How to Diagnose Pulmonary Embolism anno 2014?

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What are we going to discuss?

• Age adjusted clinical decision rule
  \textit{ADJUST} study

• The YEAR Algorithm
Age-adjusted d-dimer cut-off levels to rule out Pulmonary Embolism

a prospective outcome study: the ADJUST study

Paul den Exter, LUMC

For the Adjust study investigators

Introduction

• Signs and symptoms of acute PE are aspecific

• Overlap with other cardiopulmonary conditions

• Suspicion of PE is frequently raised in the ER

• Diagnostic tests are always necessary to rule out or establish PE
Current diagnostic algorithm

Suspected PE

Clinical Decision Rule (Wells)

Unlikely

D-dimer

DD \leq 500 \mu g/l

No PE

DD > 500 \mu g/l

CT

Likely

CT

Christopher Study, JAMA 2006;295:172
Background D-dimer

• D-dimers are released when fibrin is degraded
• When combined with a low a-priori chance: very sensitive to exclude the presence of (acute) PE
• Low specificity (+-55%)
  – ↑ Infection
  – ↑ Malignancy
  – ↑ Older age
• A positive D-dimer does not confirm PE, imaging (CT) is indicated
Effect of age on D-dimer

- Currently we use a D-dimer cut-off 500 μg/L for all patients

- **Patients with suspected PE:**
  - < 40 years: 60% normal D-dimer
  - > 80 years: 5% normal D-dimer


- D-dimer less useful to rule out PE among older patients
- Consequently, CT-scans are frequently indicated among elderly
CT-scans are very accurate to exclude or diagnose PE, however:

- Radiation exposure (risk of cancer)
- Expensive, time-consuming
- No 24h/day availability in some hospitals → hospital admissions
- Risk of contrast allergy and contrast-induced nephropathy

Therefore, we want to *reduce* the number of CTs, *without* missing cases of PE
Objective:

• To derive a new, age-dependent D-dimer cut-off
• To assess the safety and efficiency of this cut-off in two validation samples
D-dimer cut-off per decade

D-dimer cut-off in μg/L

Age (yrs)

Douma et al. BMJ.340:c1475. 2010:
D-dimer cut-off per decade

Regression coefficient:
112 (± 12.03) μg/L increase per decade

\( r^2 = 0.966 \)

*D-dimer cut-off per decade*

Douma et al. BMJ.340:c1475. 2010:
New D-dimer cut-off:

11.2 μg/L increase per year

\[ \downarrow \]

10 μg/L x year

\[ \downarrow \]

new DD cut-off:

Patients > 50 years: age x 10 μg/L

i.e. Patient 76 years old: 76 x 10 μg/L = 760 μg/L

(Conventional cut-off = 500 μg/L)
Results Derivation Set

Proportion of patients in whom PE can be excluded

Age groups
- all ages
- age > 50
- age > 60
- age > 70
- age > 80

PE excluded (%)

- cut-off 500
- age-adjusted cut-off

Age groups
- all ages
- age > 50
- age > 60
- age > 70
- age > 80

PE excluded (%)
## Results Derivation Set

<table>
<thead>
<tr>
<th></th>
<th>&gt; 50</th>
<th>&gt; 60</th>
<th>&gt; 70</th>
<th>&gt; 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (% of total)</td>
<td>863 (65)</td>
<td>674 (51)</td>
<td>463 (39)</td>
<td>198 (15)</td>
</tr>
<tr>
<td>Conventional cut-off</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>False negative n, % (95%)</td>
<td>0, 0</td>
<td>0, 0</td>
<td>0, 0</td>
<td>0, 0</td>
</tr>
<tr>
<td>Age-dependent cut-off</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>False negative n, % (95%)</td>
<td>1, 0.3</td>
<td>1, 0.5</td>
<td>1, 0.9</td>
<td>0, 0</td>
</tr>
</tbody>
</table>

(0-1.8) (0-3.3) (0-7) (0-26)
Discussion

• Age-adjusted safely reduced the need for CT, however, this was a *retrospective* analysis

• Prospective validation is the next step, before implementation in clinical practice

• Clinical trials are needed to provide high-level evidence and improve clinical practice
Age-adjusted D-dimer for the exclusion of Pulmonary Embolism

- ≤ 50 years
  - DD ≤ 500 μg/l

- > 50 years
  - DD age dependent
Patients

• **Inclusion:**
  – >50 years
  – Clinical suspicion of acute PE

• **Exclusion:**
  – Contrast allergy
  – Kreatinin clearance < 30 ml/min
  – Use of anticoagulants (VKA/LMWH)
  – Life expectancy < 3 months
  – Inaccessibility for follow-up
Clinical suspicion of PE

Clinical Probability Assessment
(Simplified Revised Geneva Score/2-level Wells’ Score)

Non-high
Unlikely

D-dimer test

< 500 ng/mL
no Rx
no Ttt

500 < D-Dimer < Age-adjusted cut-off
no Rx
no Ttt

DD > age-adjusted cut-off

CTPA

No PE
Non conclusive
PE

V/Q scan and/or PA

High Likely

CTPA

No PE
Non conclusive
PE

V/Q scan and/or PA
Follow-up

• All patients followed-up for 3 months
• Instructed to return to the ER in case of recurrent/progressive symptoms
• All patients contacted by telephone after 3 mo.

• All suspected thromboembolic events and all deaths during follow-up were adjudicated by 3 independent experts
Primary outcome

The **diagnostic failure rate** in patients left untreated based on a normal age-adjusted D-dimer result, defined as:

*The rate of adjudicated thromboembolic events during 3 months of follow-up*
Sample size

Upper 95% CI failure rate must be < 3%

3200 patients > 50 years
19 hospitals in 4 countries

Prometheus Centers NL
Belgium – Brussels, Liege
France – Paris, Angers, Brest
Switzerland – Lausanne, Geneva
Results

• Between January 2010 and February 2013, 3346 patients were included

• 21 were excluded (protocol violations or withdrawn of consent)

• 3324 eligible for analyses
# Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 3,324</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, n (%)</td>
<td>1887 (56.8)</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>62.1 (15.7)</td>
</tr>
<tr>
<td>Personal history of VTE, n (%)</td>
<td>466 (14.0)</td>
</tr>
<tr>
<td>Active malignancy, n, (%)</td>
<td>429 (12.9)</td>
</tr>
<tr>
<td>Surgery within one month, (%)</td>
<td>392 (11.8)</td>
</tr>
<tr>
<td>Estrogen use, n (%)</td>
<td>183 (5.5)</td>
</tr>
<tr>
<td>Chest pain, n (%)</td>
<td>1608 (48.3)</td>
</tr>
<tr>
<td>Dyspnea, n (%)</td>
<td>2092 (62.9)</td>
</tr>
<tr>
<td>Syncope, n (%)</td>
<td>263 (7.9)</td>
</tr>
<tr>
<td>Hemoptysis, (%)</td>
<td>134 (4.1)</td>
</tr>
<tr>
<td>Heart rate, bpm (mean ± SD)</td>
<td>87.1 (19.6)</td>
</tr>
<tr>
<td>Respiratory rate, bpm (mean ± SD)</td>
<td>19.2 (6.2)</td>
</tr>
</tbody>
</table>
Flow of patients

3,324 included patients
Clinical probability assessment

Unlikely/non-high
2,898

DD <500 μg/L
817

DD 500 μg/L - age-adjusted cut-off
337

Three-month follow-up
- Lost to Follow-up 4
- Anticoagulation 3
- Adjudicated VTE 1/810

DD > Age-adjusted cut-off
1744

CT scan
2,170

No PE
1,539

PE
631

Likely/high
426


Patients between conventional and age-adjusted cut-off

- 337 patients (10%): D-dimer between 500 and their age-adjusted cut-off
- 6 received anticoagulants for other reasons: excluded
- 331 patients observed without treatment
- 7 died and 7 underwent testing for suspected VTE
- Of those, 1 was adjudicated to have VTE

Failure rate: \( \frac{1}{331} = 0.3\% \) (95% CI: 0.1-1.7%)

This is well within the predefined safety limit:
- Point estimate <2%; upper limit 95% CI <3%
Conclusions

• Using the age-adjusted cut-off, PE could be excluded in an additional 10% of patients, *without imaging tests*

• Using this strategy was safe (failure rate 0.3%; no fatal cases)

• The age-adjusted cut-off may now be used in clinical practice in ER settings
The Years algorithm

In PE diagnosis

Tom van der Hulle, Paul den Exter, Erik Klok, Menno Huisman
Leiden University Medical Centre
Why a New Algorithm?

• Current algorithm not used properly:

  *D-dimer test done on every patient
  Physicians react on positive results*

• Overdiagnostics: unnecessary CT-scans

• Underdiagnostics: untreated patients
Current diagnostic algorithm

Suspected PE

Clinical Decision Rule (Wells)

Unlikely

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No PE

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CT

Christopher Study, JAMA 2006;295:172
Background

• Integrate D-dimer test result in decision rule
• What happens with the predictive value of the Wells criteria

Derivation on Prometheus cohort
Validation on Christopher cohort

van Es, 2013 Submitted
## D-dimer integrated in decision rule

<table>
<thead>
<tr>
<th>Item</th>
<th>Wells score</th>
<th>Original OR (95% CI)</th>
<th>D-dimer included OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of VTE</td>
<td></td>
<td>3.9 (1.9-8.0)</td>
<td>3.0 (1.4-6.3)</td>
</tr>
<tr>
<td>PE most likely diagnosis</td>
<td></td>
<td>2.7 (1.8-4.0)</td>
<td>2.4 (1.6-3.8)</td>
</tr>
<tr>
<td>Hartfrequency &gt;100/min</td>
<td></td>
<td>1.6 (1.0-2.6)</td>
<td>1.3 (0.8-2.1)</td>
</tr>
<tr>
<td>Immobilisation of surgery &lt; 4 weeks</td>
<td></td>
<td>1.9 (1.2-3.0)</td>
<td>1.3 (0.8-2.1)</td>
</tr>
<tr>
<td>Prior VTE</td>
<td></td>
<td>3.3 (1.6-7.0)</td>
<td>2.3 (0.96-5.3)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td></td>
<td>2.9 (1.4-6.0)</td>
<td>2.8 (1.3-6.2)</td>
</tr>
<tr>
<td>Active malignancy</td>
<td></td>
<td>1.1 (0.9-1.9)</td>
<td>0.9 (0.5-1.7)</td>
</tr>
<tr>
<td>D-dimer result</td>
<td></td>
<td>-</td>
<td>1.6 (1.4-1.8)</td>
</tr>
</tbody>
</table>
Improving Efficiency

• Most important combination of items

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>No item</td>
<td>41%</td>
</tr>
<tr>
<td>≥1 item(s)</td>
<td>59%</td>
</tr>
</tbody>
</table>

• New D-dimer cut off level has equal sensitivity as in original algorithm
YEARS algorithm

Suspicion of Pulmonary Embolism

YEARS decision rule:
- Clinical signs of VTE
- Hemoptysis
- PE most likely diagnosis

No YEARS item

1-3 YEARS items

D-dimeer
- <1000 ng/mL: No pulmonary embolism
- ≥1000 ng/mL: CT-scan

D-dimeer
- <500 ng/mL: No pulmonary embolism
- ≥500 ng/mL: CT-scan
Results Algorithm

• Power calculation based on:
  
  – VTE during follow-up: 1,5% (1,1-2,0)
  
  – Negative pulmonalis angiography: 1,7% (1,0-2,7)
  
  – Reduction CT-scans: 11%

Sample size of 3260 patients: study recently started
Conclusions

• D-dimer values are age dependent

• Age dependent cut-off levels can be safely used in clinical decision

• The current Wells based decision rule in combination with D-dimer values is often not correctly used in daily practice

• Years algorithm will probably make our life easier