Diagnosis of thrombosis and pulmonary embolism

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Disclosures for Henri Bounameaux, MD

<table>
<thead>
<tr>
<th>Research Support/P.I.</th>
<th>Thrombosis Research Institute, Bayer Pharma, Swiss National Research Foundation</th>
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<tbody>
<tr>
<td>Employee</td>
<td>No relevant conflicts of interest to declare</td>
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<tr>
<td>Consultant</td>
<td>Janssen, Bayer Pharma (Study committees)</td>
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<tr>
<td>Major Stockholder</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Speakers Bureau</td>
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<td>Honoraria</td>
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<td>Scientific Advisory Board</td>
<td>No relevant conflicts of interest to declare</td>
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Presentation includes discussion of the following off-label use of a drug or medical device: <N/A>
My talk today

• What is the 2015 diagnostic algorithm in suspected VTE?
• Are there graded recommendations on VTE diagnosis?
• Are there pitfalls and controversies?
• Is more less?

Bates SM et al. *Chest* 2012;141(2 Suppl.):e351S–e418S.
In the 70’s-80’s

- Invasive
- Costly
- Not devoid of risks

Phlebography

Pulmonary angiography
The Diagnostic Tools

- Pulmonary angiography
- Phlebography
- Ventilation/Perfusion lung scan
- Echocardiography: reserved for hemodynamically unstable patients (not focus of the present talk)
- D-dimer
- Venous compression ultrasonography
- Clinical probability
- Single-row CTPA
- Multi-row CTPA
- MRI?
The 2014 diagnostic algorithm for suspected non high-risk VTE

1CUS (lower limb venous compression ultrasonography) in case of suspected DVT

2CTPA (multi-row) in case of suspected PE

3In case of negative CUS or MSCT and high prior clinical probability, consider additional imaging, e.g. venography (suspected DVT) or lung ventilation/perfusion scintigraphy or pulmonary angiography (suspected PE)

Rx stays for treatment

Clinical classification of PE

- **Massive (high-risk) PE** 5%
- **Non-massive (non-high risk) PE**
  - with RV dysfunction 30%
    (« submassive »)
  - without RV dysfunction 65%
    (« truly non massive »)
Suspected massive PE

- Massive PE
  - Schock or cardiorespiratory arrest
  - Timing: minutes …
  - Treatment: thrombolysis/embolectomy

- Diagnostic work-up less important than emergency treatment
  - Echocardiography useful (differential diagnosis, indirect arguments in direction of PE)
  - V/Q scan, CTPA for confirmation
  - No place for D-dimer or lengthy diagnostic sequences
The Diagnostic Tools

- Pulmonary angiography
- Phlebography
- Ventilation/Perfusion lung scan
- Echocardiography: reserved for hemodynamically unstable patients (not focus of the present talk)

- D-dimer
- Venous compression ultrasonography
- Clinical probability
- Single-row CTPA
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- MRI?
D-dimer for PE: what evidence?

ER: Dr. Green says:
« Electrolytes, CBC, blood gases and D-dimer! »

Seen on TV
Which level of evidence??
## D-dimer in Suspected DVT

<table>
<thead>
<tr>
<th>Type of D-dimer</th>
<th>Deep vein thrombosis</th>
<th>Pulmonary embolism</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Sn, %</td>
<td>Sp, %</td>
</tr>
<tr>
<td><strong>(number of studies)</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Microplate ELISA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asserachrome (24)</td>
<td>94 (83-98)</td>
<td>47 (29-65)</td>
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<td>65 (43-81)</td>
</tr>
<tr>
<td>Nycocard (23)</td>
<td>88 (68-96)</td>
<td>50 (31-68)</td>
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<tr>
<td><strong>Latex quantitative</strong></td>
<td></td>
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</tr>
<tr>
<td>Tinaquant (12)</td>
<td>92 (75-98)</td>
<td>53 (32-73)</td>
</tr>
<tr>
<td>STA- lia test (25)</td>
<td>94 (83-98)</td>
<td>46 (28-64)</td>
</tr>
<tr>
<td><strong>ELFA</strong></td>
<td></td>
<td></td>
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<tr>
<td>VIDAS (40)</td>
<td>96 (93-98)</td>
<td>44 (36-52)</td>
</tr>
<tr>
<td><strong>Whole-blood assay</strong></td>
<td></td>
<td></td>
</tr>
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<td>SimpliRed (40)</td>
<td>82 (59-93)</td>
<td>72 (56-84)</td>
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# D-dimer in Suspected PE

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<td>96 (80-99)</td>
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RIETE data (N>17,000) | 90.6 (87.0-94.1) | 97.3 (96.7-97.8) | 97.6 (97.0-98.2) |

Receiver Operating Characteristic (ROC) Curve to Define the Diagnostic Cut-off in Suspected PE

### Controversy: DD and Age (Individuals Suspected of PE*)

<table>
<thead>
<tr>
<th>Age</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>DD &lt;500, % pts.</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>100 (86-100)</td>
<td>67 (60-74)</td>
<td>58</td>
<td>2</td>
</tr>
<tr>
<td>40-49</td>
<td>100 (86-100)</td>
<td>67 (59-75)</td>
<td>56</td>
<td>2</td>
</tr>
<tr>
<td>50-59</td>
<td>100 (83-100)</td>
<td>56 (47-65)</td>
<td>49</td>
<td>2</td>
</tr>
<tr>
<td>60-69</td>
<td>99 (93-100)</td>
<td>40 (3-49)</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>70-79</td>
<td>99 (93-100)</td>
<td>26 (19-34)</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>80+</td>
<td>100 (98-100)</td>
<td>9 (44-51)</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

*n=1034 patients

Excluded patients: 1,074
- Age <18 years: 7
- Ongoing anticoagulant therapy: 122
- Life expectancy < 3 months: 8
- Pregnancy: 15
- Diagnostic testing performed before inclusion: 134
- Discharged from ER before inclusion: 113
- Contra-indication to CT
  - Allergy to contrast: 49
  - Renal failure: 88
- Unavailable for follow-ups: 25
- Inability to give informed consent: 301
- Refusal to participate: 187
- Other reasons: 65
- Consent withdrawal: 1
- Protocol violation (D-Dimer not performed): 21

**Cut-off (above age of 50) = Age x 10**

**Number Needed to Test (NNT)** to rule out one event

<table>
<thead>
<tr>
<th>Conventional</th>
<th>Age-adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>3.4</td>
</tr>
</tbody>
</table>

in patients aged 75+

Among the 766 patients 75 years or older, of whom 673 had a non-high clinical probability, using the age-adjusted cutoff instead of the 500 μg/L cutoff increased the proportion of patients in whom PE could be excluded on the basis of D-dimer from 43 of 673 patients (6.4% [95% CI, 4.8%-8.5%]) to 200 of 673 patients (29.7% [95% CI, 26.4%-33.3%]), without any additional false-negative findings.
The Diagnostic Tools

- Pulmonary angiography
- Phlebography
- Ventilation/Perfusion lung scan
- Echocardiography: reserved for hemodynamically unstable patients (not focus of the present talk)
- D-dimer
  - Venous compression ultrasonography
- Clinical probability
- Single-row CTPA
- Multi-row CTPA
- MRI?
Compression ultrasonography (CUS)

Controversy: Proximal or complete CUS?

1. Proximal CUS only*
2. Complete (proximal and distal) CUS

* Often in combination or not with repeat exam (after 7 days) (so-called serial CUS), ideally in combination with other tests (DD, clinical probability) in order to increase the yield and cost-effectiveness

• In patients with a **low pretest clinical probability**, we recommend initial testing with D-dimer or **ultrasound (US)** of the proximal veins over no testing (1B), venography (1B) or whole-leg US (2B).

• In patients with **moderate pretest clinical probability**, we recommend initial testing with a highly sensitive D-dimer test, **proximal or whole-leg US** rather than no testing (1B) or venography (1B).

• In patients with a **high pretest clinical probability**, we recommend **proximal or whole-leg US** over no testing (1B) or venography (1B).
• Using whole-leg CUS rather than just proximal CUS is associated with a substantial increase of patients who require anticoagulant treatment.

• With no obvious benefit in 3-month outcome.

• With an increased risk of adverse bleeding events.
Controversy: why using these algorithms?

<table>
<thead>
<tr>
<th>Diagnostic Work-up</th>
<th>Patients Receiving Appropriate Management (n = 418)</th>
<th>Patients Receiving Inappropriate Management (n = 506)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total thromboembolic events, n (%)</td>
<td>5 (1.2)</td>
<td>39 (7.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonfatal thromboembolic event, n</td>
<td>2</td>
<td>10</td>
<td>0.045</td>
</tr>
<tr>
<td>Unexplained sudden death, n</td>
<td>3</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
</tbody>
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The Diagnostic Tools

- Pulmonary angiography
- Phlebography
- Ventilation/Perfusion lung scan
- Echocardiography: reserved for hemodynamically unstable patients (not focus of the present talk)
- D-dimer
- Venous compression ultrasonography
- **Clinical probability (implicit or explicit)**
- Single-row CTPA
- Multi-row helical CTPA
- MRI ?
### PIOPED II: Results in relation to clinical probability assessment (explicit, after Wells)

<table>
<thead>
<tr>
<th>Clinical probability</th>
<th>CT positive</th>
<th>CT negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>22/38 (58%)</td>
<td>8/164 (4%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>93/101 (92%)</td>
<td>15/136 (11%)</td>
</tr>
<tr>
<td>High</td>
<td>22/23 (96%)</td>
<td>6/15 (40%)</td>
</tr>
</tbody>
</table>

23% of positive CTs

2% of negative CTs


*as compared with a composite reference standard.*
Revised Geneva CPR for suspected PE

- Age > 65 years + 1
- Previous DVT/PE + 3
- Surgery/fracture (4 w) + 2
- Active cancer + 2
- Pulse rate
  - 75–94 /min + 3
  - ≥ 95 /min + 5
- Pain by palpation of leg and edema + 4

- Symptoms
  - Unilateral leg pain + 3
  - Haemoptysis + 2

- Maximum score + 25

<table>
<thead>
<tr>
<th>Probability of PE</th>
<th>Score</th>
<th>Prevalence of PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0–3</td>
<td>8%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4–10</td>
<td>29%</td>
</tr>
<tr>
<td>High</td>
<td>≥ 11</td>
<td>74%</td>
</tr>
</tbody>
</table>

ACCP guidelines: 9th edition

To treat or not to treat while awaiting test results

- In patients with a **high clinical suspicion** of DVT/PE, we suggest treatment with parenteral anticoagulants over no treatment (2C).
- In patients with an **intermediate clinical suspicion** of DVT/PE, we suggest treatment with parenteral anticoagulants over no treatment if the results of the diagnostic tests are expected to be delayed for more than 4 hours (2C).
- In patients with a **low clinical suspicion** of DVT/PE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 hours (2C).

Kearon C et al. *Chest* 2012;141(2 Suppl.):e419S–e494S.
Multi-row Detector CTPA in Suspected PE: Outcome Studies

**Aim:** To assess safety of a negative mrCT for ruling out PE

- Without lower limb venous ultrasonography
- In patients with a non-high clinical probability (Geneva score) or a dichotomized Wells’ score below 4 points (« unlikely »)

3-month venous thromboembolic risk in patients not given anticoagulant therapy based on a negative mrCT AND a negative CUS:

<table>
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<tr>
<th>Swiss-Belgian-French Consortium</th>
<th>1.7% (0.7 to 3.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHRISTOPHER Study</td>
<td>1.3% (0.7 to 2.2)</td>
</tr>
</tbody>
</table>

Both studies suggest that mrCTpPA may safely rule out PE without lower limb venous compression ultrasonography, which was subsequently confirmed in a RCT*

CHRISTOPHER Study Investigators. *JAMA* 2006;295:172–9
Controversy: Do we overdiagnose PE?

Figure 1. Expected change in mortality and case fatality in various scenarios of rising apparent incidence. PE indicates pulmonary embolism.
Pitfall: Evidence for increased risk of anticoagulation treatment

Figure 3. Rates of potential complications of anticoagulation treatment among US adults hospitalized with a pulmonary embolism, 1993-2006. APC indicates annual percentage change; and CTPA, computed tomographic pulmonary angiography.

Is more less? (II)

- Using CTPA as diagnostic test for suspected PE is associated with a **substantial increase** in patients who require anticoagulant treatment.

- With **no change** in disease mortality.

- With an **increased incidence of bleeding** events.

- With increased **radiation**.
The true question

Is not which patients do have a clot?

but

Which patients with VTE do need anticoagulant treatment?

- Patients with subsegmental PE (NCT01455818)
- Patients with isolated distal DVT (NCT00421538)

Of note, these studies have recruitment and funding problems. These issues should encourage a move towards a model where funds are pooled into a central and impartial agency that decides what trials to administer.

Take home messages

• Diagnosis of DVT and PE has changed considerably over the past two decades (it has become non-invasive, sequential, and easy)

• It includes initial clinical assessment, D-dimer measurement (except for high-probability patients) and CUS (suspected DVT) or CTPA (suspected PE)

• Recent “advances” (whole-leg CUS instead of proximal CUS for suspected DVT, new generations of scanners with increased sensitivity to minor, potentially clinically non-relevant PE) may lead to overdiagnosis and hence overtreatment with its inherent risks
Thank you for your attention