Pulmonary embolism: Acute management

Cecilia Becattini
University of Perugia, Italy
Acute pulmonary embolism: Acute management

- Diagnosis
- Risk stratification
- Treatment
Non-high risk PE: diagnosis

Suspected PE without shock or hypotension

- Assess clinical probability of PE
  - Clinical judgment or prediction rule

  - Low/intermediate clinical probability or PE unlikely
    - D-dimer
      - positive
        - CT angiography
          - no PE
            - No treatment
          - PE confirmed
            - Treatment
      - negative
        - No treatment

  - High clinical probability or PE likely
    - CT angiography
      - no PE
        - No treatment or investigate further
      - PE confirmed
        - Treatment
Non-high risk PE: diagnosis

3-mo VTE 0.14%
95% CI 0.05-0.41
Non-high risk PE: diagnosis

**Suspected PE without shock or hypotension**

- Assess clinical probability of PE
  - Clinical judgment or prediction rule

- Low/intermediate clinical probability or PE unlikely
  - D-dimer
    - Negative: No treatment
    - Positive: CT angiography
      - No PE: No treatment or investigate further
      - PE confirmed: Treatment

- High clinical probability or PE likely
  - CT angiography
    - No PE: No treatment
    - PE confirmed: Treatment

3-mo VTE 1.5%
95% CI 0.8-3.0
None of the clinical rules by itself is able to avoid overuse of imaging tests.
1. Is the patient older than 49 years of age?
2. Is the pulse rate above 99 beats min\(^{-1}\)?
3. Is the pulse oximetry reading <95% in room air?
4. Is there a present history of hemoptysis?
5. Is the patient taking exogenous estrogen?
6. Does the patient have a prior diagnosis of VTE?
7. Has the patient had recent surgery or trauma? (Requiring endotracheal intubation or hospitalization in the previous 4 weeks.)
8. Does the patient have unilateral leg swelling? (Visual observation of asymmetry of the calves.)

Kline J, J Thromb Haemost 2008
A cluster randomized trial in France. **Primary objective** to assess the non-inferiority of a PERC-based diagnostic strategy for PE low-risk emergency patients, compared to the standard strategy of D-dimer testing, on the occurrence of undiagnosed VTE events.

Freund J, JAMA 2018
Among very low-risk patients with suspected PE, randomization to a PERC strategy vs conventional strategy did not result in an inferior rate of thromboembolic events over 3 months. These findings support the safety of PERC for very low-risk patients presenting to the emergency department.

Freund J, JAMA 2018
## Clinical prediction rules for pulmonary embolism

<table>
<thead>
<tr>
<th>Wells rule</th>
<th>Clinical decision rule points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Original version</td>
</tr>
<tr>
<td>Previous PE or DVT</td>
<td>1.5</td>
</tr>
<tr>
<td>Heart rate ≥100 b.p.m.</td>
<td>1.5</td>
</tr>
<tr>
<td>Surgery or immobilization within the past 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Active cancer</td>
<td>1</td>
</tr>
<tr>
<td>Clinical signs of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than PE</td>
<td>3</td>
</tr>
</tbody>
</table>

### Clinical probability

#### Three-level score

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–1</td>
<td>2–6</td>
<td>≥7</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

#### Two-level score

<table>
<thead>
<tr>
<th></th>
<th>PE unlikely</th>
<th>PE likely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–4</td>
<td>≥5</td>
</tr>
<tr>
<td></td>
<td>0–1</td>
<td>≥2</td>
</tr>
</tbody>
</table>
The YEARS algorithm

Suspected acute pulmonary embolism

Order D-dimer test and score presence of the three YEARS items:
Clinical signs of deep vein thrombosis
Haemoptysis
Pulmonary embolism the most likely diagnosis

- 0 YEARS items
  - D-dimer <1000 ng/mL
    - Pulmonary embolism excluded

- 0 YEARS items
  - D-dimer ≥1000 ng/mL
    - Order CTPA

- ≥1 YEARS items
  - D-dimer <500 ng/mL
    - Pulmonary embolism excluded

- ≥1 YEARS items
  - D-dimer ≥500 ng/mL
    - Order CTPA

Van der Hulle T, Lancet 2017
<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Total venous thromboembolism (n [% , 95% CI])</th>
<th>Fatal pulmonary embolism* (n [% , 95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed algorithm</td>
<td>2946</td>
<td>18 (0.61%, 0.36–0.96)</td>
</tr>
<tr>
<td>Patients managed without CTPA</td>
<td>1629</td>
<td>7 (0.43%, 0.17–0.88)</td>
</tr>
<tr>
<td>Patients managed with CTPA</td>
<td>1317</td>
<td>11 (0.84%, 0.47–1.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 (0.20%, 0.07–0.44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (0.12%, 0.01–0.44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 (0.30%, 0.12–0.78)</td>
</tr>
</tbody>
</table>

Patients in whom pulmonary embolism was excluded by either a low YEARS score or CT scanning were left untreated. CTPA=computed tomography pulmonary angiography. *Patients who remained untreated and were not lost to follow-up.

Table 2: Primary outcomes of venous thromboembolism events during 3-month follow-up
the YEARS approach should not lead to the indiscriminate use of D-dimer testing in all outpatients or inpatients with dyspnoea or chest pain
3324 Patients with clinical probability assessment

2898 PE unlikely or non-high probability

817 D-d <500

337 D-d >500 but < age-adjusted

1744 D-d ≥ age-adjusted

426 PE likely or high probability

2170 CTPA

3-month VTE risk

0.01 (0-0.7)

0.3 (0.1-1.7)

Righini M, JAMA 2014
Using the age-adjusted (instead of the ‘standard’ (500 µg/L) D-dimer cut-off) increased the number of patients in whom PE could be excluded from 6.4% to 30%, without additional false-negative findings.
Acute pulmonary embolism: Acute management

- Diagnosis
- Risk stratification
- Treatment
The spectrum of clinical presentation of PE

PE-related shock

Mild clinical symptoms

The spectrum of clinical outcome of PE

>30% Mortality

1%
PE: blood pressure

Casazza F, Thromb Res. 2012
Kucher N, Circulation 2006
PE: across the severity spectrum

**Classification of patients with acute PE based on early mortality risk**

<table>
<thead>
<tr>
<th>Early mortality risk</th>
<th>Risk parameters and scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shock or hypotension</td>
</tr>
<tr>
<td>High</td>
<td>+</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Intermediate-high</td>
<td>-</td>
</tr>
<tr>
<td>Intermediate-low</td>
<td>-</td>
</tr>
<tr>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> PESI: Pulmonary Embolism Severity Index

<sup>b</sup> RV: Right Ventricular

<sup>c</sup> Cardiac laboratory biomarkers: BNP (Brain Natriuretic Peptide)

<sup>d</sup> Sign of high risk

<sup>e</sup> Sign of low risk
Right ventricle dysfunction or injury and death

Value of prognostic markers in hemodynamically stable patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR/HR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricle dysfunction at echo</td>
<td>1.94</td>
<td>(1.23-3.06)</td>
</tr>
<tr>
<td>Right ventricle dilation at CT</td>
<td>1.64</td>
<td>(1.06-2.52)</td>
</tr>
<tr>
<td>Increased troponin</td>
<td>5.90</td>
<td>(2.68-12.95)</td>
</tr>
</tbody>
</table>

Kucher N et al. Arch Intern Med, 2005
# PE: ESC model for risk stratification

## Classification of patients with acute PE based on early mortality risk

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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shock or hypotension</td>
<td>PESI Class III-V or sPESI &gt; 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Signs of RV dysfunction on an imaging test&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Cardiac laboratory biomarkers&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>High</td>
<td>+</td>
<td>(±)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>+</td>
<td>(±)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intermediate-high</td>
<td>-</td>
<td>+</td>
<td>Both positive</td>
<td></td>
</tr>
<tr>
<td>Intermediate-low</td>
<td>-</td>
<td>+</td>
<td>Either one (or none) positive&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>-</td>
<td>-</td>
<td>Assessment optional; if assessed, both negative&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

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<sup>a</sup> PESI: Pulmonary Embolism Severity Index; RV: Right Ventricular; sPESI: simplified PESI.

<sup>b</sup> Imaging test: This could refer to diagnostic tests such as echocardiography, computed tomography (CT), or magnetic resonance imaging (MRI).

<sup>c</sup> Cardiac laboratory biomarkers: Specific biomarkers are usually tested in the blood to assess cardiac function.

<sup>d</sup> (±): This indicates that the parameter is either positive or negative, depending on the context.

<sup>e</sup> Positive/negative: Positive biomarker indicates the presence of a condition while a negative biomarker indicates the absence of the condition.

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Eur Heart J 2014
906 patients with acute symptomatic objectively confirmed PE

30-day Mortality based on risk category

High
Intermediate high
Intermediate low
Low

CONTEMPORARY CLINICAL MANAGEMENT OF ACUTE PULMONARY EMBOLISM (COPE Observational Study)

Cecilia Becattini
University of Perugia
On behalf of
This is a prospective, non-interventional, multicenter study in patients with acute pulmonary embolism admitted to Cardiology, Emergency and Internal Medicine Departments in Italy
CONTEMPORARY CLINICAL MANAGEMENT OF ACUTE PULMONARY EMBOLISM

- **acute PE diagnosed**
- **Risk stratification**
- **Anticoagulant therapy**

**Death**
- Death due to PE, major bleedings

7 days / discharge 30 days
Acute pulmonary embolism: Acute management

- Diagnosis
- Risk stratification
- Treatment
Goals of acute treatment
Reduce mortality
Reduce early recurrences

Goals of long-term treatment
Complete treatment of acute PE
Reduce recurrences

Goals of extended treatment
Reduce recurrences in high risk pts

Initial treatment
≥ 5 days

Long-term treatment
at least 3 months

Extended treatment
indefinite
**Treatment for PE**

**Acute treatment**
- UFH
- LMWH/Fondaparinux
- Thrombolysis
- Interventional Surgery

**Long-term treatment**
- VKAs
- DOACs
- LMWH
- Rivaroxaban
- Apixaban

**Extended treatment**
- VKAs
- DOACs, ASA, sulodexide

**Initial treatment**
- ≥ 5 days

**Long-term treatment**
- at least 3 months

**Extended treatment**
- indefinite
PE: abrupt closure of pulmonary arteries
PE: acute right heart overload
PE: acute right heart overload

### Acute PE: intrapulmonary vs systemic rt-PA

35 patients with acute PE undergoing thrombolysis

<table>
<thead>
<tr>
<th></th>
<th>Intrapulmonary</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean PA systolic pressure</strong></td>
<td>31±7</td>
<td>31±12</td>
</tr>
<tr>
<td><strong>Mean modified Miller index</strong></td>
<td>25±4</td>
<td>26±2</td>
</tr>
</tbody>
</table>

**pre- rt-PA**  **2-hours**

Verstraete M, Circulation 1988
Patients with acute PE Randomized to TNK or placebo

Time course of R/L end-diastolic dimension ratio at echocardiography

Becattini et al, 2009
Acute PE: thrombolysis and mortality

Marti C et al, *Eur Heart J* 2015
## Thrombolysis for PE: the counterbalance

<table>
<thead>
<tr>
<th>Outcome of Interest (No. of Studies Reporting)</th>
<th>No. of Events/No. of Patients, Absolute Event Rate (%)</th>
<th>No. Needed to Treat or Harm</th>
<th>P Value</th>
</tr>
</thead>
</table>
| **All-cause mortality (16)**                  | Thrombolytic Group: 23/1061 (2.17)  
Anticoagulant Group: 41/1054 (3.89) | NNT = 59  
NNH = Not Calculated | .01     |
| **Major bleeding (16)**                       | Thrombolytic Group: 98/1061 (9.24)  
Anticoagulant Group: 36/1054 (3.42) | NNH = 18  
NNH = Not Calculated | <.001   |
| **ICH (15)**                                  | Thrombolytic Group: 15/1024 (1.46)  
Anticoagulant Group: 2/1019 (0.19) | NNH = 78  
NNH = Not Calculated | .002    |
| **Recurrent PE (15)**                         | Thrombolytic Group: 12/1024 (1.17)  
Anticoagulant Group: 31/1019 (3.04) | NNT = 54  
NNH = Not Calculated | .003    |

### Age >65 y

<table>
<thead>
<tr>
<th>Outcome of Interest (No. of Studies Reporting)</th>
<th>No. of Events/No. of Patients, Absolute Event Rate (%)</th>
<th>No. Needed to Treat or Harm</th>
<th>P Value</th>
</tr>
</thead>
</table>
| **All-cause mortality (5)**                   | Thrombolytic Group: 14/673 (2.08)  
Anticoagulant Group: 24/658 (3.65) | NNT = 64  
NNH = Not Calculated | .07     |
| **Major bleeding (5)**                        | Thrombolytic Group: 87/673 (12.93)  
Anticoagulant Group: 27/658 (4.10) | NNH = 11  
NNH = Not Calculated | <.001   |

### Age ≤65 y

<table>
<thead>
<tr>
<th>Outcome of Interest (No. of Studies Reporting)</th>
<th>No. of Events/No. of Patients, Absolute Event Rate (%)</th>
<th>No. Needed to Treat or Harm</th>
<th>P Value</th>
</tr>
</thead>
</table>
| **All-cause mortality (11)**                  | Thrombolytic Group: 9/388 (2.32)  
Anticoagulant Group: 17/396 (4.29) | NNT = 51  
NNH = Not Calculated | .09     |
| **Major bleeding (11)**                       | Thrombolytic Group: 11/388 (2.84)  
Anticoagulant Group: 9/396 (2.27) | NNH = 176  
NNH = Not Calculated | .89     |

### Intermediate-risk PE

<table>
<thead>
<tr>
<th>Outcome of Interest (No. of Studies Reporting)</th>
<th>No. of Events/No. of Patients, Absolute Event Rate (%)</th>
<th>No. Needed to Treat or Harm</th>
<th>P Value</th>
</tr>
</thead>
</table>
| **All-cause mortality (8)**                   | Thrombolytic Group: 12/866 (1.39)  
Anticoagulant Group: 26/889 (2.92) | NNT = 65  
NNH = Not Calculated | .03     |
| **Major bleeding (8)**                        | Thrombolytic Group: 67/866 (7.74)  
Anticoagulant Group: 20/889 (2.25) | NNH = 18  
NNH = Not Calculated | <.001   |

Chatterije S et al, *JAMA 2014*
<table>
<thead>
<tr>
<th>Event</th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality within 7 days</td>
<td>6 (1.2)</td>
<td>9 (1.8)</td>
<td>0.43</td>
</tr>
<tr>
<td>Hemodynamic collapse within 7 days</td>
<td>8 (1.6)</td>
<td>25 (5.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Major</td>
<td>32 (6.3)</td>
<td>6 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Thrombolysis IS NOT RECOMMENDED in hemodynamically stable patients with acute PE

Close monitor for early assessment of hemodynamic deterioration

Use thrombolysis in case of deterioration

Limit percutaneous procedures to high-risk patients at high risk for bleeding
Low-dose thrombolysis

<table>
<thead>
<tr>
<th>Odds ratio (95% CI) for bleeding</th>
<th>Full-dose thrombolysis</th>
<th>Low-dose thrombolysis</th>
<th>Catheter-directed thrombolysis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.28 (0.40 to 4.12)</td>
<td>1.93 (0.07 to 51.33)</td>
<td>0.60 (0.36 to 1.01)</td>
<td></td>
</tr>
<tr>
<td>2.22 (0.71 to 6.89)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.07 (0.03 to 126.08)</td>
<td>0.93 (0.01 to 65.65)</td>
<td></td>
<td>0.31 (0.01 to 7.96)</td>
<td></td>
</tr>
<tr>
<td>2.00 (1.06 to 3.78)</td>
<td>0.90 (0.25 to 3.21)</td>
<td>0.97 (0.02 to 56.03)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TAFI Inhibitor

Procoagulant effects

Anticoagulant effects

Antifibrinolytic effects

Platelet activation

Fibrinogen → Fibrin monomer → Cross-linked fibrin
The CHEST guidelines

DVT of the leg or PE

Concomitant cancer

Yes
LMWH

No
LMWH followed by VKAs

NOACs

*Same grade of recommendation for different NOACs*

### Efficacy & safety of DOACs in VTE

Meta-analysis of RCT studies with DOACs in initial and long-term VTE treatment

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>0.89</td>
<td>(0.75-1.05)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.63</td>
<td>(0.51-0.77)</td>
</tr>
<tr>
<td>CRNMB</td>
<td>0.74</td>
<td>(0.59-0.93)</td>
</tr>
</tbody>
</table>

6 studies 27023 patients

Kakkos et al, 2014
# DOACs in pulmonary embolism

5 phase III studies included: 11,539 patients

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>0.89</td>
<td>(0.70-1.12)</td>
</tr>
<tr>
<td>anti-Xa</td>
<td>0.89</td>
<td>(0.69-1.15)</td>
</tr>
<tr>
<td>anti-IIa</td>
<td>0.87</td>
<td>(0.46-1.64)</td>
</tr>
<tr>
<td>Major Bleeding*</td>
<td>0.30</td>
<td>(0.10-0.95)</td>
</tr>
<tr>
<td>Clinically Relevant Bleeding*</td>
<td>0.89</td>
<td>(0.77-1.03)</td>
</tr>
</tbody>
</table>

* two studies included

Vedovati MC et al, Int J Cardiol 2014
DOACs for VTE: study design

**Conventional anticoagulation:**
Heparin + warfarin

- **DOAC front-loaded maintaining dose**
- **LMWH**
- **DOAC**

- **Treatment period 3, 6 or 12 mo**
- **Confirmed symptomatic DVT or PE**
PE: anatomical extent of PE as defined in DOACs trials

- **Limited extent**
  - ≤25% of the vasculature of a single lobe

- **Intermediate extent**
  - >25% of vasculature of a single lobe or multiple lobes with ≤25% of entire vasculature

- **Extensive extent**
  - multiple lobes with ≥25% of entire vasculature

5.5. In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (eg, after first 5 days of treatment) (Grade 2B).

Remarks: Patients who prefer the security of the hospital to the convenience and comfort of home are likely to choose hospitalization over home treatment.
Home treatment: the Hot-PE trial

**IN-HOSPITAL MANAGEMENT**

- Acute PE is clinically suspected
- Anticoagulant started
- PE confirmed by imaging <24 hours
- Eligibility criteria applied + collection of informed consent
- Hospital discharge <48 hours

**HOME TREATMENT**

- Additional baseline tests
- First dose of rivaroxaban
- Rivaroxaban 15 mg bid for 3 weeks

**STUDY PERIOD (12 MONTHS)**

- Rivaroxaban 20 mg qd for a total of at least 3 months (15 mg qd in selected patients)

**FOLLOW-UP VISITS**: 8 days, 3 weeks, 3 months, 12 months from enrolment

**PRIMARY OUTCOME**: symptomatic recurrent VTE or PE-related death (<3 months)

**SECONDARY OUTCOMES**: all-cause mortality, major and clinically relevant bleeding, serious adverse events, duration of hospital stay, re-hospitalization due to PE, quality of life, treatment satisfaction, utilization of health care resources
Acute pulmonary embolism: Acute management

Cecilia Becattini
University of Perugia, Italy