New Anticoagulants in treatment of DVT

Dr Neil Smith
Consultant Haematologist
Heart of England NHS Foundation Trust
Venous thromboembolism

- UK: 90,000 DVT cases/year, 54,000 of them associated with PE\(^1\)
- France: 100,000 DVT cases/year, fatal PEs: 20,000/year\(^2\)
- Germany: 180,000 DVT cases/year, fatal PEs: 30,000–40,000/year
Venous Ulcers

Chronic PE

DVT

PE

Deep vein insufficiency

Death

Post-thrombotic syndrome

Pulmonary hypertension

Chronic PE

Venous Ulcers
What methods of treating VTE
LMWH + VKA - is effective but demanding

NHS Choices. Treating deep vein thrombosis
Parenteral anticoagulants—drawbacks

Unfractionated Heparin, LMW Heparin, (fondaparinux) ¹

- Parenteral administration
- Monitoring and dose adjustment
- Heparin-induced thrombocytopenia
- Weight-adjusted dosing
- Osteoporosis
- Renal excretion (higher bleeding if low CrCl)
  - Cost
  - Long plasma half-life, increased risk of bleeding?

Vitamin K antagonists – major drawbacks

- Unpredictable response
- Slow onset/offset of action
- Narrow therapeutic window (INR range 2-3)
- Numerous food-drug interactions
- Routine coagulation monitoring
- Numerous drug-drug interactions
- Frequent dose adjustments
- Risk of Bleeding Complications

Warfarin therapy has several limitations that make it difficult to use in practice

- Warfarin was #1 in 2003 and 2004 in the number of mentions of “deaths for drugs causing adverse effects in therapeutic use”
- Warfarin caused 6% of the 702,000 ADEs treated in the ED/year; 17% required hospitalization

The ‘ideal’ oral anticoagulant

- Fixed doses,
- No need for routine coagulation monitoring
- Wide therapeutic window
- Rapid onset and offset of action
- Few side effects
- Predictable PK and PD
- Low propensity for food and drug interactions
- Preferably once daily
- Availability of a reversal strategy
VKAs target multiple coagulation factors

VKAs inhibit the synthesis of functional coagulation Factors II, VII, IX and X
LMWH: indirect inhibitor of FXa and thrombin

Indirect inhibition by LMWH via AT

Where to inhibit the coagulation cascade?

Inactive factor  
Active factor  
Transformation  
Catalysis  
Clot formation  
Initiation  
Propagation  
Thrombin  
Fibrinogen  
Fibrin  
Prothrombin  
X  
IX  
II  
TF  
VIIa  
VII  
IX  
Xa  
IIa
## Clotting proteins

<table>
<thead>
<tr>
<th>Clotting protein</th>
<th>Mol Weight</th>
<th>Plasma Conc</th>
<th>g/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>340000</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Prothrombin</td>
<td>72000</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Factor XII</td>
<td>80000</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Factor V</td>
<td>330000</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Factor X</td>
<td>56000</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Factor IX</td>
<td>56000</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Factor XI</td>
<td>160000</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Factor VII</td>
<td>50000</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>Factor VIII</td>
<td>330000</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>
Vitamin K antagonists (VKA) inhibit the synthesis of the coagulation Factors II, VII, IX, X.

**Legend:**
- inactive factor
- active factor
- transformation
- catalysis

**Direct Factor Xa inhibition:**
- Rivaroxaban
- Apixaban
- Edoxaban

**Indirect via antithrombin:**
- Fondaparinux

**Indirect via antithrombin:**
- Low molecular weight heparin
- Unfractionated heparin

**Direct thrombin inhibition:**
- Hirudin
- Argatroban
- Bivalirudin
- Dabigatran

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www.thrombosisadviser.com
What is rivaroxaban?
Rivaroxaban

- Binds clot-bound and free factor Xa with high affinity and specificity
- Bioavailability: 80–100%
- Renal excretion: 33% (active component)
- Half-life: 5–9 hours for young patients
- Half-life: 11–13 hours for elderly patients
Rivaroxaban

- No interaction with food
- No interaction with CYP450
- Predictable anticoagulant effect
- Fixed dose, 10, 15 and 20 mg tabs
- No routine coagulation monitoring or platelet monitoring
- No liver toxicity based on available clinical data
Rapidly absorbed: $C_{\text{max}}$ within 2–4 hours of oral administration

![Graph showing plasma concentration over time for different doses of rivaroxaban.](image-url)
Licensed, recommended and accepted by national guidelines

- Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery
- Prevention of stroke and systemic embolism in eligible adult patients with non-valvular atrial fibrillation - SPAF
- Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults

1. NICE. Technology appraisal guidance 261. July 2012
Licensed:

- Treatment of acute symptomatic pulmonary embolism with or without symptomatic deep vein thrombosis and the prevention of recurrent venous thromboembolic events

- Awaiting NICE Approval - May 2013
Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

Rivaroxaban EINSTEIN Acute DVT Study

Confirmed acute symptomatic DVT without symptomatic PE

N=3,449

R

EINSTEIN DVT¹
Treatment period of 3, 6 or 12 months

Day 1

Day 21

Rivaroxaban

15 mg bid

Rivaroxaban

20 mg od

Enoxaparin 1.0 mg/kg bid for at least 5 days, followed by VKA to start ≤48 hours, target INR range 2.0–3.0

30-day observation after treatment cessation
<table>
<thead>
<tr>
<th>Outcome Efficacy</th>
<th>Rivaroxaban</th>
<th>Enoxaparin–VKA</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat population</td>
<td>1731</td>
<td>1718</td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>36 (2.1)</td>
<td>51 (3.0)</td>
<td>0.68 (0.44–1.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p &lt;0.001†</td>
</tr>
<tr>
<td>Type of recurrent VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal PE</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PE could not be ruled out</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Nonfatal PE</td>
<td>20</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Recurrent DVT plus PE</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>14</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Net clinical benefit in terms of VTE plus major bleeding</td>
<td>51 (2.9)</td>
<td>73 (4.2)</td>
<td>0.67 (0.47–0.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p = 0.03</td>
</tr>
</tbody>
</table>
EINSTEIN DVT: primary efficacy outcome
- Time to first event

## EINSTEIN DVT: principal safety outcome analysis

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n=1,718)</th>
<th>Enox/VKA (n=1,711)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n  (%)</td>
<td>n  (%)</td>
<td>p-value</td>
</tr>
<tr>
<td>First major or non-major clinically relevant bleeding</td>
<td>139 (8.1)</td>
<td>138 (8.1)</td>
<td>0.97 (0.76–1.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.77</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>14 (0.8)</td>
<td>20 (1.2)</td>
<td>0.65 (0.33–1.30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.21</td>
</tr>
<tr>
<td>Contributing to death</td>
<td>1 (&lt;0.1)</td>
<td>5 (0.3)</td>
<td></td>
</tr>
<tr>
<td>In a critical site</td>
<td>3 (0.2)</td>
<td>3 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Associated with fall in haemoglobin ≥2 g/dl and/or transfusion of ≥2 units</td>
<td>10 (0.6)</td>
<td>12 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Non-major clinically relevant bleeding</td>
<td>126 (7.3)</td>
<td>119 (7.0)</td>
<td></td>
</tr>
</tbody>
</table>

Net clinical benefit in Acute DVT Study:
- primary efficacy outcome + major bleeding

HR = 0.67
ARR = 1.3%
RRR = 33%
p=0.03 for superiority

Rivaroxaban
(n=1731)

Enoxaparin/VKA
(n=1718)

Rivaroxaban EINSTEIN extension

Confirmed symptomatic DVT or PE completing 6 or 12 months of rivaroxaban or VKA

EINSTEIN Extension
Treatment period of 6 or 12 months

N=1,197
Rivaroxaban 20 mg od
R
Placebo
Day 1
30-day observation after treatment cessation
EINSTEIN Extension:
- primary efficacy outcome analysis – time to first event

NNT=15

Placebo (n=594)
HR=0.18; p<0.001
RRR=82%
ARR=5.8%

Rivaroxaban (n=602)

<table>
<thead>
<tr>
<th>Outcome</th>
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<th>Enoxaparin–VKA</th>
<th>Hazard Ratio (95% CI) P Value no. (%)</th>
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<td>18</td>
<td></td>
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<td>73 (4.2)</td>
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</tr>
<tr>
<td>Outcome Safety</td>
<td>Rivaroxaban</td>
<td>Enoxaparin–VKA</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>----------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Safety population</td>
<td>1718</td>
<td>1711</td>
<td></td>
</tr>
<tr>
<td>First major or clinically relevant nonmajor bleeding occurring during treatment</td>
<td>139 (8.1)</td>
<td>138 (8.1)</td>
<td>0.97 (0.76–1.22)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>14 (0.8)</td>
<td>20 (1.2)</td>
<td>0.65 (0.33–1.30)</td>
</tr>
<tr>
<td>Contributing to death In a critical site</td>
<td>1</td>
<td>5 (0.3)</td>
<td>(0.2)</td>
</tr>
<tr>
<td>Associated with a fall in Hb of ≥2 g/dl and/or transfusion ≥2 units</td>
<td>10</td>
<td>12 (0.7)</td>
<td>(&lt;0.1)</td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding</td>
<td>126 (7.3)</td>
<td>119 (7.0)</td>
<td>(0.6)</td>
</tr>
<tr>
<td>Total deaths through end of intended treatment period</td>
<td>38 (2.2)</td>
<td>49 (2.9)</td>
<td>0.67 (0.44–1.02)</td>
</tr>
<tr>
<td>Outcome Safety</td>
<td>Rivaroxaban</td>
<td>Enoxaparin–VKA</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>----------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE, or PE not ruled out</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
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<tr>
<td>Any event emerging during treatment</td>
<td>1078 (62.7)</td>
<td>1080 (63.1)</td>
<td></td>
</tr>
<tr>
<td>Any serious event emerging during treatment</td>
<td>201 (12.0)</td>
<td>233 (13.6)</td>
<td></td>
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<tr>
<td>Any event resulting in permanent discontinuation of study drug</td>
<td>85 (4.9)</td>
<td>81 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Any event leading to or prolonging hospitalization</td>
<td>193 (11.2)</td>
<td>211 (12.3)</td>
<td></td>
</tr>
</tbody>
</table>
## NICE’s Incremental Cost-effectiveness Ratios (ICER)

<table>
<thead>
<tr>
<th>Patient group</th>
<th>ICER (£/QALY)</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months anticoagulation</td>
<td>RIV dominates</td>
<td>Rivaroxaban is cost saving and more effective than standard of care</td>
</tr>
<tr>
<td>6 months anticoagulation</td>
<td>£3,200</td>
<td>Rivaroxaban cost-effective</td>
</tr>
<tr>
<td>12 months anticoagulation</td>
<td>£14,900</td>
<td>Rivaroxaban cost-effective</td>
</tr>
<tr>
<td>Long term</td>
<td>£19,400</td>
<td>Rivaroxaban cost-effective</td>
</tr>
<tr>
<td>Cancer</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
The Heart of England NHS Foundation
Trust experience

◆ June-September 2012:
  Recurrent DVT patients on long-term phenindione anticoagulation

  Special cases: patients on LMWH, cancer patients, AF patients intolerant of other anticoagulation drugs

◆ Late November 2012:
  First choice for DVT treatment
Referral pathway for Acute DVT:

- AMU - Prescription of 15 mg bd for 3 weeks only
- Day 14-20 Review visit to NOAC clinic
  Check for side-effects, change to 20 mg od
  Send RiCAD to GP and discharge
PATIENT ALERT CARD

Xarelto® 15mg
Xarelto® 20mg

• KEEP THIS CARD WITH YOU AT ALL TIMES
• PRESENT THIS CARD TO EVERY PHYSICIAN OR DENTIST PRIOR TO TREATMENT
**PATIENT RECEIVING RIVAROXABAN THERAPY: HAEMORRHAGE PROTOCOL**

**STOP: RIVAROXABAN**

Request: 1. Coagulation screen to include PT (INR), APTT (consider thrombin time) [Important to document time of last dose of RIVAROXABAN]
2. Full blood count and renal function / eGFR

PT (and TT) prolonged

Rivaroxaban anticoagulant effect maybe present (consider oral charcoal if Rivaroxaban ingestion < 2 hours)

MAJOR BLEED

- Optimise tissue oxygenation
- Control haemorrhage
  - Compression
  - Surgical intervention
- Tranexamic Acid (25 mg/kg i.v.)
- Red Cell transfusion
  - Aim Hb > 7 g/dl
- Platelet transfusion
  - Aim Plt > 50 x 10⁹/l or
  - If CNS bleed aim Plt > 100 x 10⁹/l

Prothrombin Complex Concentrate (PCC)
- Beriplex 35 - 50 U/kg or
- Octaplex 40 U/kg (max 3000 U in one dose)

LIFE THREATENING BLEED

Continues to bleed

MILD BLEED

- Mechanical compression
- Tranexamic Acid
  - oral 25 mg/kg
  - i.v. 15 mg/kg
- Delay next Rivaroxaban dose or discontinue treatment

**Contact Haematologist**

PT (and TT) normal

NO Rivaroxaban anticoagulant effect likely to be present

**MAJOR BLEED**

**LIFE THREATENING BLEED**

**MILD BLEED**

**Rivaroxaban anticoagulant effect maybe present**

**Major Bleed:** Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome
Case Studies
Young patient, recurrent DVTs

- Mr Bean, 31 years old

- 1st DVT/PE in 2003 following immobility,
- Rx Warfarin for 3 months
- One week off VKA developed new multiple DVTs, put again on warfarin (INR: 2.0-3.0), post-phlebitic leg
Young patient, recurrent DVTs

- 02-03/2012: Multiple visits to AMU for suspicion of DVT, eventual diagnosis of left saphenous vein thrombosis, thrombophilia screening negative, INR target raised

- 05/2012: New DVT episode, VKA changed to enoxaparin 200 mg daily

- 10/2012: Happy to change LMWH for rivaroxaban 20 mg od
Mrs Marple, 78 years old

- July 2011: left calf DVT, Rx clexane for 3 months
- 4 weeks after finishing: new calf DVT, Rx clexane
- PMH: dementia, diabetes, epilepsy, hypelipidemia
- Current medication: metformin, levothyroxine, propranolol, simvastatin, solpadeine, valproate, thiamine
- September 2012: needlephobia, refused to have injections, put on rivaroxaban, no problems
Who’s eligible for the NOACs?

- Good idea!
  - Unexplained poor warfarin control
  - Poor level of control because of unavoidable drug-drug interactions
  - On long term LMWH except pregnancy
  - New patients with DVT
Who’s eligible for the NOACs?

Not indicated

- Good level of control on warfarin
- Renal failure (eGFR<30 ml/min)
- Mechanical heart valve replacement
- Poor compliance with warfarin
- Gastrointestinal disease i.e. angiodysplasia, diverticulosis, inflammatory bowel disease
DVT in cancer patients

- 72 years old male
- March 2012: proximal DVT, diagnosis of renal cell carcinoma with lung and bone metastases
- April 2012: IVC filter insertion, on warfarin
- Later put on chemotherapy, warfarin changed to clexane
- August 2012: Seen in the NOAC clinic, on sunitinib chemo, ?interaction with rivaroxaban
- Nov 2012: Patient happy with rivaroxaban, on steroids for brain metastases, due to have radiotherapy
NICE recommends Rivaroxaban¹

“Rivaroxaban is recommended as an option for treating deep vein thrombosis and preventing recurrent deep vein thrombosis and pulmonary embolism after diagnosis of acute deep vein thrombosis in adults.”

The appraisal indicated that:

- There was no restriction based on patient characteristics, DVT type or duration of treatment
- Rivaroxaban should not be excluded as an option in cancer patients with VTE

¹ NICE. Technology appraisal guidance 261. July 2012
Drug interactions with rivaroxaban

◆ Rivaroxaban not recommended in combination with
  ● Systemicazole-antimycotics (ketoconazole,itraconazole)
  ● HIV protease inhibitors
  ● Dronedarone (lack of information)
Drug interactions with rivaroxaban

Use rivaroxaban with caution in combination with

- Other anticoagulants
- NSAIDS
- Platelet inhibitors
- Strong CYP3A4 inducers such as rifampicin or St John’s Wort
Perioperative management

- Shorter half-life compared to warfarin
- Onset of effect within 2h

**PRE**-
- Interruption 24h earlier for low risk procedures i.e. cardiac catheterization, diagnostic endoscopy, minor orthopedic procedures
- Interruption 48h before high risk procedure, longer if decreasing renal function
- No need for bridging

**POST**-
- Major surgery + incomplete haemostasis: wait
- Good haemostasis: start with $\frac{1}{2}$ dose 4-6 h after
- Bowel paralysis: bridge with LMWH
PATIENT RECEIVING RIVAROXABAN THERAPY: HAEMORRHAGE PROTOCOL

STOP: Rivaroxaban

Request: 1. Check PT urgently
2. Document time of last dose of Rivaroxaban
3. Full blood count and renal function / eGFR

PT prolonged

Rivaroxaban anticoagulant effect maybe present (consider oral charcoal if Rivaroxaban ingestion < 2 hours)

MILD BLEED

- Mechanical compression
- Tranexamic Acid
  - oral 25 mg/kg
  - i.v. 15 mg/kg
- Delay next Rivaroxaban dose or discontinue treatment

MAJOR BLEED

Standard Resuscitation methods
Maintain BP and Urine Output

- Optimise tissue oxygenation
- Control haemorrhage
  - Compression
  - Surgical intervention
- Tranexamic Acid (25 mg/kg i.v.)
- Red Cell transfusion
  - Aim Hb > 7 g/dl
- Platelet transfusion
  - Aim Plt > 50 x 10^9/l or
  - If CNS bleed aim Plt >100 x10^9/l
- Consider PCC 30 IU / Kg

LIFE THREATENING BLEED

PCC*
- Beriplex 35 - 50 U/kg or
- Octaplex 40 U/kg
max 3000 U in one dose

Major Bleed: Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome

Summary

- Rivaroxaban is effective and well tolerated enough to qualify as a potential ideal oral anticoagulant.

- Rivaroxaban does not require an initial parenteral treatment and can be given in once daily administration after the first 3 weeks.

- Limitation: treatment of patients with severe renal failure.

- Need for consideration of a reversal strategy.