2500 patients compared anti-embolism stockings against usual care in stroke patients. This study has some minor limitations (Evidence table 23, Appendix D) but the GDG agreed that the generality of the results could be applied to the stroke population.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>One study showed that anti-embolism stockings are ineffective in reducing the risk of VTE in stroke patients, but are associated with an increased risk of cutaneous adverse events. This contradicts previous beliefs based on the extrapolation of efficacy observed in surgical patients that GCS may be effective at reducing VTE and challenged the notion that mechanical prophylaxis methods are harmless. In the study, the number of patients who were using aspirin during the study was not reported but is expected to be high as currently aspirin is the standard treatment for most patients with ischaemic stroke. The GDG had considered whether this could have reduced the observed efficacy of stockings, but concluded that the results of the study were still applicable as the current NICE guidelines recommend initial treatment with aspirin for ischaemic stroke.</td>
</tr>
</tbody>
</table>
No patient views evidence was found specifically for this population.

**Recommendation**

Consider offering prophylactic-dose LMWH* (or UFH for patients with renal failure) if:

- a diagnosis of haemorrhagic stroke has been excluded, and
- the risk of bleeding (haemorrhagic transformation of stroke or bleeding into another site) is assessed to be low, and
- the patient has one or more of:
  - major restriction of mobility
  - previous history of VTE
  - dehydration
  - comorbidities (such as malignant disease).

Continue until the acute event is over and the patient’s condition is stable.

* At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off label use should be obtained and documented.

**Relative values of different outcomes**

The outcomes identified as important by the Guideline Development Group were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). The risk of bleeding was felt to be important in this population as ischaemic stroke patients have a risk of haemorrhagic transformation.

**Trade off between clinical benefit and harms**

Patients are likely to be relatively immobile after stroke and therefore are predisposed to an increased risk of VTE. However, the Guideline Development Group felt that this should be balanced against the risk of bleeding, including haemorrhagic transformation which can have very serious consequences. In addition, the risk of bleeding on admission may not be known and so caution should be applied before prescribing pharmacological thromboprophylaxis agents.

**Economic considerations**

No economic model was run specifically for stroke patients. The economic model for general medical patients indicated that pharmacological prophylaxis was cost effective for this broader population. Given the high risk of VTE in stroke patients, it is possible that prophylaxis is cost-effective. However, given that
the consequences of bleeding are likely to be very serious for this group, drug prophylaxis is likely only to be cost-effective if the risk of intracranial bleeding is minimised. Therefore the guideline development group recommended only considering pharmacological prophylaxis to a subset of stroke patients who have been established as at increased risk for VTE and only those in whom the bleeding risks have been established as low.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). Seven of the 17 studies (41.2%) were published prior to 2000. The treatment of stroke has changed over the last 10 years. There were only two studies which compared heparin prophylaxis in addition to aspirin treatment and so the remaining studies may not be directly applicable to the current stroke population.

Other considerations

The current NICE Stroke guidelines recommend initial treatment with aspirin for ischaemic stroke, which should not be discontinued in order to provide thromboprophylaxis. The three conditions identified within the recommendation (major restriction of mobility, previous history of VTE, and dehydration or medical comorbidity) are based on the stroke guideline. Adding prophylactic-dose anticoagulant agents to aspirin is likely to increase bleeding and so it is important that the bleeding risk is established as low before thromboprophylaxis is commenced.

The Department of Health has published the National Stroke strategy.

Recommendation

Until the patient can have pharmacological VTE prophylaxis, consider offering a foot impulse or intermittent pneumatic compression device.

Relative values of different outcomes

The outcomes identified as important to the Guideline Development Group (GDG) were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). The risk of bleeding was of particular importance to stroke patients, with significance adverse impact on patients’ morbidity and mortality.

Trade off between clinical benefit and harms

Patients with haemorrhagic stroke have already experienced bleeding into a critical location (brain) while patients with ischaemic stroke are also at risk of haemorrhagic transformation. The GDG agreed that bleeding was a more immediate risk for this population than the risk of developing
VTE and measures should be taken to prevent increasing this risk. Pharmacological prophylaxis is likely to increase additional bleeding risk and may lead to long-term morbidity in this population. Foot impulse or intermittent pneumatic compression devices do not increase the risk of bleeding but may cause damage to the skin. In the absence of evidence of benefit or harm for this group which is at a high risk of VTE, foot impulse or intermittent pneumatic compression devices may offer some protection without the risk of bleeding.

**Economic considerations**

No economic model was run specifically for stroke patients. There were no studies investigating the effectiveness of mechanical prophylaxis using foot impulse or IPC devices for stroke or other medical patients but mechanical prophylaxis has been shown to be cost-effective for general surgical patients compared with no prophylaxis (Chapter 9). Although there is insufficient trial evidence in stroke patients, we believe that these patients are likely to have the same biological mechanisms of clotting that may be alleviated by the active pumping actions generated by foot impulse and IPC devices. The Guideline Development Group believed that foot impulse and IPC devices are likely to be cost-effective for patients with haemorrhagic stroke, where pharmacological prophylaxis is contraindicated since the risk of VTE in this group is relatively high.

**Quality of evidence**

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

Randomised controlled trials in surgical populations showed that these methods are effective at reducing venous thromboembolism without an associated increase in bleeding.

One small study (n=26) investigated the use of IPC devices compared with no prophylaxis in stroke patients. There was no statistically significant difference in DVT events. Two RCTs in patients who also used GCS also showed no significant difference.

**Other considerations**

No patient views evidence was found specifically for this population.

The stakeholder comments during the consultation reflected the concern that a large proportion of stroke patients who are at high risk of VTE and contraindicated to pharmacological prophylaxis may be left without any protection since anti-embolisms stockings are no longer recommended for patients admitted for stroke and foot impulse or IPC devices are not being mentioned in the guideline. The GDG had considered these important concerns carefully against the evidence available and also noted that there is a large, ongoing RCT among stroke patients to evaluate the effectiveness of IPC.
devices.

In the absence of evidence (either of effectiveness or of harm), the GDG did not want to exclude the possibility that these devices have a different mechanism of action from anti-embolism stockings in VTE prevention. Therefore, the (lack of) effectiveness of anti-embolism stockings in stroke patients should not preclude the use of foot impulse and IPC devices in patients who are contraindicated to pharmacological prophylaxis. However, clinicians will have to carefully consider the risk vs benefits in each patient. Factors which should be considered include the risk of VTE and the exclusion of acute DVT (mechanical devices are contraindicated in acute DVT and there is a high risk of DVT in stroke patients).

There was a clear consensus with regard to this decision.

24.7.1 Other recommendations of relevance

The specific recommendations for patients with stroke in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- patients using anticoagulants or antiplatelets for reasons other than VTE prophylaxis (Chapter 1)

24.8 Recommendations for research

The GDG recommended the following research question:

- What is the overall risk/benefit of low molecular weight heparin and/or fondaparinux sodium in respect of both stroke outcome and the development of VTE for patients with acute stroke?

Why this is important

Patients with either ischaemic or haemorrhagic stroke have a risk of both VTE and bleeding into the brain. ‘Stroke: diagnosis and management of acute stroke and transient attack [TIA]’ (NICE clinical guideline 68, published July 2008) recommends the use of aspirin for treatment of ischaemic stroke but does not recommend anticoagulants. There is recent evidence to suggest that prophylactic-doses of anticoagulants in addition to aspirin reduce the risk of VTE in patients with ischaemic stroke but there are no data showing an effect of these anticoagulants on the stroke itself. Do they increase the risk of haemorrhagic transformation and so increase neurological damage? This research should
include patients with haemorrhagic or ischaemic strokes to identify which patients would benefit from additional pharmacological prophylaxis.

**Recommended design:** RCT

Further details are provided in Appendix F

### 24.9 Summary of recommendations

- Do not offer anti-embolism stockings for VTE prophylaxis to patients who are admitted for stroke.

- Consider offering prophylactic-dose LMWH* (or UFH for patients with renal failure) if:
  
  - a diagnosis of haemorrhagic stroke has been excluded, and
  
  - the risk of bleeding (haemorrhagic transformation of stroke or bleeding into another site) is assessed to be low, and

  - the patient has one or more of:
    
    - major restriction of mobility
    - previous history of VTE
    - dehydration
    - comorbidities (such as malignant disease).

  Continue until the acute event is over and the patient's condition is stable.

*At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off label use should be obtained and documented.

- Until the patient can have pharmacological VTE prophylaxis, consider offering a foot impulse or intermittent pneumatic compression device.
25 Acute coronary syndromes

25.1 Introduction

All patients admitted with acute coronary syndrome (ACS) consisting of a history of chest pain, and raised cardiac enzymes or altered electrocardiogram should have a VTE assessment performed on admission (section 5.9). The risk of DVT in patients with ACS is estimated from the nil prophylaxis arms of trials to be 21% (95% confidence intervals 17% to 25%).

Patients diagnosed with ACS are treated with anti-thrombotics. These treatments primarily consist of aspirin, clopidogrel and heparin. The duration of each therapy varies, with aspirin often being life-long, clopidogrel in the order of 12 months and heparin for a period of three to five days post event. Patients who receive full dose anti-coagulation with either intravenous unfractionated heparin (UFH) or low molecular weight heparin (LMWH) do not require further VTE prophylaxis whilst receiving full anticoagulation. Once full dose anti-coagulation is stopped the protection it provides diminishes allowing an increased risk of VTE. A repeat VTE risk assessment is required. VTE prophylaxis should be given if the assessment indicates unless the patient has significant bleeding risk.

For patients who are admitted and do not require treatment with full-dose anticoagulation, a VTE assessment is required. Studies indicate that neither aspirin nor clopidogrel when given alone provides adequate VTE protection and patients remain at risk of VTE. Patients should receive additional pharmacological prophylaxis unless the patient has a significant bleeding risk.

None of the studies identified in this chapter investigated the anti-thrombotic effect of clopidogrel and aspirin combinations. Several studies investigate the long term use of clopidogrel (which was not within the scope of this guideline) and have concluded that these combinations were relatively ineffective at reducing venous thromboembolic endpoints 61,95,118.

25.2 Evidence of methods of prophylaxis

25.2.1 Summary of comparisons identified for any outcome

Seven RCTs were identified which investigated VTE prophylaxis in patients with acute coronary syndrome 42,70,209,251,338,522,672. Most of the evidence was conducted in patients after myocardial infarction.
All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

### Figure 25-55: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

### 25.2.2 Results from pairwise comparisons

**Table 25-130: DVT – summary of results from RCTs**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Dose Aspirin vs nil</td>
<td>1</td>
<td>2/25</td>
<td>1/14</td>
<td>1.12 (0.11, 11.28)</td>
<td>0.01 (-0.16, 0.18)</td>
<td>ET: 29 FP: 28</td>
</tr>
<tr>
<td>UFH vs nil</td>
<td>5</td>
<td>16/213</td>
<td>51/215</td>
<td>0.33 (0.16, 0.69)</td>
<td>-0.17 (-0.23, -0.10)</td>
<td>ET: 27 FP: 17</td>
</tr>
</tbody>
</table>

| Double proph vs single | | | | | | |
| GCS + Asp LD vs Asp LD | 1 | 0/80 | 8/80 | 0.06 (0.00, 1.00) | -0.10 (-0.17, -0.03) | ET: 38 FP: 114 |

* FP – forest plot number in appendix E; ET – evidence table number in appendix D
Proph - prophylaxis

Table 25-131: Pulmonary embolism – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose aspirin vs nil</td>
<td>1</td>
<td>0/25</td>
<td>1/14</td>
<td>0.19</td>
<td>0.07</td>
<td>ET: 29, FP: 29</td>
</tr>
<tr>
<td>42,251</td>
<td>2</td>
<td>1/76</td>
<td>3/74</td>
<td>0.46</td>
<td>-0.03</td>
<td>ET: 27, FP: 18</td>
</tr>
</tbody>
</table>

* FP = forest plot number in appendix E; ET = evidence table number in appendix D

Proph - prophylaxis

Table 25-132: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose aspirin vs nil</td>
<td>1</td>
<td>0/25</td>
<td>0/14</td>
<td>Not Estimable</td>
<td>0.00</td>
<td>ET: 29, FP: 30</td>
</tr>
<tr>
<td>42,251</td>
<td>1</td>
<td>6/63</td>
<td>5/64</td>
<td>1.22</td>
<td>-0.02</td>
<td>ET: 27, FP: 20</td>
</tr>
</tbody>
</table>

* FP = forest plot number in appendix E; ET = evidence table number in appendix D

Proph - prophylaxis

25.2.3 Additional information

25.2.3.1 All cause mortality

Only two studies reported all cause mortality as an outcome 70,672.

25.2.3.2 Other outcomes

No studies reported heparin induced thrombocytopenia, post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension as outcomes.

25.3 Network meta-analysis results

No network meta-analysis was completed for this population.
25.4 Cost-effectiveness evidence

We did not prioritise this population for original cost-effectiveness analysis and no relevant cost-effectiveness studies were found in the literature.

25.5 Patient views

No patient view papers were found for this population. Section 6.6 contains more information on patient views about specific prophylaxis agents.

25.6 Summary of evidence

Table 25-133: Summary of evidence from direct evidence for DVT, symptomatic pulmonary embolism and major bleeding outcomes.

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DVT</td>
</tr>
<tr>
<td>Prophylaxis vs no prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (high dose)</td>
<td>no prophylaxis</td>
<td>Not Sig</td>
</tr>
<tr>
<td>UFH</td>
<td>no prophylaxis</td>
<td>UFH</td>
</tr>
<tr>
<td>Double prophylaxis vs single</td>
<td>Asp (LD) + GCS</td>
<td>Asp (LD) + GCS</td>
</tr>
</tbody>
</table>

Cost Effectiveness

There is no relevant cost-effectiveness evidence specifically for this group.

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.

Not sig - not statistically significant difference; ‘-’= not reported; no events – nobody in the study had the outcome. MB = Major bleeding

25.7 Recommendations and link to evidence

Recommendation

Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are having full anticoagulant therapy (for example, fondaparinux sodium, LMWH or UFH).

Relative values of different outcomes

The outcomes identified as important by the Guideline Development Group were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

Trade off between clinical benefit and harms

The risk of developing venous thromboembolism was weighed against the increased risk in bleeding caused by
pharmacological prophylaxis.

**Economic considerations**

There is no relevant cost-effectiveness evidence specifically for this group. However, we have built an economic model for the general medical patients and we believe that the baseline risk of VTE in the acute coronary syndrome subgroup will at least be similar to that in the general medical group. The result of the model suggests that LMWH and UFH are cost-effective strategies in general medical patients, with the former being more cost-effective than the latter. For patients with acute coronary syndromes there are further benefits from anticoagulants in addition to their usual thromboprophylactic properties and therefore these drugs are likely to be even more cost-effective than for other population subgroups.

**Quality of evidence**

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). The quality of evidence for this section is low. All of the studies included within this section were conducted over 15 years ago. The Guideline Development Group noted that since this time, the treatment of ACS conditions had changed and there were concerns that the included studies did not reflect the current situation.

Additionally the population of patients included in this study may not be representative of all those patients with acute coronary syndromes. Most of the studies were conducted after myocardial infarction.

**Other considerations**

The current treatment for acute coronary syndrome usually involves anticoagulant treatment. In this situation where anticoagulants are provided for treatment, no additional prophylaxis is required for reducing the risk of VTE.
### Recommendation

Consider offering additional mechanical or pharmacological VTE prophylaxis to patients who are having antiplatelet agents to treat other conditions and who are assessed to be at increased risk of VTE (see section 5.9). Take into account the risk of bleeding (see Box 2) and of comorbidities such as arterial thrombosis.

- If the risk of VTE outweighs the risk of bleeding, consider offering pharmacological VTE prophylaxis according to the reason for admission
- If the risk of bleeding outweighs the risk of VTE, offer mechanical VTE prophylaxis

### Recommendation—from section 5.9

Regard medical patients as being at increased risk of VTE if they:

- have had or are expected to have significantly reduced mobility for 3 days or more, or
- are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.

### Box 1 –Risk Factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum)

### Recommendation—from

Assess all patients for risk of bleeding before offering
section 5.9

pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.

*Consult the summary of product characteristics for the pharmacological VTE prophylaxis being used or planned for further details.

Box 2 - Bleeding Risk Factors

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10^9/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand’s disease)

Trade off between clinical benefit and harms

The outcomes identified as important by the Guideline Development Group were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

Patients who are using anticoagulants and/or antiplatelets for treatment of their condition may still be at risk of VTE. The risks associated with DVT need to be traded against the risk of bleeding. In addition, some antiplatelet treatment is provided to reduce the risk of arterial side thrombosis. The risks associated with stopping these treatments should be carefully considered.

Economic considerations

No cost effectiveness model was completed for this population. The health gain and cost savings of preventing VTE events should be balanced against the morbidity and costs associated
with providing pharmacological prophylaxis including treatment of prophylaxis related adverse events such as major bleeding.

Other considerations

The decisions about whether to add additional pharmacological prophylaxis should be based on a risk assessment of the individual patient taking into account their risk of patients. Such decisions should be made by healthcare professionals and should be documented in the patient’s notes.

25.7.1 Other recommendations of relevance

The specific recommendations for patients with acute coronary syndromes in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- patients using anticoagulants or antiplatelets for reasons other than VTE prophylaxis (Chapter 1)

25.8 Summary of recommendations

- Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are having full anticoagulant therapy (for example, fondaparinux sodium, LMWH or UFH).
- Consider offering additional mechanical or pharmacological VTE prophylaxis to patients who are having antiplatelet agents to treat other conditions and who are assessed to be at increased risk of VTE (see section 5.9). Take into account the risk of bleeding (see Box 2) and of comorbidities such as arterial thrombosis.
  - If the risk of VTE outweighs the risk of bleeding, consider offering pharmacological VTE prophylaxis according to the reason for admission
  - If the risk of bleeding outweighs the risk of VTE, offer mechanical VTE prophylaxis.
- Regard medical patients as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more or
  - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors in Box 1.
Box 1 – Risk factors for VTE
- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and 6 weeks post partum)

Box 2 Risk factors for bleeding
- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10⁹/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand’s disease)
26 Cancer

26.1 Introduction

Active cancer is an additional risk factor for VTE and the prothrombotic tendency varies with tumour type.556. Furthermore, many surgical procedures are carried out as part of curative or palliative cancer treatment.

Whilst the increased bleeding risk of cancer patients receiving full anticoagulation is well recognised when compared to non cancer patients, there has been no evidence identified suggesting this is the case with primary thromboprophylaxis. However the studies reviewed excluded those at highest risk of bleeding. Based on the clinical evidence standard contraindications to VTE prophylaxis should apply to this group.

This chapter deals with two populations:

- cancer patients admitted to hospital with an acute illness which may or may not be due to their cancer diagnosis
- cancer patients admitted to hospital for oncological treatment.

For patients with cancer who are undergoing surgery, refer to guidance provided for the specific types of surgery in chapters 9 to 18.

26.2 Evidence of methods of prophylaxis

26.2.1 Summary of comparisons identified for any outcome

A number of studies reported on the use of VTE prophylaxis in general medical patients, and most of these trials included some cancer patients within their population, although the proportion of patients included varied. The full review of these studies is detailed in chapter 23 and details on the proportion of cancer patients included can be found in the evidence tables (Appendix D).

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). Although a number of studies have been completed which investigate the potential anti-cancer properties of anticoagulants, only studies reporting VTE outcomes were included in this review. Only one study was identified which met these criteria which compared
adjusted low dose warfarin (target INR 1.3-1.9) against no prophylaxis in women with metastatic breast carcinoma. The average duration of prophylaxis in this study was 180 days.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKA vs nil</td>
<td>1</td>
<td>1/152</td>
<td>1/159</td>
<td>1.05</td>
<td>0.00</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Table 26-135: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKA vs nil 398</td>
<td>1</td>
<td>1/152</td>
<td>2/159</td>
<td>0.52</td>
<td>-0.01</td>
<td>ET: 28</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D
Proph - prophylaxis

26.2.3 Additional information

26.2.3.1 All cause mortality

Table 26-136: All cause mortality – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKA vs nil 398</td>
<td>1</td>
<td>87/152</td>
<td>99/159</td>
<td>0.92</td>
<td>-0.05</td>
<td>ET: 28</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D
Proph - prophylaxis

26.2.3.2 Other outcomes

No studies reported chronic thromboembolic pulmonary hypertension or post-thrombotic syndrome.

26.3 Network meta-analysis results

Network meta-analysis was not completed for this population.

26.4 Cost-effectiveness evidence

No cost-effectiveness model was created for this population.

26.5 Patient views

One study qualitative study was conducted among 28 cancer patients receiving palliative care in the UK492. This study recruited patients who received LMWH for at least 5 days, and recruitment stopped when theme saturation was achieved. The study found that patients were aware of the purpose of subcutaneous LMWH thromboprophylaxis, and they understood that death could be a consequence of VTE. The potential benefit of reducing the risk of VTE was balanced against potential side effects (bruising was quoted) and patients found it acceptable to receive the LMWH injections492 (Evidence table 62, Appendix D).

Patient views about specific prophylaxis agents are within section 6.6.
26.6 Summary of evidence

Table 26-137: Summary of evidence from network meta-analysis results for DVT, symptomatic pulmonary emboli and major bleeding outcomes.

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis vs no prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKA</td>
<td>nil</td>
<td>Not sig</td>
</tr>
</tbody>
</table>

Cost-effectiveness

No cost-effectiveness model was completed for this population

The prophylaxis strategy which is significantly more effective in reducing DVT or symptomatic PE; or resulting in significantly less major bleeding is stated in bold. Not sig = not a statistically significant difference. * = not reported.

MB = Major bleeding

26.7 Recommendations and link to evidence

**Recommendation**

Offer pharmacological VTE prophylaxis to patients with cancer who are assessed to be at increased risk of VTE (see Section 5.9). Choose any one of:

- fondaparinux sodium
- LMWH*
- UFH (for patients with renal failure).

Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

*At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.

**Recommendation – from section 5.9**

Regard medical patients as being at increased risk of VTE if they:

- have had or are expected to have significantly reduced mobility for 3 days or more, or
- are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors in Box 1.

**Box 1 – Risk Factors for VTE**

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)

Personal history or first-degree relative with a history of VTE

Use of hormone replacement therapy

Use of oestrogen-containing contraceptive therapy

Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum)

Relative values of different outcomes

The outcomes identified as important by the Guideline Development Group were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

The Guideline Development Group noted that although the reduction of risk of fatal events was the most important outcome, when the evidence was reviewed for general medical patients there was not enough evidence to conclude that prophylaxis reduced all cause mortality.

In the absence of this evidence the Guideline Development Group identified symptomatic VTE and bleeding events as the most important outcomes.

Trade off between clinical benefit and harms

The benefit of reducing VTE events is balanced with the potential harms of bleeding due to anticoagulation.

Economic considerations

An economic model was developed for general medical patients. The model concluded that LMWH and UFH were the most cost-effective strategies in general medical patients.

However, the cost-effectiveness of drug prophylaxis in cancer patients is harder to assess because although these patients have increased risk of VTE they might also have an increased risk of bleeding. Furthermore, the QALYs gained might be less for cancer patients if their life expectancy is low even in the absence of a VTE.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). The quality of the evidence specific to cancer patients was low.
Although 92% (12/13) RCTs of prophylaxis in general medical patients included some patients with cancer, there was only one study which provided results specifically for this population. This showed that LMWH reduced VTE events by approximately 50% compared with no prophylaxis, although this was not statistically significant, probably due to the small numbers of patients included (72 cancer patients).

The quality of the studies for general medical patients has been discussed elsewhere (chapter 23).

**Other considerations**

**Recommendation**

Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with cancer having oncological treatment who are ambulant.

**Relative values of different outcomes**

The outcomes identified as important by the Guideline Development Group were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

The Guideline Development Group agreed that reducing the risk of symptomatic VTE balanced against the risk of major bleeding were the most important outcomes.

**Trade off between clinical benefit and harms**

The benefit of reducing VTE events is balanced with the potential harms of bleeding due to anticoagulation.

**Economic considerations**

There was no economic model developed for this population.

The GDG considered that, as with other patient groups, if these patients are ambulant the risk of VTE is not large enough to justify the adverse events and costs of prophylaxis.

**Quality of evidence**

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

There was only one study investigating prophylaxis for the reducing the risk of VTE in patients undergoing treatment for cancer. This was a small study (n=315) of people undergoing treatment for breast cancer and so these data may not be applicable to other populations. Likewise, this was an ambulant population with prophylaxis provided over 180 days. Additionally, this study was published more than 10 years ago and since then treatment methods have changed.

**Other considerations**

If these patients have central venous catheters, more guidance for this population can be found in Chapter 27.
26.7.1 Other recommendations of relevance

The specific recommendations for patients with cancer in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- mechanical alternatives for patients contraindicated to pharmacological VTE prophylaxis (Section 23.7)
- the provision of patient information (Section 32.5)
- patients using anticoagulants or antiplatelets for reasons other than VTE prophylaxis (Chapter 1)
- patients with central venous catheters (Section 27.7)

26.8 Recommendations for research

The current evidence for thromboprophylaxis in hospitalised cancer patients is based on studies in general medical patients that had included cancer patients. Therefore a study to identify best practice within the cancer population alone should be conducted.

Recognition that some cancers are more thrombogenic than others, supports a view that this should be done in specific cancer groups. Such cancer groups worthy of consideration include myeloma, pancreatic, lung, ovarian and primary brain.

New oral anticoagulant agents such as dabigatran and rivaroxaban should be evaluated in the general cancer population.

26.9 Summary of recommendations

- Offer pharmacological VTE prophylaxis to patients with cancer who are assessed to be at increased risk of VTE (see Section 5.9). Choose one of the following:
  - fondaparinux sodium
  - LMWH*
  - UFH (for patients with renal failure).

Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

* At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.

- Regard medical patients as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more, or
• are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.

**Box 1 - Risk factors for VTE**
- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and 6 weeks post partum)

➢ Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with cancer having oncological treatment who are ambulant.
27 Patients with central venous catheters

27.1 Introduction

Central venous catheters (CVCs) are commonly used in a wide variety of patients for indications such as monitoring of haemodynamics, administration of parenteral nutrition, blood products, chemotherapy, and infusion fluids. One important complication of the use of CVCs is catheter-related thrombosis (CRT), the majority of which are asymptomatic. These are of uncertain clinical significance, but CRT has been reported in adult patients with cancer to cause morbidities including pulmonary embolism and postphlebitic syndrome.

The incidence of CRT in adult patients with cancer has been described in a number of clinical observational and interventional studies; however it is impossible to define the incidence of thrombotic events precisely, given the variation in a range of relevant factors that make an inter-study comparison difficult. These include differences in study design and the observed patient population, variation in the method of catheter type and insertion, inconsistent description of the thrombotic event e.g. difficulty in separating mural thrombosis from catheter occlusion by catheter sleeve, significant differences in patient follow up and the sensitivity and specificity of the radiological methods used to confirm the diagnosis.

An average of approximately 40% of all patients with CVCs are reported to develop venographically demonstrable thrombi. There is, however, a wide variation in the published incidence of symptomatic CRT in adult cancer patients, from 0.3-28.3%. If the study endpoint is venography-detected venous thromboembolism (VTE), the thrombosis rate rises to 27-66%, most of which are asymptomatic. More recent studies, however, have shown a marked decline in incidence of CRT which is likely to be due to improvements in catheter technology, placement and aftercare.

The risk of thrombosis and the risk of bleeding differ among different patient populations. Firstly, the underlying disease can affect the risk of thrombosis as in cancer. The risk is further increased when patients receive treatment such as surgery or chemotherapy. The nature of the substances administered again increases the risk. Chemotherapy may directly damage vascular endothelium and the hyperosmolality of parenteral nutrition may also change the vessel wall. The type and location of the catheter is important but there is a paucity of properly powered trials with adequate follow up on risk factors. In adult patients with cancer, patient history of VTE and previous catheter insertions, inadequate position of CVC tip, left-sided CVC insertion and chest radiotherapy have been identified as significant risk factors for CRT. Many other risk factors have been postulated but not proven.
Chemotherapy may lower the number of circulating platelets which may induce bleeding. The dose of the anticoagulant may increase major bleeding.

27.2 Evidence of methods of VTE prophylaxis

As the outcomes used in other chapters are not appropriate for patient with central venous catheters the Guideline Development Group defined the important outcomes as:

- symptomatic and/or asymptomatic catheter related thrombosis
- major bleeding
- all cause mortality

Pulmonary Embolism and post-thrombotic syndrome are not presented as they are poorly reported in thromboprophylaxis trials for this population.

12 randomised controlled trials which reported at least one of the following outcomes;
all cause mortality, catheter related thrombosis or major bleeding

No methodologically strong studies have been performed in patients receiving parenteral nutrition, in renal patients or in the intensive care setting. Thromboprophylaxis in cancer patients with CVCs has been studied most widely and therefore forms the basis of the evidence of thromboprophylaxis in patients with central venous catheters. No generalisations should be made from this specific population.
27.2.1 Summary of comparisons identified for any main outcomes

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA vs no MPA</td>
<td>4</td>
<td>50/506</td>
<td>51/359</td>
<td>0.81</td>
<td>-0.06</td>
<td>ET: 68</td>
</tr>
<tr>
<td>MPA vs nil</td>
<td>3</td>
<td>9/108</td>
<td>25/106</td>
<td>0.41</td>
<td>-0.14</td>
<td>ET: 68</td>
</tr>
<tr>
<td>MPA vs nil</td>
<td>1</td>
<td>4/42</td>
<td>15/40</td>
<td>0.25</td>
<td>-0.28</td>
<td>ET: 68</td>
</tr>
</tbody>
</table>

*FP – forest plot number in appendix E; ET – evidence table number in appendix D
Proph - prophylaxis
(a) There is substantial statistical heterogeneity between studies for this population (I² = 55.9%, χ² on 2 df = 6.80, p=0.08).
Table 27-139: Clinically relevant (symptomatic) catheter related thrombosis—summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>3</td>
<td>12/490</td>
<td>12/346</td>
<td>0.68 (0.29, 1.57)</td>
<td>-0.01 (-0.04, 0.01)</td>
<td>ET: 68 FP: 236</td>
</tr>
<tr>
<td>VKA vs nil</td>
<td>4</td>
<td>36/637</td>
<td>40/626</td>
<td>0.89 (0.57, 1.39)</td>
<td>0.00 (-0.03, 0.03)</td>
<td>ET: 68 FP: 236</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed VKA vs Adjusted dose VKA</td>
<td>1</td>
<td>34/471</td>
<td>13/473</td>
<td>2.63 (1.40, 4.91)</td>
<td>0.04 (0.02, 0.07)</td>
<td>ET: 68 FP: 241</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D
Proph - prophylaxis

Table 27-140: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH vs nil</td>
<td>1</td>
<td>2/65</td>
<td>2/63</td>
<td>0.97 (0.14, 6.67)</td>
<td>0.00 (-0.06, 0.06)</td>
<td>ET: 68 FP: 237</td>
</tr>
<tr>
<td>VKA vs nil</td>
<td>2</td>
<td>7/538</td>
<td>4/529</td>
<td>1.13 (0.02, 52.56)</td>
<td>0.00 (-0.01, 0.01)</td>
<td>ET: 68 FP: 237</td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>4</td>
<td>2/557</td>
<td>1/408</td>
<td>0.97 (0.12, 7.68)</td>
<td>0.00 (-0.04, 0.04)</td>
<td>ET: 68 FP: 237</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKA vs LMWH</td>
<td>1</td>
<td>2/24</td>
<td>1/21</td>
<td>1.75 (0.17, 17.95)</td>
<td>0.04 (-0.11, 0.18)</td>
<td>ET: 68 FP: 239</td>
</tr>
<tr>
<td>Fixed dose VKA vs Adjusted dose VKA</td>
<td>1</td>
<td>7/471</td>
<td>16/473</td>
<td>0.44 (0.18, 1.06)</td>
<td>-0.02 (-0.04, 0.00)</td>
<td>ET: 68 FP: 242</td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D
Proph - prophylaxis

(a) There is substantial statistical heterogeneity between studies for this population ($I^2 = 78.0\%$, $\chi^2$ on 1 df = 4.54, $p=0.03$).

27.2.3 Additional information

27.2.3.1 All cause mortality

Table 27-141: All cause mortality summary from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH vs nil</td>
<td>3</td>
<td>18/493</td>
<td>23/349</td>
<td>0.70 (0.38, 1.30)</td>
<td>-0.02 (-0.08, 0.05)</td>
<td>ET: 68 FP: 238</td>
</tr>
<tr>
<td>VKA vs nil</td>
<td>3</td>
<td>34/235</td>
<td>35/229</td>
<td>0.95 (0.62, 1.46)</td>
<td>0.00 (-0.04, 0.04)</td>
<td>ET: 68 FP: 238</td>
</tr>
<tr>
<td>Single proph vs single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKA vs LMWH</td>
<td>1</td>
<td>4/30</td>
<td>6/29</td>
<td>0.64</td>
<td>0.07</td>
<td>ET: 68 FP: 238</td>
</tr>
</tbody>
</table>
27.2.3.2 Other outcomes

Four studies additionally reported non-catheter related thrombosis \(^{136,449,663,706}\).

- Couban et al.\(^{136}\) reported non-significant difference between fixed dose warfarin and no VTE prophylaxis in reducing symptomatic non-CVC associated DVT or PE (RR 0.96 [95%CI: 0.20, 4.67]).

- Mismetti et al.\(^{449}\) compared LMWH with warfarin and reported non-significant changes in asymptomatic or symptomatic upper extremity thrombosis or symptomatic DVT of lower limbs. (RR=0.58 [95% CI: 0.19, 1.79])

- Verso et al.\(^{663}\) reported no significant difference in asymptomatic or symptomatic upper limb DVT between LMWH and placebo (RR=0.79 [95% CI: 0.47, 1.31]). Fatal pulmonary embolism was recorded but no events were reported in either arm.

- Young et al.\(^{706}\) reported non-significant differences between warfarin (fixed dose 1mg daily (79%) and dose adjusted warfarin to maintain the INR between 1.5 and 2.0 (21%)) and no warfarin in catheter-related plus non-catheter related thrombotic events (RR=0.78 [95% CI: 0.50, 1.24])

- Young et al.\(^{706}\) reported on a combined endpoint of CRT and major bleeding and demonstrated no significant difference between warfarin vs no warfarin (as above) (RR= 1.23 [95% CI: 0.83, 1.52]) and fixed dose vs. dose adjusted warfarin (RR=0.84 [95% CI: 0.74, 2.04]).

No studies reported chronic thromboembolic pulmonary hypertension or post thrombotic syndrome. Three studies recorded heparin induced thrombocytopenia as an outcome, but there were no events in any study\(^{4,449,489}\).
27.3 Network meta-analysis results

No network meta-analysis was completed for this population.

27.4 Cost-effectiveness evidence

We did not prioritise this population subgroup for original cost-effectiveness analysis and no relevant cost-effectiveness studies were found in the literature.

27.5 Patient views

No studies on patient views for patients with central venous catheters were identified.

Patient views about specific VTE prophylaxis agents are within section 6.6.

27.6 Summary of evidence

Table 27-142: Summary of evidence from direct evidence results for catheter related thrombosis, symptomatic catheter related thrombosis and major bleeding.

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis vs no prophylaxis</td>
<td></td>
<td>CRT</td>
</tr>
<tr>
<td>UFH</td>
<td>nil</td>
<td>UFH</td>
</tr>
<tr>
<td>LMWH</td>
<td>nil</td>
<td>Not sig</td>
</tr>
<tr>
<td>VKA</td>
<td>nil</td>
<td>VKA</td>
</tr>
<tr>
<td>Single Prophylaxis vs single</td>
<td></td>
<td>CRT</td>
</tr>
<tr>
<td>LMWH</td>
<td>VKA</td>
<td>-</td>
</tr>
<tr>
<td>Fixed VKA</td>
<td>Adjusted VKA</td>
<td>-</td>
</tr>
</tbody>
</table>

Cost Effectiveness
There is no relevant cost-effectiveness evidence specifically for this population subgroup.

CRT = Catheter related thrombosis (asymptomatic and symptomatic events); Clinical CRT = clinically relevant catheter related thrombosis; MB = major bleeding.

The prophylaxis strategy which is significantly more effective in reducing CRT or Clinical CRT; or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. ‘-’ = not reported. MB = Major bleeding.
27.7 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with central venous catheters who are ambulant.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation</td>
<td>Consider offering pharmacological VTE prophylaxis with LMWH * (or UFH for patients with renal failure) to patients with central venous catheters who are at increased risk of VTE (See Section 5.9).</td>
</tr>
<tr>
<td>* At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent should be obtained and documented.</td>
<td></td>
</tr>
<tr>
<td>Recommendation –from section 5.9</td>
<td>Regard medical patients as being at increased risk of VTE if they:</td>
</tr>
<tr>
<td></td>
<td>• have had or are expected to have significantly reduced mobility for 3 days or more, or</td>
</tr>
<tr>
<td></td>
<td>• are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors in Box1.</td>
</tr>
<tr>
<td>Box 1 –Risk Factors for VTE</td>
<td>• Active cancer or cancer treatment</td>
</tr>
<tr>
<td></td>
<td>• Age over 60 years</td>
</tr>
<tr>
<td></td>
<td>• Critical care admission</td>
</tr>
<tr>
<td></td>
<td>• Dehydration</td>
</tr>
<tr>
<td></td>
<td>• Known thrombophilias</td>
</tr>
<tr>
<td></td>
<td>• Obesity (BMI over 30 kg/m²)</td>
</tr>
<tr>
<td></td>
<td>• One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)</td>
</tr>
<tr>
<td></td>
<td>• Personal history or a first degree relative with a history of VTE</td>
</tr>
<tr>
<td></td>
<td>• Use of hormone replacement therapy</td>
</tr>
<tr>
<td></td>
<td>• Use of oestrogen-containing contraceptive therapy</td>
</tr>
<tr>
<td></td>
<td>• Varicose veins with phlebitis.</td>
</tr>
<tr>
<td></td>
<td>For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum)</td>
</tr>
</tbody>
</table>
| | The Guideline Development Group identified all cause
outcomes

mortality and both symptomatic catheter related and non-catheter related thrombosis as the most important outcomes for this population. The guideline development group also agreed that asymptomatic catheter related events could be used as a surrogate for symptomatic events in this population.

Trade off between clinical benefit and harms

The Guideline Development Group felt that the balance between the benefits of reducing thrombotic events needed to be balanced against the harms of increased bleeding.

Economic considerations

There is no relevant cost-effectiveness evidence specifically for this population subgroup. There is no clinical evidence that these patients are at higher risk of symptomatic VTE than other medical patients who do not have central venous catheters. This suggests that they should be treated as for other medical patients.

Quality of evidence

The overall quality of the evidence was poor. The studies included a wide range of populations including cancer patients and non-cancer patients (e.g. parenteral nutrition patients) surgical patients. Some members indicated that the patients who have catheters inserted currently are different to those patients included in the trials as they are less sick and therefore at a lower risk of thrombosis.

The Guideline Development Group noted that the trials used a number of different definitions and measurement methods for detecting events which made it difficult to compare the results of the individual studies.

The guideline development group were aware that some of the studies were old, particularly some of the studies comparing UFH and warfarin with no VTE prophylaxis. There were concerns that since the publication of these studies, factors such as the catheter material, method of insertion and mobility of patients had changed. Additionally the sample size of many comparisons were small, even when the studies were combined meaning that a statistical difference was unlikely to be detected even if there was one.

The above factors may be apparent in the range of incidence rates in the no prophylaxis arms in the studies which range from 9 – 62%.

Other considerations

The guideline development group agreed that although there is some evidence that VTE prophylaxis is effective at reducing all catheter related thrombosis without significant increase in major bleeding, patients should not be routinely offered VTE prophylaxis. This was based on the low quality of the evidence available (old trials)

The guideline development group agreed that if patients with catheters had reduced mobility for 3 days or additional risk
factors they should be offered VTE prophylaxis as per general medical patients.

Warfarin was not recommended for this population as in the most recent trial published there was no evidence of efficacy. In addition warfarin is difficult to monitor and the Guideline Development Group were concerned about the possible interactions between warfarin and other drugs.

As the use of a CVC is a risk factor for VTE the GDG noted that other non invasive administration routes of therapy should be considered as an alternative route to central venous catheters where possible if the efficacy is the same and after discussion with the patient. For example, oral chemotherapy should be used instead of intravenous chemotherapy via CVCs.

27.7.1 Other recommendations of relevance

The specific recommendations for patients with central venous catheters in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- mechanical alternatives for patients contraindicated to pharmacological VTE prophylaxis (Section 23.7)
- the provision of patient information (Section 32.5)
- patients with cancer (Section 26.7)

27.8 Recommendations for research

Although none of the top 5 research recommendation was identified in this population, it was felt appropriate to suggest large international trials with the new oral anticoagulants (such as dabigatran and rivaroxaban) in patients with central venous catheters.

27.9 Summary of recommendations

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with central venous catheters who are ambulant.

- Consider offering pharmacological VTE prophylaxis with LMWH * or UFH (for patients with renal failure) to patients with central venous catheters who are at increased risk of VTE (See Section 5.9)
Patients with central venous catheters

*At the time of publication (January 2010) some types of LMWH do not have UK marketing authorization for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent should be obtained and documented.

- Regard medical patients as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more or
  - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.

---

**Box 1 Risk factors for VTE**

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilies
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and 6 weeks post partum)
28 Palliative care

28.1 Introduction

The need for provision of palliative care has been recognised across all incurable malignant and non-malignant disease services. In addition, advances in therapeutic interventions have resulted in the palliative care population living longer despite incurable disease.

For the purposes of these guidelines a distinction needs to be made between a terminal patient; that is when a patient appears to be approaching death or has been admitted for end of life care and a palliative patient which encompasses any patient with incurable disease at any point of their disease journey. Palliative care patients may therefore encompass a spectrum of patients all with incurable illness, yet with a breadth of performance status, symptomatology and life expectancy. The majority of palliative care patients are admitted through the acute hospital take and the appropriateness of thromboprophylaxis should be made on an individual basis. In view of the heterogeneity of the palliative population, it could be argued that a blanket policy to withhold thromboprophylaxis in the palliative setting would be as ethically challenging as one which advocates thromboprophylaxis for all. Further discussion on the role of thromboprophylaxis in palliative care can be found in Noble et al.

There is very little evidence specifically in the palliative care population and recommendations are based on extrapolation from the general medical population. However, one study suggests a 50% prevalence of asymptomatic DVT in hospice patients with cancer, although the symptom burden of VTE is unclear since dysnoea and leg oedema are common in this population due to other pathology.

28.2 Evidence of methods of prophylaxis

One study was found which investigated low molecular weight heparin (LMWH) vs no prophylaxis in palliative care patients. This study was stopped early after failing to recruit eligible patients in a reasonable time. At the time of stopping 20 patients had been recruited. The study was underpowered to detect difference in the any of the outcomes recorded and the results have not been recorded here.

28.3 Network meta-analysis results

Network meta-analysis was not completed for this population.
28.4 Cost-effectiveness evidence

No cost effectiveness model was completed for this population.

28.5 Patient views

A recent qualitative study conducted in the United Kingdom among cancer patients receiving palliative care showed acceptability of thromboprophylaxis. This study found that patients were aware of the purpose of subcutaneous LMWH thromboprophylaxis. They balanced the potential benefit of venous thromboembolism reduction against potential side effects (bruising was quoted) and found it acceptable. It also highlighted an awareness amongst patients of some of the risks of VTE and a desire to be involved in the decision making process.

For patient views about specific prophylaxis agents, see section 6.6.

28.6 Summary of evidence

<table>
<thead>
<tr>
<th>Evidence statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no clinical effectiveness evidence for this population</td>
</tr>
<tr>
<td>There is no cost effectiveness evidence for this population</td>
</tr>
</tbody>
</table>

28.7 Recommendations and link to evidence

**Recommendation**

Consider offering pharmacological VTE prophylaxis to patients in palliative care who have potentially reversible acute pathology. Take into account potential risks and benefits and the views of patients and their families and/or carers. Choose any one of:

- fondaparinux sodium
- LMWH *
- UFH (for patients with renal failure).

* At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.

**Recommendation**

Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients admitted for terminal care or those commenced on an end-of-life care pathway.

**Recommendation**

Review decisions about VTE prophylaxis for patients in palliative care daily, taking into account the views of patients, their families and/or carers and the multidisciplinary team.

**Relative values of different outcomes**

The Guideline Development Group noted that VTE prophylaxis in palliative care patients is for symptom prevention rather than with the sole purpose of trying to prolong life. Long term
sequelae of VTE such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension are less important in the palliative care population. It is recognised that patients on an end of life care pathway (e.g. Liverpool Care Pathway; details of pathway available from: www.mcpcil.org.uk/liverpool_care_pathway), will be prescribed appropriate symptom control medicines to manage VTE related symptomatology in the last hours of life.

**Trade off between clinical benefit and harms**

The benefit of reducing VTE events was balanced with the potential harms of bleeding and qualitative aspects of receiving thromboprophylaxis.

**Economic considerations**

No economic model was completed for this population. There is evidence in medical patients that LMWH is clinically and cost effective at reducing the risk of VTE. However, the cost-effectiveness of drug prophylaxis in palliative care patients is harder to assess because although these patients might have an increased risk of symptomatic VTE, they might also have an increased risk of bleeding. Furthermore, the quality-adjusted life years (QALYs) gained might be less for palliative care patients if for example their life expectancy is low even in the absence of a VTE.

Finally, if extended prophylaxis is required then the cost-effectiveness may diminish further when the costs of home visits are taken into consideration.

**Quality of evidence**

There is no directly applicable evidence for the effectiveness of prophylaxis in the palliative care population. There is high quality evidence of effectiveness of LMWH across other medical and surgical populations.

**Other considerations**

**Patient views:** One qualitative study investigated attitudes towards prophylaxis in people within a specialist palliative care unit setting. This study indicated that LMWH was well tolerated in this population.

**When to stop prophylaxis:** Given the lack of directly applicable evidence in palliative patients it is difficult to provide precise rules for when to stop prophylaxis. The Guideline Development Group agreed it was important to review the provision of thromboprophylaxis at regular intervals and suggested 48 hrs as an appropriate time point. However, there was insufficient evidence to recommend prolonged prophylaxis once the patient was discharged.

### 28.7.1 Other recommendations of relevance

The specific recommendations for patients receiving palliative care in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:
• risk assessment for VTE and major bleeding (Section 5.9)
• the use of prophylaxis in general (Section 6.7 and 6.8)
• mechanical alternatives for patients contraindicated to pharmacological VTE prophylaxis (Section 23.7)
• the provision of patient information (Section 32.5)
• patients with cancer (Section 26.7)

28.8 Recommendations for research

Currently no sufficiently powered thromboprophylaxis studies have been completed in the palliative care population. Whilst extrapolations from the general medical studies support appropriate use of LMWH in palliative care, it has been suggested that these are not a sufficiently representative population. Furthermore, the outcome measures used for these studies are considered less appropriate in an advanced disease population in whom quality of life is as important, if not more important, than VTE related clinical outcome.

There is a need to identify the symptomatic burden of VTE in the palliative care population with emphasis on the impact of VTE on quality of life. In addition, patient relevant outcome measures specific to this population need to be established in order to evaluate the role of thromboprophylaxis. The new oral anticoagulants such as dabigatran and rivaroxaban would be appropriate agents to study in the advanced disease setting.

28.9 Summary of recommendations

➢ Consider offering pharmacological VTE prophylaxis to patients in palliative care who have potentially reversible acute pathology. Take into account potential risks and benefits and the views of patients and their families and/or carers. Choose any one of:

• fondaparinux sodium
• LMWH*
• UFH (for patients with renal failure).

* At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.

➢ Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients admitted for terminal care or those commenced on an end-of-life care pathway.

➢ Review decisions about VTE prophylaxis for patients in palliative care daily, taking into account the views of patients, their families and/or carers and the multidisciplinary team.
29 Critical care

29.1 Introduction

Patients admitted to a critical care facility (who are generally in need of level 2 or level 3 care) can be separated into some distinct groups by their disease process:

1. patients with any acute illness that has resulted in one or more organ systems failing and have a need for interventions to support organ function

2. patients who need a higher level of observation and intervention that can not safely be provided elsewhere

3. patients who have had complex or prolonged surgical procedures and hence require a duration of recovery with a higher level of observation and monitoring than can be provided elsewhere in order to rapidly detect and manage any deterioration

4. patients who are dying and there is ongoing consideration of organ donation.

The data available to support decision making in such critically ill patients were scarce and suffers from wide variations in the nature of such units around the world, the heterogeneous population served and the very high all cause mortality seen. Each group has its own unique risk factors for VTE and risks of bleeding or other complications.

The unifying feature is that during times of severe physiological upset, the inflammatory response is at a maximal and the patient is almost always immobile and likely to have a number of intravascular catheter devices. This puts the patient at a much higher risk of developing venous thrombi. The same patient may however also be at an increased risk of bleeding, either due to a coagulopathy as a consequence of their disease or interventions; or be at risk of bleeding into a surgical field with disastrous consequences such as in spinal surgery or neurosurgery.

Also, the medications and equipment used in critical care may increase the risk of bleeding further. As examples; patients who require renal replacement support usually also require co-administration of heparin to stop thrombus formation in the external circuit; coagulopathy is a recognised complication of some treatments for sepsis and of large volume blood transfusions.

The critically ill patients will have a number of such risk factors which may change in nature, number and significance many times throughout their stay. Also, many invasive procedures may be carried out during such an admission (central lines, lumbar punctures,
chest drains etc) and so relative risks of bleeding as a consequence will also change many times.

Patients admitted to critical care units have an increased risk of developing venous thromboembolic disease and steps must be taken to recognise and manage such risks at a very early stage. However, the relative risk of significant bleeding is also high and so it is incumbent on staff to evaluate these risks very frequently and consider the best form of VTE prophylaxis on an individual patient basis.

29.2 Evidence of methods of prophylaxis

29.2.1 Summary of comparisons identified for any outcome

One study conducted specifically in intensive care patients was found^{191}. This study was conducted among chronic obstructive pulmonary disease (COPD) patients with acute respiratory decompensation requiring mechanical ventilation in multiple medical intensive care centres. This study compared the effectiveness of LMWH against placebo. This study is included in the general medical patients section (Section 23) and the results are shown below.

29.2.2 Results from pairwise comparisons

Table 29-143: DVT – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td>1</td>
<td>13/84</td>
<td>24/85</td>
<td>0.55</td>
<td>-0.13</td>
<td>ET: 26, FP: 13</td>
</tr>
<tr>
<td>LMWH vs nil^{191}</td>
<td></td>
<td></td>
<td></td>
<td>(0.30, 1.00)</td>
<td>(-0.25, 0.00)</td>
<td></td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

Symptomatic Pulmonary Embolism

No study reported symptomatic pulmonary embolism as an outcome.

Table 29-144: Major bleeding – summary of results from RCTs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>Intervention</th>
<th>Control</th>
<th>Relative risk</th>
<th>Absolute effect</th>
<th>Forest plots &amp; Evidence tables *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proph vs no proph</td>
<td>1</td>
<td>6/108</td>
<td>3/113</td>
<td>2.09</td>
<td>0.03</td>
<td>ET: 26, FP: 15</td>
</tr>
<tr>
<td>LMWH vs nil^{191}</td>
<td></td>
<td></td>
<td></td>
<td>(0.54, 8.16)</td>
<td>(-0.02, 0.08)</td>
<td></td>
</tr>
</tbody>
</table>

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph – prophylaxis
29.2.3 Additional information

29.2.3.1 All cause mortality

Table 29-145: All cause mortality – summary of results from RCTs

| Comparison            | No. of studies | Intervention | Control | Relative risk | Absolute effect | Forest plots & Evidence tables *
|-----------------------|----------------|--------------|---------|---------------|-----------------|---------------------------------------------------------
| Proph vs no proph     | 1              | 8/108        | 8/113   | 1.05          | 0.00            | ET: 26                                                  |
| LMWH vs nil           | 1              | 8/108        | 8/113   | (0.41, 2.69)  | (-0.07, 0.07)   | FP: 16                                                   |

* FP – forest plot number in appendix E; ET – evidence table number in appendix D

Proph - prophylaxis

29.2.3.2 Additional studies

One additional study was identified which was designed to evaluate whether heparin interfered with the efficacy of activated protein C (drotrecogin alfa) in patients with severe sepsis\(^\text{397}\). Patients were randomised to receive low molecular weight heparin (LMWH) or unfractionated heparin (UFH) (evaluated as a combined heparin group) or no prophylaxis during their treatment period with activated protein C (usually 96 hours) and revert back to their usual prophylaxis strategy after the activated protein C administration had stopped. In this study, there were no statistically significant difference between the groups in all cause mortality (28 days follow up), major bleeding, or a composite outcomes of venous thrombotic events (Evidence Table 26, Appendix D)

29.3 Network meta-analysis results

No network meta-analysis was completed for this population.

29.4 Cost-effectiveness evidence

We did not prioritise this population subgroup for original cost-effectiveness analysis and no relevant cost-effectiveness studies were found in the literature.

29.5 Patient views

No patient view papers conducted specifically in this population were identified.

For patient views about specific prophylaxis agents, see section 6.6.
29.6 Summary of evidence

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Intervention favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis vs no prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>Nil</td>
<td>LMWH</td>
</tr>
</tbody>
</table>

Cost Effectiveness Analysis
There is no relevant cost-effectiveness evidence specifically for this population subgroup.

The prophylaxis strategy which is significantly more effective in reducing DVT or PE, or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. ‘-‘ = not reported. MB = Major bleeding

The only study found in this population showed a significant reduction in DVT events with LMWH compared with no prophylaxis but was not significant for major bleeding.

29.7 Recommendations and link to evidence

**Recommendation**
Assess all patients on admission to the critical care unit for their risks of VTE and bleeding (see section 5.9). Reassess patients’ risks of VTE and bleeding daily and more frequently if their clinical condition is changing rapidly.

*Note: Relevant recommendations from section 5.9 are reproduced in section 29.8, below*

**Recommendation**
Offer VTE prophylaxis to patients admitted to the critical care unit based on the reason for admission, taking into account:
- any planned interventions
- the use of other therapies that may increase the risk of complications.

**Recommendation**
Review decisions about VTE prophylaxis for patients in critical care daily and more frequently if their clinical condition is changing rapidly. Take into account the known views of the patient, comments from their family and/or carers and the multidisciplinary team.

**Trade off between clinical benefit and harms**
This is a critically ill group of patients. Survival of patients is the most immediate concern.

The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of adverse events due to prophylaxis including major bleeding.

**Economic considerations**
There will be a cost in staff time to complete the assessment on admission to the critical care unit but this is outweighed by the potential benefits for reducing the risk of venous thromboembolism.

No cost effectiveness analysis was completed specifically for
this population subgroup. However, the cost-effectiveness model for general medical patients included trial evidence from 1 RCT in intensive care patients. The cost-effectiveness model for medical patients found that drug prophylaxis with LMWH was cost-effective.

Given that critical care patients are likely to be at increased risk of VTE compared to general medical patients; it is likely that prophylaxis will also be cost effective for the critical care population, unless the risk of bleeding is high.

Other considerations

Admission to critical care may be from a different ward within the hospital and may represent a worsening of the patient\’s condition. It is important to assess the patients\’ VTE risk as it may have been identified as low on initial admission. A review of risk factors (chapter 5) identified admission to the critical care unit as an independent factor for increasing VTE risk.

There was a strong consensus among the Guideline Development Group members that the risk of VTE among critical care patients is higher than the normal wards. As the clinical situation changes it is necessary to reassess the risks of VTE and bleeding. The incidence of DVT in no prophylaxis arm in the study in intensive care patients was 28%, which is higher than the incidence for general medical patients (13%). Therefore the guideline development group agreed that in the absence of bleeding risk factors and after taking into account any planned interventions or therapies which may increase complications, VTE prophylaxis should be offered.

Patients treated in the critical care may be unconscious or not capable of making decisions about their treatment. In such situations, decisions about care should take into account the known view of patients and discussions with family members, where appropriate.

As there is a lack of RCT evidence in critical care patients, consensus guidelines developed by other organisations were reviewed for relevance and quality. The International Surviving Sepsis Campaign Guideline\textsuperscript{155} has been developed using appropriate consensus methods involving international expert panels. This guideline would be adequate for patients with severe sepsis patients in the intensive care unit.

29.7.1 Other recommendations of relevance

The specific recommendations for patients in critical care in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
• recommendations specific to their condition where applicable (Chapters 9 to 28)

• the use of prophylaxis in general (Section 6.7 and 6.8) Note, if anti-embolism stockings are used, it should be noted that due to the changes in fluid status among critical care patients, it may be challenging to ensure a good fit.

• the provision of patient information (Section 32.5)

29.8 Summary of recommendations

➢ Assess all patients on admission to the critical care unit for their risks of VTE and bleeding (see section 5.9). Reassess patients' risks of VTE and bleeding daily and more frequently if their clinical condition is changing rapidly.

➢ Offer VTE prophylaxis to patients admitted to the critical care unit based on the reason for admission, taking into account:

- any planned interventions
- the use of other therapies that may increase the risk of complications.

➢ Review decisions about VTE prophylaxis for patients in critical care daily and more frequently if their clinical condition is changing rapidly. Take into account the known views of the patient, comments from their family and/or carers and the multidisciplinary team.

➢ Regard medical patients as being at increased risk of VTE if they:

- have had or are expected to have significantly reduced mobility for 3 days or more or
- are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.

➢ Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more risk factors shown in Box 1.

➢ Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.

*Prescribers should consult the summary of product characteristics for the pharmacological VTE prophylaxis being used or planned for further details.
**Box 1 Risk factors for VTE**

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilies
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum)

**Box 2 Risk factors for bleeding**

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalised ratio [INR] higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10⁹/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand’s disease)
Pregnancy and up to 6 weeks post partum

30.1 Introduction

Venous thromboembolism (VTE) remains the leading direct cause of maternal death in the UK. In the latest Confidential Enquiry into Maternal and Child Health (CEMACH) report ‘Saving Mothers’ Lives: Reviewing maternal deaths to make motherhood safer, 2003-5’ there were 33 deaths from pulmonary embolism (18 events occurring antenatally, 8 after vaginal delivery and 7 after caesarean section). There is an overall incidence of approximately two episodes of VTE (including non-fatal events) per 1000 deliveries.

The risk of VTE is present from early pregnancy because the prothrombotic and flow changes occur from this time. The prothrombotic changes of pregnancy do not revert completely to normal until up to 6 weeks after delivery especially after an emergency Caesarean section. The time of greatest risk for VTE associated with pregnancy is the early postpartum period and, although, in absolute terms, most VTE events occur antenatally, the risk per day is greatest in the weeks immediately after delivery.

Indeed the Confidential Enquiries into Maternal Deaths have shown that two thirds of antenatal fatal pulmonary VTE in 2003-2005 occurred in the first trimester, and just over half of the postnatal deaths from PE were after vaginal delivery. Admission to hospital in any trimester poses an increased risk of VTE.

Women with specific factors such as family history of thrombophilia or a history of VTE require specialised evaluation, ideally before conception. Advice for these patients and all women who are pregnant or postpartum but who are not admitted to hospital is outside the remit of this guideline. There are guidelines produced by the Royal College of Obstetrician and Gynaecologist’s (RCOG) Green-top Guideline number 37,”Thromboprophylaxis During Pregnancy, Labour and After Vaginal Delivery” which contains a review of the evidence and recommendations for the management of women at risk of VTE in pregnancy or the postpartum period for more information. The RCOG guideline (available on the RCOG website www.rcog.org.uk/index.asp?PageID=8) was published in January 2004 and was in the process of being updated at the time of writing.

The scope for this guideline relates only to patients admitted to hospital. Women who are pregnant or postpartum are usually admitted to obstetric wards, however, some women are admitted to non-obstetric wards, particularly in early pregnancy, for reasons such as management of pre-existing disease such as diabetes, or acute surgery. Pregnancy is a highly prothrombotic state and temporary illness and/or immobilisation will lead to an increased risk of VTE. Thus any woman admitted to hospital who is pregnant or postpartum should be risk assessed for their VTE risk as per the
recommendation in section 5.9, and should be considered for thromboprophylaxis. Repeated risk assessment (as recommended in section 5.9) should be completed, particularly during the postpartum period if they develop intercurrent problems or require surgery.

The general recommendations for reducing the risks of VTE contained within section 7 which include encouraging early mobilisation and preventing dehydration are applicable to women admitted to hospital during pregnancy, labour and postpartum.

Pregnant women, who are admitted to hospital and are already receiving thromboprophylaxis on admission should still be risk assessed for their risk of VTE and bleeding. They will normally continue their prophylaxis during their stay unless they develop risk factors for bleeding, when the risk-benefit analysis of thromboprophylaxis should be reconsidered.

A full review of the RCT evidence for preventing VTE in women admitted to hospital during pregnancy or postpartum was completed (section 30.3). When a lack of evidence was identified for this population and following stakeholder comments during consultation, a group of expert advisors (Acknowledgements section, page 15) were invited to discuss the issues and to develop draft recommendations which were then agreed by the guideline development group and their considerations are included in the link between evidence and recommendations in section 30.8.

### 30.2 Evidence for risk factors for pregnancy and postpartum

The factors increasing the risk of VTE in all patients admitted to hospital are discussed in section 5.7, which was developed after completing a full literature search for high quality systematic reviews of risk factors for all patients. No high quality systematic reviews specifically looking at the VTE risk factors for women admitted to hospital during pregnancy or postpartum period were identified.

However, the expert advisors identified that some modification of the VTE risk factor list specifically for women who are pregnant or in the postpartum period was required. These specific risk factors are discussed below:

- **Age.** In the UK obstetric surveillance study (UKOSS) study of antenatal pulmonary embolism unadjusted odds ratio for age > 35 was 1.29 (95% CI: 0.82 – 2.06)\(^{352}\). This evidence is supported by other studies\(^{404,603}\) and therefore, age >35 years is considered as a risk factor for VTE in pregnant women.

- **Excess blood loss and blood transfusion:** Excess blood loss and blood transfusion has been found to be a risk factor for VTE\(^{143,305,307}\) although this will obviously need to be weighed against the risk of further bleeding and, if prophylaxis is deemed necessary, may have an impact on the timing of initiation.

- **Obesity:** Although this factor has already been mentioned in section 5.7, the expert advisors felt that it warranted particular consideration as a risk factor during pregnancy. Nearly all women (7/8) dying from VTE following vaginal delivery in the last Confidential Enquiry were overweight or obese\(^{401}\). The UKOSS study of antenatal PE demonstrated that one of the main risk factors was a BMI >30 with an adjusted odds ratio of 2.65 (95% CI 1.09-6.45)\(^{352}\).
• **Pregnancy-related risks:** Additional risk factors may complicate the first trimester, for example: hyperemesis gravidarum, surgery for miscarriage, termination of pregnancy, ectopic pregnancy or ovarian hyperstimulation following IVF. For example in one study the odds ratio for VTE in women with hyperemesis gravidarum was 2.5 (95% CI: 2.0-3.2). A recent case-control study from Norway found the adjusted odds ratio for VTE in pregnancy following assisted reproductive techniques was 4.3 (95% CI, 2.0-9.4). Women with ovarian hyperstimulation syndrome (OHSS) are particularly prone to VTE in the upper body and require consideration for thromboprophylaxis for at least the period of in-patient stay.

Risk factors are discussed in more detail in the RCOG guideline, from which the following table has been extracted.

**Table 30-146: Risk factors for VTE in pregnancy and the postpartum period (adapted from RCOG guideline)**

<table>
<thead>
<tr>
<th>Risk factors for VTE in pregnancy and the postpartum period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRE-EXISTING</strong></td>
</tr>
<tr>
<td>Previous VTE</td>
</tr>
<tr>
<td>Thrombophilia</td>
</tr>
<tr>
<td>Inherited</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
</tr>
<tr>
<td>Protein C deficiency</td>
</tr>
<tr>
<td>Protein S deficiency</td>
</tr>
<tr>
<td>Factor V Leiden</td>
</tr>
<tr>
<td>Prothrombin gene variant</td>
</tr>
<tr>
<td>Acquired (Antiphospholipid syndrome)</td>
</tr>
<tr>
<td>Medical co-morbidities e.g. Heart or lung disease; acute systemic lupus erythematosus; cancer; inflammatory conditions (inflammatory bowel or joint disease) nephrotic syndrome (proteinuria &gt; 3g/day), sickle cell disease, intravenous drug users, paraplegia, pyelonephritis, sepsis</td>
</tr>
<tr>
<td>Age &gt; 35 years</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30 kg/m²) either pre-pregnancy or in early pregnancy</td>
</tr>
<tr>
<td>Parity ≥ 3</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Gross varicose veins (symptomatic or above knee or with associated phlebitis, oedema/skin changes)</td>
</tr>
<tr>
<td><strong>OBSTETRIC RISK FACTORS</strong></td>
</tr>
<tr>
<td>Multiple pregnancy, assisted reproduction therapy [ART]</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td>Caesarean section</td>
</tr>
<tr>
<td>Postpartum haemorrhage (&gt; 1 litre) / requiring transfusion</td>
</tr>
<tr>
<td>Prolonged labour, mid-cavity rotational operative delivery</td>
</tr>
<tr>
<td><strong>NEW ONSET / TRANSIENT</strong></td>
</tr>
<tr>
<td>Surgical procedure in pregnancy or postpartum</td>
</tr>
<tr>
<td>e.g. ERPC, appendicectomy, postpartum sterilisation, postpartum wound infection</td>
</tr>
<tr>
<td>Ovarian Hyperstimulation syndrome</td>
</tr>
<tr>
<td>Immobility (&gt;3 days bed rest)</td>
</tr>
<tr>
<td>e.g. symphysis pubis dysfunction restricting mobility</td>
</tr>
</tbody>
</table>
30.3 Evidence of methods of prophylaxis

A search was conducted for evidence from RCTs and systematic reviews for all populations (section 3.8). Any papers which included patients who pregnant or up to 6 weeks postpartum were identified from this initial search and were reviewed.

One Cochrane review of evidence (which included 8 RCTs for prophylaxis against VTE in pregnancy and the early postnatal period) was found and reviewed\textsuperscript{215}. One additional paper\textsuperscript{214} published after the Cochrane review was identified which contained details of two separate pilot RCTs conducted in different populations.

- Four RCTs in the Cochrane review and one of the RCTs within the additional paper evaluated antenatal, or antenatal and postnatal prophylaxis in women with increased risk (n=314). These patients received long term prophylaxis delivered in community care settings and were considered by the GDG to be outside the scope of the guideline as they were not admitted to hospital.

- Four RCTs in the Cochrane review and the second of the RCTs within the additional paper evaluated prophylaxis after caesarean section. Of these 5 studies, four were excluded; one as it did not compare interventions under consideration by the guideline, one due to VTE not being reported as an outcome and two due to VTE outcomes not being well defined. This is consistent with the criteria outlined in section 3.8. The remaining RCT\textsuperscript{214} compared LMWH with placebo in 141 women and reported one symptomatic PE event in the placebo arm.

The Cochrane review concluded that, on the basis of trials included, it was not possible to make a conclusive recommendation for thromboprophylaxis during pregnancy and postpartum due to the small sample sizes and the small number of trials comparing the same interventions.

There is no evidence for VTE prophylaxis for pregnant women who are admitted to hospital for non-pregnancy related reasons. All of the studies comparing different types of VTE prophylaxis included in Chapter 9 to 29 excluded patients who were pregnant. A search for evidence from RCTs and systematic reviews was conducted in this patient population.

One Cochrane review of evidence (which included 8 trials) for prophylaxis against VTE in pregnancy and the early postnatal period was found and reviewed\textsuperscript{215}. One additional study containing the results of two separate pilot trials was published subsequent to the systematic review\textsuperscript{214}.

- Four studies in the Cochrane review and one part of the pilot study evaluated antenatal, or antenatal and postnatal prophylaxis in women with increased risk (n=314). These patients were outside the scope of the guideline as they were not admitted to hospital.

- Four studies in the Cochrane review and the second part of the pilot study evaluated prophylaxis after caesarean section. Of these 5 studies, four were excluded; one as it did not compare interventions under consideration by the guideline, one due to VTE not being reported as an outcome and two due to VTE outcomes not being well defined. The remaining study\textsuperscript{214}
compared LMWH and placebo in 141 women and reported one symptomatic PE event in the placebo arm.

The Cochrane review concluded that, on the basis of trials included, it was not possible to make a conclusive recommendation for thromboprophylaxis during pregnancy and postpartum due to the small sample sizes and the small number of trials making the same comparisons.

There is no evidence for VTE prophylaxis of pregnant women who are admitted to hospital for non-pregnancy related reasons. All of the studies comparing different types of VTE prophylaxis included in Chapter 9 to 29 excluded patients who were pregnant.

30.4 Network meta-analysis results

Network meta-analysis was not completed for this population.

30.5 Cost-effectiveness evidence

We did not prioritise this population subgroup for cost-effectiveness analysis and no relevant cost-effectiveness studies were found in the literature.

30.6 Patient views

No studies conducted specifically in pregnant women were found.

For patient views about specific prophylaxis agents, see section 6.6.

30.7 Summary of evidence

<table>
<thead>
<tr>
<th>Evidence statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>A review of prophylaxis efficacy in this population did not find conclusive evidence from randomised clinical trials.</td>
</tr>
<tr>
<td>There is no relevant cost-effectiveness evidence specifically for this population subgroup.</td>
</tr>
</tbody>
</table>
30.8 Recommendations and link to evidence

**Recommendation**  Consider offering pharmacological VTE prophylaxis with LMWH (or UFH for patients with renal failure) to women who are pregnant or have given birth within the previous 6 weeks who are admitted to hospital but are not undergoing surgery, and who have one or more of the following risk factors:

- expected to have significantly reduced mobility for 3 or more days
- active cancer or cancer treatment
- age over 35
- critical care admission
- dehydration
- excess blood loss or blood transfusion
- known thrombophilias
- obesity (pre-pregnancy or early pregnancy BMI over 30 kg/m²)
- one or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- personal history or a first-degree relative with a history of VTE
- pregnancy-related risk factor (such as ovarian hyperstimulation, hyperemesis gravidarum, multiple pregnancy or pre-eclampsia)
- varicose veins with phlebitis.

**Relative Values of Outcomes**  The outcomes identified as important by the Guideline Development Group included thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

**Trade off between clinical benefit and harms**  The benefits of reducing the risk of VTE and long term consequences were considered against potential harmful effects to both the mother and her unborn child (if the admission was antenatal).

**Economic considerations**  A cost effectiveness analysis was not completed specifically for this population subgroup. However, the cost-effectiveness model for medical patients indicates that prophylaxis with LMWH is cost-effective for patients at increased risk.

**Quality of evidence**  No RCT studies on methods of prophylaxis were found in pregnant or postpartum women admitted to hospital not undergoing surgery.
The recommendations were developed based on the expert consensus. These are supported by epidemiological studies although no systematic review of these studies was completed.

**Other considerations**

Pregnancy and the postpartum period (up to and including 6 weeks after delivery) have been identified as an independent risk factor for VTE. If these patients are admitted and have one of the risk factors listed, they should be considered for prophylaxis. Most women having vaginal deliveries will not require an extended stay in hospital and women are unlikely to have restricted mobility for extended periods of time.

The risk factors for VTE within the recommendation are similar to those used for other hospitalised patients. The evidence for these factors is reviewed in section 5.7.

The risk factors added or modified are based on additional information presented within section 30.2 specifically for pregnant women and those ≤6 weeks postpartum. The age criterion of 35 was added as the evidence suggests that this is when pregnant women are at increased risk. Two other risk factors were added; excess blood loss or blood transfusion and other specific pregnancy related risk factors. The evidence for these are discussed in section 30.2.

**Choice of prophylactic agents**

The summary of product characteristics contains further information on the use of pharmacological prophylaxis agents during pregnancy and postpartum.

**LMWH:** Although it has not been tested extensively in this population, low molecular weight heparin (LMWH) is regarded as the most appropriate prophylaxis for pregnant women. LMWH has been used widely in pregnancy and is considered to be relatively safe. It is preferred over over unfractionated heparin, due to its better safety profile and convenience. The summary of product characteristics indicates that animal studies have not shown evidence of fetotoxicity or teratogenicity. Heparin induced thrombocytopenia (HIT) with LMWH has not been reported and the risk of osteoporotic fracture with LMWH is known to be much lower than the risk with unfractionated heparin (UFH), although the actual risk is uncertain.

**Fondaparinux:** There is inadequate safety information for the use of fondaparinux during pregnancy and should not be prescribed unless clearly necessary.

**Warfarin:** has been identified to have teratogenic and bleeding risks to the foetus and should not be used without a careful risk-benefit analysis and discussion with the patient.

**Prophylaxis dosing:**

There is debate about the appropriate frequency and size of doses of LMWH in pregnancy due to inadequate information from clinical trials. Due to the increased plasma volume,
increased glomerular filtration rate and, therefore, decreased half-life of LMWH during pregnancy, dose adjustment (based on weight) may be necessary. More details are available in the summary of product characteristics and the in the RCOG green-top guidelines\(^5\).

**Recommendation**

Consider offering combined VTE prophylaxis with mechanical methods and LMWH (or UFH for patients with renal failure) to women who are pregnant or have given birth within the previous 6 weeks who are undergoing surgery, including caesarean section.

**Relative values of Outcomes**

The outcomes identified as important by the Guideline Development Group included thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

**Trade off between clinical benefit and harms**

The benefits of reducing the risk of VTE and long term consequences were considered against potential harmful effects to both the mother and her unborn child (if the admission was antenatal).

**Economic considerations**

No cost effectiveness analysis was completed specifically for this population subgroup. However, the cost-effectiveness model for general surgical patients indicates that combined mechanical and pharmacological prophylaxis is cost-effective for patients at increased risk of VTE where the risk of major bleeding is less than 1%.

**Quality of evidence**

There was only one small randomised controlled trial included for this population which compared the use of LMWH with placebo. Only one event occurred in either arm (1 PE in the placebo) and so no firm conclusions can be drawn from these data.

**Other considerations**

Pregnancy and postpartum has been identified as an independent risk factor for VTE. If these patients undergo surgery during this time (up to 6 weeks after delivery) they would be exposed to an additional risk of VTE which the Guideline Development Group decided should warrant combined prophylaxis with mechanical methods and LMWH. There is no evidence for mechanical methods in pregnant women but providing appropriate precautions are taken they are likely to be safe in this population.
**Recommendation**

Offer mechanical and/or pharmacological VTE prophylaxis to women who are pregnant or have given birth within the previous 6 weeks only after assessing the risks and benefits and discussing these with the woman and with healthcare professionals who have knowledge of the proposed method of VTE prophylaxis during pregnancy and post partum. Plan when to start and stop pharmacological VTE prophylaxis to minimise the risk of bleeding.

**Trade off between clinical benefit and harms**

The benefits of reducing the risk of VTE and long term consequences were considered against potential harmful effects to both the mother and her unborn child (if the admission was antenatal).

**Economic considerations**

No cost effectiveness analysis was completed specifically for this population subgroup.

**Other considerations**

Due to the lack of evidence in this area it was felt by the GDG that decisions for prophylaxis in pregnant women and those up to 6 weeks post partum should be made after a careful consideration of the risks and benefits and after discussion with experts in this area.

**Timing of prophylaxis**

The initiation of prophylaxis should generally be given as soon as it is safe to do so. Within this population the expert advisors highlighted two circumstances which need particular discussion, namely the use of anaesthesia and the timing of post partum VTE prophylaxis.

**Use of anaesthesia:** Regional anaesthesia can only be sited after discussion with the obstetric anaesthetist in keeping with local obstetric anaesthetic protocols. It is important to discuss the implication of treatment with LMWH for regional anaesthesia/analgesia with the women prior to labour or Caesarean section.

Careful planning of the timing of pharmacological prophylaxis around regional anaesthetic techniques is required to minimise the risk of epidural haematoma (see section 19.4). This should include preventing further injections of LMWH once labour has started to allow for the use of regional anaesthesia. The summary of product characteristics should be consulted according to the prophylaxis drug that is being, or is planned to be, used.

There is an increased risk of wound haematoma following caesarean section with both unfractionated heparin and LMWH of around 2%. Women at high risk of haemorrhage with risk factors including major antepartum haemorrhage, coagulopathy, progressive wound haematoma, suspected intra-abdominal bleeding and post partum haemorrhage may be more conveniently managed with unfractionated heparin or anti-embolism stockings (GCS). If a woman develops a haemorrhagic problem while on pharmacological VTE
prophylaxis the treatment should be stopped and expert haematological advice sought. However, excess blood loss and blood transfusion have been identified as risk factors for VTE for these women (section 30.2) and so pharmacological VTE prophylaxis should begin or be reinstituted as soon as the immediate risk of haemorrhage is reduced.

Postpartum thromboprophylaxis: The first thromboprophylactic dose of LMWH should be given as soon as possible after delivery provided there is no postpartum haemorrhage or regional analgesia (see ‘regional anaesthesia’ discussion above for guidance). If postpartum haemorrhage has occurred our expert advisors advised that the risk of further bleeding should be evaluated considered but that LMWH can normally be given by four hours after delivery.

Duration of prophylaxis

The duration of prophylaxis should be carefully planned. As always, decisions should be made according to individual patient characteristics and should be discussed with patients and, where doubt exists, with healthcare professionals who have knowledge of VTE in these patients.

Although decisions on duration should be made on the balance of risks and benefits for individual patients, our expert advisors proposed that 7 days thromboprophylaxis is used for all women undergoing an emergency caesarean section, all women undergoing an elective caesarean section with an additional risk factor and all women with Class 3 obesity (BMI > 40kg/m2) after delivery. This is consistent with the RCOG guideline. A duration of prophylaxis of up to 6 weeks may be considered appropriate for women assessed to be at a high risk of postpartum VTE for example those who have had a previous VTE, or women who have additional persisting (greater than 7 days) risk factors such as a wound infection. This is consistent with the RCOG guidelines and is in line with the evidence that there is an extended risk of VTE up to 6 weeks postpartum.

30.8.1 Research Recommendations

There is a lack of evidence for prophylaxis in this population, which may be due to the difficulty in conducting clinical trials in this patient group. Further research for prophylaxis for women who are pregnant or or have given birth within the previous 6 weeks post-partum and who are admitted to hospital is required.

30.8.2 Other recommendations of relevance

The specific recommendations for women who are pregnant or post partum in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:
• risk assessment for VTE and major bleeding (Section 5.9)
• the use of prophylaxis in general (Section 6.7 and 6.8)
• the provision of patient information (Section 32.5)

30.9 Summary of recommendations

➢ Consider offering pharmacological VTE prophylaxis with LMWH (or UFH for patients with renal failure) to women who are pregnant or have given birth within the previous 6 weeks who are admitted to hospital but are not undergoing surgery, and who have one or more of the following risk factors:

• expected to have significantly reduced mobility for 3 or more days
• active cancer or cancer treatment
• age over 35
• critical care admission
• dehydration
• excess blood loss or blood transfusion
• known thrombophilias
• obesity (pre-pregnancy or early pregnancy BMI over 30 kg/m²)
• one or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
• personal history or a first-degree relative with a history of VTE
• pregnancy-related risk factor (such as ovarian hyperstimulation, hyperemesis gravidarum, multiple pregnancy or pre-eclampsia)
• varicose veins with phlebitis.

➢ Consider offering combined VTE prophylaxis with mechanical methods and LMWH to women who are pregnant or have given birth within the previous 6 weeks who are undergoing surgery, including caesarean section.

➢ Offer mechanical and/or pharmacological VTE prophylaxis to women who are pregnant or have given birth within the previous 6 weeks only after assessing the risks and benefits and discussing these with the woman and with healthcare professionals who have knowledge of the proposed method of VTE prophylaxis during pregnancy and post
partum. Plan when to start and stop pharmacological VTE prophylaxis to minimise the risk of bleeding.
31 Patients requiring antiplatelet agents and anticoagulants for other reasons

31.1 Antiplatelet agents

Aspirin, clopidogrel and dipyridamole are prescribed for their anti-platelet actions. Aspirin has been shown to be beneficial to patients with arterial blood vessel disease at a dose of 75mg daily. At this dose it has minimal anti-thrombotic effect. Even at high doses (greater than 300mg daily) it is less efficient at reducing the risk of VTE formation than standard pharmacological methods. Clopidogrel although prescribed predominantly for its antiplatelet effect in the treatment of acute coronary syndromes and following stent insertion is not licensed for VTE prophylaxis as a single agent and is less cost effective than standard pharmacological methods (chapters 9 -1). Dipyridamole is used as an adjunct to anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves. It is also licensed for secondary prevention of ischaemic stroke and transient ischaemic attacks. There are no trials regarding its efficacy in the prophylaxis of VTE.

Patients admitted to hospital whilst taking these medicines are required to have assessment of their VTE risk performed (chapter 5). Patients who have a clinical need for their anti-platelet agents should continue to take their medication. Patients who are assessed as being at increased risk of VTE should receive appropriate prophylaxis with low molecular weight heparin (LMWH) or fondaparinux, once the bleeding risk is reviewed and has been established as low. Mechanical methods can be used where appropriate or if the bleeding risk is considered to be too high for additional pharmacological prophylaxis.
### 31.2 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Do not regard aspirin or other antiplatelet agents as adequate prophylaxis for VTE.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
<td>Consider offering additional mechanical or pharmacological VTE prophylaxis to patients who are having antiplatelet agents to treat other conditions and who are assessed to be at increased risk of VTE (see section 5.9). Take into account the risk of bleeding (see Box 2) and of comorbidities such as arterial thrombosis.</td>
</tr>
<tr>
<td></td>
<td>• If the risk of VTE outweighs the risk of bleeding, consider pharmacological VTE prophylaxis according to the reason for admission.</td>
</tr>
<tr>
<td></td>
<td>• If the risk of bleeding outweighs the risk of VTE, offer mechanical VTE prophylaxis.</td>
</tr>
<tr>
<td><strong>Recommendation —from section 5.9</strong></td>
<td>Regard medical patients as being at increased risk of VTE if they:</td>
</tr>
<tr>
<td></td>
<td>• have had or are expected to have significantly reduced mobility for 3 days or more, or</td>
</tr>
<tr>
<td></td>
<td>• are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors in</td>
</tr>
<tr>
<td><strong>Box 1 —Risk Factors for VTE</strong></td>
<td>• Active cancer or cancer treatment</td>
</tr>
<tr>
<td></td>
<td>• Age over 60 years</td>
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<tr>
<td></td>
<td>• Critical care admission</td>
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<tr>
<td></td>
<td>• Dehydration</td>
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<tr>
<td></td>
<td>• Known thrombophilias</td>
</tr>
<tr>
<td></td>
<td>• Obesity (BMI over 30 kg/m²)</td>
</tr>
<tr>
<td></td>
<td>• One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)</td>
</tr>
<tr>
<td></td>
<td>• Personal history or a first degree relative with a history of VTE</td>
</tr>
<tr>
<td></td>
<td>• Use of hormone replacement therapy</td>
</tr>
<tr>
<td></td>
<td>• Use of oestrogen-containing contraceptive therapy</td>
</tr>
<tr>
<td></td>
<td>• Varicose veins with phlebitis.</td>
</tr>
</tbody>
</table>
|                  | For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6
**Recommendation—from section 5.9**

Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis *. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.

*Consult the summary of product characteristics for the pharmacological VTE prophylaxis being used or planned for further details.

**Box 2-Bleeding Risk Factors**

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10⁹/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand’s disease)

**Relative values of different outcomes**

The outcomes considered important by the Guideline Development Group (GDG) were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

Additionally patients who are receiving antiplatelet agents are likely to have additional comorbidities, such as a high arterial side thrombosis risk. These factors meant that the GDG felt that although existing antiplatelet agents should not be stopped, additional thromboprophylaxis should be considered to ensure that patients are adequately protected.

**Trade off between clinical benefit and harms**

The risks of developing VTE may be high and these need to be weighed up against the risks of possible side effects such as bleeding which is increased if antiplatelet agents are also being used.
Economic considerations

There is no relevant cost-effectiveness evidence specifically for this population subgroup.

In four out of five of the population subgroups that we modelled, there was enough evidence to include aspirin (Chapters 9 to 12). In all four models, aspirin alone was one of the least effective strategies at increasing quality adjusted life years (QALYs) and least cost-effective. Conversely low molecular weight heparin (LMWH) was consistently one of the most effective and cost-effective strategies. Mechanical prophylaxis in population subgroups where there is evidence, also seems to be more effective and cost-effective than aspirin alone.

Two of our models (Chapters 9 and 10) considered the combination of high dose aspirin and unfractionated heparin. In both cases the strategy reduced QALYs compared with no prophylaxis and hence the combination was neither effective nor cost-effective. This was due to a very high bleeding increase, as estimated from our network meta-analysis. However, these studies did use very high doses of aspirin (sometimes up to 1000mg per day).

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

The evidence for adding other pharmacological agents to aspirin is very sparse. There are two studies in general surgery patients where all patients received high dose aspirin (>300mg per day) and patient in one arm of the trial also received UFH. These trials reported a significant decrease in DVT events and a significant increase in major bleeding (Forest plots 149-151, Appendix E).

There were five studies in patients undergoing surgery (2 general surgery, 1 elective hip replacement surgery, 2 mixed surgery) which compared the addition of high dose aspirin (>300mg per day) to a background of UFH, which was received by patients in both arms of the study. The combined results of these studies do not report any statistically different findings for DVT, PE or major bleeding (Forest plots 161-163, Appendix E).

In addition, two studies in stroke patients which add UFH or LMWH to aspirin (unknown dose). Combining these studies showed that LMWH and aspirin had a statistically significant reduction in DVT events without significant increase in bleeding compared with UFH and aspirin (chapter 24, Forest plots 183-186, Appendix E).

Other considerations

The GDG found it difficult to identify situations where it was clear that pharmacological thromboprophylaxis should be used
in addition to antiplatelet agents and felt that healthcare professionals should use guidance provided in the BNF or summary of product characteristics for the agents being used or those which are planned. Individual assessment of the risks and benefits is key and this is likely to require clinical judgement.

For patients in whom additional pharmacological thromboprophylaxis was deemed inappropriate but who are considered at high risk of VTE, mechanical methods (such as anti-embolism stockings, intermittent pneumatic compression devices) can be considered as an alternative which does not increase the risk of bleeding. Where mechanical methods are provided they should be used in line with the recommendations in section 6.7.

31.3 Anticoagulant agents

Patients who are admitted who are already receiving anticoagulation therapy, or who are started on full dose anti-coagulation using heparin, do not require additional pharmacological VTE prophylaxis. Patients (including those admitted taking oral thrombin or oral Xa inhibitors) should still have a VTE assessment performed (section 5.9). Treatment should be continued unless a clinical contraindication has arisen. If treatment is stopped the patients are at risk of VTE and they should be considered for VTE prophylaxis accordingly.

31.3.1 Warfarin bridging

Some patients admitted to hospital for surgical procedures will already be receiving warfarin. Healthcare professionals involved in their care will be required to make decisions about whether to, and when to stop, the warfarin and replace with other anticoagulant agents such as low molecular weight heparin. Warfarin bridging was not prioritised for a full systematic review. However, the guideline development group considered it to be an important and complex area which will involve the assessment of risks and benefits for each patient. An example of a strategy for warfarin bridging is included in Appendix H. When unsure of the appropriate action to take, healthcare professionals should consult colleagues with specialist knowledge in this area.

31.4 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are taking vitamin K antagonists and who are within their therapeutic range, providing anticoagulant therapy is continued.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative values of different outcomes</td>
<td>The outcomes considered important by the GDG were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).</td>
</tr>
<tr>
<td><strong>Trade off between clinical benefit and harms</strong></td>
<td>The risk of developing venous thromboembolism is weighed against the increase risk in bleeding caused by pharmacological prophylaxis.</td>
</tr>
<tr>
<td><strong>Economic considerations</strong></td>
<td>There is no relevant cost-effectiveness evidence specifically for this population subgroup. Vitamin K antagonists (VKA) are shown to be an effective and cost-effective strategy in several groups of patient (Chapters 9 to 12). In the case of patients already on VKAs, they can obtain the benefits of prophylaxis without any additional drug and monitoring costs.</td>
</tr>
<tr>
<td><strong>Quality of evidence</strong></td>
<td>There is evidence across a number of different populations that vitamin K antagonists are effective at reducing the risk of VTE.</td>
</tr>
<tr>
<td><strong>Other considerations</strong></td>
<td>Doses of anticoagulants used for treatment are usually higher than for prophylaxis use and so are likely to be suitable for reducing VTE risk although they will increase bleeding risk.</td>
</tr>
</tbody>
</table>

| **Recommendation** | Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are having full anticoagulant therapy (for example, fondaparinux sodium, LMWH or UFH). |

| **Relative values of different outcomes** | The outcomes considered important by the GDG were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). |

| **Trade off between clinical benefit and harms** | The risk of developing venous thromboembolism is weighed against the increase risk in bleeding caused by pharmacological prophylaxis. |
| **Economic considerations** | There is no relevant cost-effectiveness evidence specifically for this population subgroup. These drugs have been shown to be an effective and cost-effective strategy in several groups of patient (Chapters 9 to 12 and 23). In the case of patients already on these drugs, they can obtain the benefits of prophylaxis without any additional drug and costs. |
| **Quality of evidence** | There is evidence across a number of different populations that LMWH, UFH and fondaparinux are all effective at reducing the risk of VTE. |
| **Other considerations** | Doses of anticoagulants used for treatment are usually higher than for prophylaxis use and so are likely to be suitable for reducing VTE risk although they will increase bleeding risk. |
31.4.1 Other recommendations of relevance

The specific recommendations for patients already using antiplatelets and/or anticoagulants in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- patients undergoing cardiac surgery (Section 15.7)
- patients undergoing vascular surgery (Section 16.7)
- patients with stroke (Section 24.7)
- patients with acute coronary syndromes (Section 25.7)
- patients with cancer (Section 26.7)

31.5 Recommendations for research

A top priority research recommendation was identified for the use of prophylactic-dose anticoagulants in stroke patients (section 2.3.4).

31.6 Summary of recommendations

- Do not regard aspirin or other antiplatelet agents as adequate prophylaxis for VTE.
- Consider offering additional mechanical or pharmacological VTE prophylaxis to patients who are having antiplatelet agents to treat other conditions and who are assessed to be at increased risk of VTE (see section 5.9). Take into account the risk of bleeding (see Box 2) and of comorbidities such as arterial thrombosis.
  - If the risk of VTE outweighs the risk of bleeding, consider offering LMWH or UFH (for patients with renal failure).
  - If the risk of bleeding outweighs the risk of VTE, offer mechanical VTE prophylaxis.
- Regard medical patients as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more or
  - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors in Box 1
- Regard surgical and trauma patients as being at increased risk of VTE if they meet one of the following criteria:
- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more risk factors shown in Box 1.

- Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.

**Box 1 Risk factors for VTE**

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m²)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and 6 weeks post partum)
PATIENTS REQUIRING ANTIPLATELET AGENTS AND ANTICOAGULANTS FOR OTHER REASONS

Box 2 Risk factors for bleeding

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international noramlised ratio [INR] higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10^9/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand’s disease)

- Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are taking vitamin K antagonists and who are within their therapeutic range, providing anticoagulant therapy is continued.

- Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are having full anticoagulant therapy (for example, fondaparinux sodium, LMWH or UFH).
32 Provision of information to patients and planning for discharge

32.1 Introduction

Medical professionals have a responsibility to inform patients under their care about their proposed interventions. In this context it means providing information on venous thromboembolism (VTE) risk, the optimal methods to prevent this, the consequences of not receiving prophylaxis and possible side effects of the prophylactic intervention. This opportunity for discussion should be made available before provision of prophylaxis, unless this is not clinically possible (for example unconsciousness) or when any delays could be seriously detrimental.

Good communication between the healthcare professionals and patients is essential. In the context of this guideline, the patients may be newly admitted to the hospital and often find the situation overwhelming. This is not the best time to assimilate complex information and make decisions, and healthcare professionals should take this into account when communicating with the patients. Patients should be encouraged to ask questions at any point during their stay and healthcare professionals may have to check that the patients understand the information from time to time.

The main class of drugs used for thromboprophylaxis is heparin; either low molecular weight heparins (LMWH) or unfractionated heparin (UFH). Heparin is a sulphated glycosaminoglycan derived from animal tissues, and those marketed in the UK are principally of porcine origin. Using animal derived products may be of concern to patients of certain religious or personal beliefs. Therefore, healthcare professionals should be prepared to discuss these concerns with the patients (or their caregivers) and provide them with information to help them to address any ethical or religious concerns. Depending on the individual clinical condition of the patients, the synthetic alternatives to heparin may be less suitable or have its disadvantages. Clinicians should ensure that patients are aware of these issues.

32.1.1 Aim

The aim of this section is two fold:

- to examine whether the education of patients who were admitted to hospital about VTE or its prophylaxis methods:
- reduced the number of DVTs and pulmonary embolisms or
- affected any of the outcomes identified as important by the Guideline Development Group (Section 3.5) or
- influenced patient adherence to thromboprophylaxis

- to find out what type of information might be required by patients receiving thromboprophylaxis measures.

32.1.2 Methods

We searched for studies that examined the effect of providing information to patients on VTE or on methods of prophylaxis. We also searched for studies which were designed to examine the information required by patients. This search was not limited to randomised control trials but included observational and qualitative studies as these can provide information which is applicable to current practice. The focus of this evidence review was to obtain relevant information and to interpret it in a meaningful manner. For more details about study designs and quality, see Chapter 3.

32.2 Summary of identified studies

32.2.1 Impact of providing information on VTE outcomes

No studies which examined the impact of providing patient information on reducing VTE outcomes were identified.

32.2.2 Impact of providing information on patient adherence

One observational study examined the impact of providing surgical patients with a small leaflet along with increasing nursing awareness through discussions on patient adherence. The leaflet was printed with the phrase “Please notify your nurse if your compression stockings are not on. They are important for preventing blood clots during the hospital stay”. Patient adherence to intermittent pneumatic compression devices (IPCD) did not significantly change after these interventions.

32.2.3 Information requirement for patients who need thromboprophylaxis

Two qualitative studies conducted in the UK provided some insight about areas where patients may benefit from receiving more information about VTE prevention.

A semi-structured interview study among 28 palliative care patients who received at least 5 days of LMWH prophylaxis found that most patients interviewed were not aware of the signs and symptoms of VTE. Patients in this study indicated that the main source of information about VTE was about long distance flights (Evidence Table 62, Appendix D).

The other study was telephone interviews conducted to investigate what type of information should go into a patient information leaflet for anti-embolic stocking (Evidence table 61, Appendix D). Twelve patients who had been hospitalised within the past two months and had worn anti-embolism stockings for at least 48 hours participated; recruitment stopped when theme saturation was reached. The patients were asked about their experience and whether they had received information for specific aspects of anti-embolism stocking usage.
The study identified areas which will benefit from providing more patient information by examining aspects which went “wrong” due to patient’s lack of awareness. The following are some relevant findings from the study:

- Most patients did not remember receiving information about VTE or anti-embolism stockings. Some patients did not understand why they had to wear the anti-embolism stockings; this resulted in misunderstanding that they could take them off if they did not “work” for them. Not all patients understood how or when to put on or take off the anti-embolic stockings.

- Some patients had indicated that it would be useful to have some information, especially something to read. Despite that, they were unlikely to actively ask for information about anti-embolism stockings. Reasons given include:
  - They believed they would have been told, if there was something important they needed to know. Otherwise, a lot of things should be based on “common sense”
  - In the hospital setting, their role as a patient is “You do as you are told”, i.e. not asking questions.

- Patients depended on their health care professionals, as there were few alternative sources of information other than from friends or family with history of thromboembolism and long haul flights.

32.3 Conclusions on information for patients

The evidence suggests that the provision of patient information about risks of VTE and methods of VTE prophylaxis may be inadequate in some circumstances. Patients in the studies were confused about the condition and therefore unlikely to act appropriately. Provision of relevant and adequate information is a prerequisite for the empowerment of patients, which will contribute to their acceptance and adherence to the treatment provided.

32.4 Summary of evidence

<table>
<thead>
<tr>
<th>Evidence statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>No studies on the impact of patient education on venous thromboembolism outcomes were identified.</td>
</tr>
<tr>
<td>One observational study which provided only a small patient information leaflet did not find significant improvement in patient adherence to intermittent pneumatic compression devices after the intervention.</td>
</tr>
<tr>
<td>Two small qualitative studies found patients lack information about signs and symptoms of venous thromboembolism.</td>
</tr>
<tr>
<td>One small qualitative study among patients who received anti-embolism / graduated compression stockings found patients lacked certain information which could have improved their adherence or experience of care.</td>
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</tbody>
</table>
32.5 Recommendations and link to evidence – in hospital patient information

**Recommendation**

Before starting VTE prophylaxis, offer patients and/or their families or carers verbal and written information on:

- the risks and possible consequences of VTE
- the importance of VTE prophylaxis and its possible side effects
- the correct use of VTE prophylaxis (for example, anti-embolism stockings, foot impulse or intermittent pneumatic compression devices)
- how patients can reduce their risk of VTE (such as keeping well hydrated and, if possible exercising and becoming more mobile).

**Relative values of different outcomes**

Reducing the risk of venous thromboembolism and its associated short and long term consequences; and reducing unwanted effects of thromboprophylaxis methods are the most important outcomes. Increased patient awareness, adherence and correct use of prophylaxis methods could lead to a reduction in these VTE outcomes as well as improving the patient’s experience and satisfaction.

**Trade off between clinical benefit and harms**

The Guideline Development Group considered that it was important that patients are fully aware of their VTE risks and the methods of reduction available. Opportunities for discussing and addressing any concerns about methods of thromboprophylaxis and associated risks must also be given. An informed patient would be better able to balance the benefits of thromboprophylaxis against the inconvenience or concerns. There is potential for harm if this information is not provided, for example resulting in low concordance with prophylaxis or delaying seeking medical help due to lack of symptom awareness. Improved understanding of how to reduce the risk of VTE also has the potential to reduce anxiety and improve patient participation.

**Economic considerations**

Information provision comes with its associated costs, such as time of health care professionals and costs associated with producing materials. However, the potential benefits of improving thromboprophylaxis adherence and reducing subsequent VTE events are likely to be cost-effective.

**Quality of evidence**

All studies were quality assessed using quality checklists appropriate to the study design where available. Where appropriate study design checklists were not available, attempts were made to ensure the results of the included studies were as free from bias as possible.

There is not a large body of evidence to support the
recommendations.

The setting, population studied and type of intervention used are important factors which could affect the relevance of studies about provision of patient information to the various subpopulations of patients in this guideline.

Only two UK qualitative studies provided some relevant evidence about the potential issues in two intervention methods. Both studies were consistent in pointing out that patients may not be aware of signs and symptoms of VTE. An observational study was conducted in the United States and it is uncertain how applicable this evidence is.

It is particularly difficult to interpret studies on the impact of information provision. Information provision could only be expected to be effective if the information is relevant, acceptable to patients and provided using an effective medium. The study which provided limited information did not show any improvement in adherence. This could be due to limited amount of information provided or ineffective method of delivery.

Other considerations

Despite limited evidence, the Guideline Development Group considered that it was good practice and important to provide patients with information about the risk of VTE and what general methods they can do to reduce it such as early mobilisation, the importance of using prophylaxis correctly and information on the use any prophylaxis that they have been provided with.

Language barriers should not be a reason for non-provision of information. Provision on a national basis of translated documents should be undertaken.

Recommendation

Be aware that heparins are of animal origin and this may be of concern to some patients*. For patients who have concerns about using animal products, consider offering synthetic alternatives based on clinical judgement after discussing their suitability, advantages and disadvantages with the patient.


Trade off between clinical benefit and harms

Different prophylaxis methods have different levels of evidence of efficacy and safety in different populations. Ideally, the choice of agent should be based on the most evidence-based and cost-effective agent for a given population. However, in situations where there are strong
patient concerns, these need to be discussed openly.

**Economic considerations**

Where a choice of agents is provided within a recommendation this is based either on the results of the cost-effectiveness model for that population, or on the extrapolation of cost-effectiveness results in other populations. In these circumstances the guideline development group were unable to conclusively state which of the strategies were the most cost-effective. Another of the reasons for local factors to influence choice of drug is that the contract prices (and therefore cost-effectiveness) of some of the drugs vary considerably between NHS Trusts.

**Other considerations**

While it is important to offer patients alternatives if there are concerns about using animal based products, it is also important that patients are aware of the clinical benefits or disadvantages (if any) of using these alternative products. If religious beliefs are a source of concern, the patients should be aware of the official stand of religious bodies about the product. Patients will only be able to make a good decision if they have a complete picture of the pros and cons of using these products. Where information is available, it will be useful to direct the patients to these information sources. There is information for patients with specific concerns e.g. “Porcine Derived Products” booklet which is refered to in the Department of Health document titled “Religion or belief: a practical guide for the NHS” (available from [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_093133](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PolicyAndGuidance/DH_093133)).

If the relative risks and benefits are explained to the patient (e.g. that fondaparinux may not be as effective as heparin), and the decisions clearly documented in the patient’s notes, the patient is perfectly within their rights to choose a less effective option, however difficult that might be for the clinician who wants to provide the best care.
32.6 Recommendations and link to evidence – planning for discharge

**Recommendation**  
As part of the discharge plan, offer patients and/or their families or carers verbal and written information on:

- the signs and symptoms of deep vein thrombosis and pulmonary embolism
- the correct and recommended duration of use of VTE prophylaxis at home (if discharged with prophylaxis)
- the importance of using VTE prophylaxis correctly and continuing treatment for the recommended duration (if discharged with prophylaxis)
- the signs and symptoms of adverse events related to VTE prophylaxis (if discharged with prophylaxis)
- The importance of seeking help and who to contact if they have any problems using the prophylaxis (if discharged with prophylaxis)
- the importance of seeking medical help if deep vein thrombosis, pulmonary embolism or other adverse events are suspected.

**Recommendation**  
Ensure that patients who are discharged with anti-embolism stockings:

- understand the benefits of wearing them
- understand the need for daily hygiene removal
- are able to remove and replace them, or have someone available who will be able to do this for them
- know what to look for such as skin marking, blistering or discolouration, particularly over the heels and bony prominences
- know who to contact if there is a problem.

**Recommendation**  
Ensure that patients who are discharged with pharmacological and/or mechanical VTE prophylaxis are able to use it correctly, or have arrangements made for someone to be available who will be able to help them.

**Recommendation**  
Notify the patient’s GP if the patient has been discharged with pharmacological and/or mechanical VTE prophylaxis to be used at home.

**Relative values of different outcomes**  
Reducing the risk of venous thromboembolism and its associated short and long term consequences; and reducing unwanted effects of thromboprophylaxis methods are the most important outcomes. Increased patient awareness, adherence and correct use of prophylaxis methods could lead to a reduction in these...
VTE outcomes as well as improving the patient's experience and satisfaction.

**Trade off between clinical benefit and harms**

The Guideline Development Group considered that it was important that patients are fully aware of their VTE risks and the methods of reduction available. Opportunities for discussing and addressing any concerns about methods of thromboprophylaxis and associated risks must also be given. An informed patient would be better able to balance the benefits of thromboprophylaxis against the inconvenience or concerns. There is potential for harm if this information is not provided, for example resulting in low concordance with prophylaxis or delaying seeking medical help due to lack of symptom awareness. Improved understanding of how to reduce the risk of VTE also has the potential to reduce anxiety and improve patient participation.

**Economic considerations**

Information provision comes with its associated costs, such as time of health care professionals and costs associated with producing materials. However, the potential benefits of improving thromboprophylaxis adherence and reducing subsequent VTE events are likely to be cost-effective.

**Quality of evidence**

All studies were quality assessed using quality checklists appropriate to the study design where available. Where appropriate study design checklists were not available, attempts were made to ensure the results of the included studies were as free from bias as possible.

There is not a large body of evidence to support the recommendations.

The setting, population studied and type of intervention used are important factors which could affect the relevance of studies about provision of patient information to the various subpopulations of patients in this guideline.

Only two UK qualitative studies provided some relevant evidence about the potential issues in two intervention methods. Both studies were consistent in pointing out that patients may not be aware of signs and symptoms of VTE. An observational study was conducted in the United States and it is uncertain how applicable this evidence is.

It is particularly difficult to interpret studies on the impact of information provision. Information provision could only be expected to be effective if the information is relevant, acceptable to patients and provided using an effective medium. The study which provided limited information did not show any improvement in adherence. This could be due to limited amount of information provided or ineffective method of delivery.
**Other considerations**

Despite limited evidence, the Guideline Development Group considered that it was good practice and important to provide patients with information about the risk of VTE and what they can do to reduce it, the signs and symptoms of VTE, how to use any prophylaxis that they will be administering at home and the importance of using these methods correctly. Additionally, patients should know who to call if they have a problem with their prophylaxis and be advised to consult their GP after they are discharged from hospital if they suspect VTE, even if they are using thromboprophylaxis.

Expert advice from a general practitioner (GP) highlighted that the GP should be informed if a patient is discharged with prophylaxis to ensure that appropriate follow-up care can be offered.

Language barriers should not be a reason for non-provision of information. Provision on a national basis of translated documents should be undertaken.

**32.7 Related recommendations**

The specific recommendations for provision of information to patients should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

**32.8 Summary of recommendations on provision of information for patients**

- Before starting VTE prophylaxis, offer patients and/or their families or carers verbal and written information on:
  - the risks and possible consequences of VTE
  - the importance of VTE prophylaxis and its possible side effects
  - the correct use of VTE prophylaxis (for example, anti-embolism stockings, foot impulse or intermittent pneumatic compression devices).
  - how patients can reduce their risk of VTE (such as keeping well hydrated and, if possible exercising and becoming more mobile)

- Be aware that heparins are of animal origin and this may be of concern to some patients*. For patients who have concerns about using animal products, consider offering synthetic alternatives based on clinical judgement after discussing their suitability, advantages and disadvantages with the patient.


- As part of the discharge plan, offer patients and/or their families or carers verbal and written information on:
• the signs and symptoms of deep vein thrombosis and pulmonary embolism
• the correct and recommended duration of use of VTE prophylaxis at home (if discharged with prophylaxis)
• the importance of using VTE prophylaxis correctly and continuing treatment for the recommended duration (if discharged with prophylaxis)
• the signs and symptoms of adverse events related to VTE prophylaxis (if discharged with prophylaxis)
• the importance of seeking help and who to contact if they have any problems using the prophylaxis (if discharged with prophylaxis)
• the importance of seeking medical help if deep vein thrombosis, pulmonary embolism or other adverse events are suspected.

➢ Ensure that patients who are discharged with anti-embolism stockings:
  • understand the benefits of wearing them
  • understand the need for daily hygiene removal
  • are able to remove and replace them, or have someone available who will be able to do this for them
  • know what to look for such as skin marking, blistering or discolouration, particularly over the heels and bony prominences
  • know who to contact if there is a problem.

➢ Ensure that patients who are discharged with pharmacological prophylaxis are able to use it correctly, or have arrangements made for someone to be available who will be able to help them

➢ Notify the patient’s GP if the patient has been discharged with pharmacological and/or mechanical VTE prophylaxis to be used at home.


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