Venous Thromboembolism
2013 ACOI Board Review

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Pulmonary Embolism
Its severity ranges from asymptomatic, incidentally discovered subsegmental thrombi to massive, pressor-dependent PE complicated by cardiogenic shock and multisystem organ failure.
Risk Factors for Venous Thromboembolism

ACQUIRED

- Virchow's Triad
  (stasis, venous injury, hypercoagulable)
- Prior history of thromboembolic disease
- Prior surgical history or trauma
- Immobilization/paralysis
- Cancer
- Estrogen Therapy
- Pregnancy/Postpartum
- Antiphospholipid antibody syndrome
<table>
<thead>
<tr>
<th>Established or Potential Hypercoagulable States</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Activated protein C resistance</td>
</tr>
<tr>
<td>• Alpha-macroglobulin deficiency</td>
</tr>
<tr>
<td>• Anticardiolipin antibodies</td>
</tr>
<tr>
<td>• Antithrombin deficiency</td>
</tr>
<tr>
<td>• Dysfibrinogenemia</td>
</tr>
<tr>
<td>• Factor V Leiden</td>
</tr>
<tr>
<td>• Factor V deficiency/excess</td>
</tr>
<tr>
<td>• Factor VII excess</td>
</tr>
<tr>
<td>• Factor VIII excess</td>
</tr>
<tr>
<td>• Factor XI excess</td>
</tr>
<tr>
<td>• Heparin cofactor II deficiency</td>
</tr>
</tbody>
</table>

| • Hyperhomocysteinemia                       |
| • Hyperfibrinogenemia                        |
| • Lupus anticoagulants                       |
| • PAI-1 excess                               |
| • Plasminogen deficiency                     |
| • Protein C deficiency                       |
| • Protein S deficiency                       |
| • Prothrombin G20210A                        |
| • tPA deficiency                             |
| • TFPI deficiency                            |
| • Thrombomodulin deficiency                  |

PAI-1=plasminogen activator inhibitor-1; TFPI=tissue factor pathway inhibitor; tPA=tissue plasminogen activator
When to suspect a hypercoagulable state?

- Clots in low risk patient
- Clots in odd locations
- Recurrent clots
- Family history of clots
Hypercoagulable states associated with BOTH Arterial and Venous Thrombosis

Cancer
Myeloproliferative syndromes
Antiphospholipid antibodies (APA)
Hyperhomocysteinemia
Heparin-induced thrombocytopenia.
Incidence of VTE in various risk categories

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Low risk</th>
<th>Medium risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgery</td>
<td>Age &lt; 40 years</td>
<td>Age &gt; 40 years</td>
<td>Age &gt; 60 years</td>
</tr>
<tr>
<td></td>
<td>Surgery &lt; 30 minutes</td>
<td>Surgery &gt; 30 minutes</td>
<td>Surgery &gt; 60 minutes</td>
</tr>
<tr>
<td></td>
<td>No risk factors</td>
<td>No other risk factors</td>
<td>Plus additional risk factors</td>
</tr>
<tr>
<td>Orthopaedic surgery, traumatology</td>
<td>Minor trauma</td>
<td>Leg plaster cast</td>
<td>Hip or knee surgery, hip fracture, polytrauma</td>
</tr>
<tr>
<td>Medical conditions</td>
<td>Pregnancy</td>
<td>Heart failure, stroke, malignancy</td>
<td>Long immobility</td>
</tr>
<tr>
<td>Incidence (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal DVT</td>
<td>2</td>
<td>10–40</td>
<td>40–80</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>0.4</td>
<td>6–8</td>
<td>10–15</td>
</tr>
<tr>
<td>Symptomatic PE</td>
<td>0.2</td>
<td>1–2</td>
<td>5–10</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>0.002</td>
<td>0.1–0.8</td>
<td>1–5</td>
</tr>
</tbody>
</table>

Pulmonary Embolism Sources

- Lower extremity DVT
  - 70% cases of PE
- Unusual sites
  - Right heart
  - Upper extremity
  - Renal veins
  - Iliac veins
  - Hepatic veins
Pathophysiology

• Key consequences are hemodynamic
  – Emboli abruptly increase pulmonary vascular resistance to a level of afterload which cannot be matched by the RV.

• Sudden death may occur
  – usually in the form of electromechanical dissociation

• These effects of depend:
  – Extent of obstruction
  – Duration over which obstruction accumulates
  – Pre-existing cardiopulmonary state of patient
From Ghaye B et al. Radiographics 2006.
Outcomes in Pulmonary Embolism

Mortality

- Sudden Death
- Cardiac Arrest
- Shock

Stratification by RV dysfunction?

Embolism Size
Severity
Cardiopulmonary Status
Clinical forms of PE

<table>
<thead>
<tr>
<th>Pulmonary embolism</th>
<th>History</th>
<th>Vascular obstruction</th>
<th>Presentation</th>
<th>Typical pressures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute minor</td>
<td>Short, sudden onset</td>
<td>&lt; 50%</td>
<td>Dyspnoea with or without pleuritic pain and haemoptysis</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Acute massive</td>
<td>Short, sudden onset</td>
<td>&gt; 50%</td>
<td>Right heart strain with or without haemodynamic instability and syncope</td>
<td>45/20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Subacute massive</td>
<td>Several weeks</td>
<td>&gt; 50%</td>
<td>Dyspnoea with right heart strain</td>
<td>70/35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>

PAP, pulmonary artery pressure; RAP, mean right atrial pressure.

From Riedel. *Heart* 2001
European Heart Journal
Pulmonary Embolism
Risk Assessment and Management
Stavros Konstantinides, Samuel Z. Goldhaber

Initial Risk Stratification

- Effective treatment of PE in the acute phase lies in the assessment of the patient's early death risk.
- Crucial determinant is the presence and severity of right ventricular (RV) dysfunction resulting from acute pressure overload.
Clinical Definitions

- The definition of high-risk (European classification) or massive (North American classification) PE is usually straightforward and relies on the presence of clinically overt RV failure which results in haemodynamic compromise.
Initial Risk Stratification

• High-risk (European classification[5])
• Massive (North American classification[7])
• Patients present with hypotension or syncope
• Some would add refractory hypoxemia to this group


High Risk or Massive PE

• This condition, which is encountered in <5% of all patients presenting with acute PE constitutes a medical emergency, since it is associated with at least a 15% risk of in-hospital death, particularly during the first hours after admission.
Some of the (initially) normotensive patients with acute PE may have an elevated risk of death or major complications (intermediate-risk PE in Europe; submassive PE in North America) which warrants further risk stratification and possibly specific advanced therapy.
BNP and proBMP

• A meta-analysis of 13 studies found that 51% of 1132 patients with acute PE had elevated brain natriuretic peptide (BNP) or N-terminal (NT)-proBNP concentrations; these were associated with an increased risk of early death and a complicated in-hospital course.[34] Nevertheless, their positive predictive value for an elevated risk has been consistently low.[35]
Troponin

• Elevated cardiac troponin I or T levels are also found in up to 50% of the patients with acute PE.[36]
• A meta-analysis of studies published between 1998 and 2007, with a total of 1985 patients, showed that cardiac troponin elevation was associated with an increased risk of death and major adverse events in the acute phase.[37]
• However, another meta-analysis which excluded hypotensive patients did not confirm the prognostic value of circulating troponin levels.[38]
• Recently developed high-sensitivity assays may improve the prognostic performance of this biomarker, at least at the low-risk end of the severity spectrum. More specifically, a derivation study showed that high-sensitivity troponin T (hsTnT) was useful for excluding an adverse outcome in the acute phase of PE.[39] In a multicentre, multinational cohort of 526 normotensive patients with acute PE, hsTnT exhibited a high NPV (98%).
The extent of thrombotic load on computed tomography does not always correlate with the clinical severity of acute pulmonary embolism or its impact on right ventricular function. (A) A straightforward case in which massive thrombi are present in both the right and the left pulmonary artery of a patient presenting with haemodynamic instability (persistent tachycardia, systolic blood pressure between 90 and 100 mmHg). (B) However, a patient presenting with similar clinical findings had an apparently much smaller thrombotic load on computed tomography; in this latter patient, the size of thrombi was also in discordance with the impressive enlargement (as a surrogate for dysfunction) of the right ventricle (C).
Advanced Risk Stratification: Imaging Findings

• Registries and cohort studies demonstrate an association between echocardiographic parameters of RV dysfunction and a poor in-hospital outcome.

• Nevertheless, the prognostic value of cardiac ultrasound in haemodynamically stable patients appears moderate at best, mostly due to the poor standardization of echocardiographic criteria.

• It thus appears that an abnormal echocardiogram needs to be accompanied by clinical signs indicating severe PE, or by a positive biomarker test indicating the presence of heart failure or myocardial injury (as explained below), to justify advanced therapy in normotensive patients with acute PE.
Acute Pulmonary Embolism

Persistent hypotension or shock?

- yes
  - High-risk (massive) PE
    - Thrombolysis
      (if contraindicated: surgical or interventional embolectomy)
      Unfractionated heparin

- no
  - Non-massive PE
    - RV dysfunction
      (echocardiography or MDCT) and/or
    - Myocardial injury
      (e.g. cardiac troponins)
      - Submassive PE
        - LMWH or fondaparinux
          No routine thrombolysis
          (can be given in selected cases)
          Hemodynamic monitoring
      - Low-risk PE
        - LMWH or fondaparinux
          No thrombolysis
          (possible candidates for home treatment)
Risk Stratification

No shock
- ↓ Troponin
- ↓ RV on CT
- Echocardiography
  - No or mild RV dysfunction
  - Moderate or severe RV dysfunction
  - Anticoagulation alone

Shock
- ↑ Troponin
- ↑ RV on CT
- Consider fibrinolysis or embolectomy
Advanced Risk Stratification: Clinical Scores

• Prediction rules based on clinical findings at diagnosis can help with the prognostic assessment of patients with acute PE.
• These scores account both for the clinical severity of the acute event and the patient's comorbidity
The Pulmonary Embolism Severity Index (PESI) is the most extensively validated prognostic clinical score to date. Its major strength lies in excluding (ruling out) an adverse outcome as indicated by the high negative predictive value (NPV) of the lowest PESI classes I and II. A recently published randomized trial successfully employed a low PESI score as the main inclusion criterion for home treatment of acute PE.
Advanced Risk Stratification: Clinical Scores

- The Pulmonary Embolism Severity Index (PESI) is the most extensively validated prognostic clinical score to date.
- Its major strength lies in excluding (ruling out) an adverse outcome as indicated by the high negative predictive value (NPV) of the lowest PESI classes I and II.
- The main limitation of the index is that it requires numerous variables and is relatively complex to calculate, which may reduce its practicability in high-volume centres.
Simplified PESI

- Reliable prognostic information can also be obtained with a simplified version of the score (sPESI) which focuses on six equally weighted variables:
  - age >80 years
  - history of cancer
  - history of heart failure or chronic lung disease
  - systolic blood pressure <100 mmHg
  - pulse rate >110 b.p.m.
  - arterial oxyhaemoglobin saturation <90%.

- In an external validation study, the sPESI was at least as accurate as imaging and biomarker criteria for excluding an elevated risk. The implications of this latter score for patient management remain to be shown.
Wells’ Criteria for Assessment of Pretest Probability

The Wells Criteria for assessing pretest probability is important for diagnosing DVT and PE. Below describes the criteria and scoring system:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected DVT</td>
<td>3.0</td>
</tr>
<tr>
<td>An alternative diagnosis is less likely than PE</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt; 100 beats per minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization or surgery in the previous four weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemothysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy (on treatment, treated in the past six months or palliative)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score range</th>
<th>Mean probability of PE</th>
<th>% with this score</th>
<th>Interpretation of risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 points</td>
<td>3.6%</td>
<td>40</td>
<td>Low</td>
</tr>
<tr>
<td>2 to 6 points</td>
<td>20.5%</td>
<td>53</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt;6 points</td>
<td>66.7%</td>
<td>7</td>
<td>High</td>
</tr>
</tbody>
</table>

Pulmonary vascular disease: pulmonary thromboembolism and pulmonary hypertension

Rachel Davies, Luke Howard

Medicine Volume 40, Issue 4, April 2012, Pages 214–220
### Revised Geneva score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predisposing factors</td>
<td></td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>+1</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>+3</td>
</tr>
<tr>
<td>Surgery or fracture within 1 month</td>
<td>+2</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>+2</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Unilateral lower limb pain</td>
<td>+3</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>+2</td>
</tr>
<tr>
<td>Clinical signs</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
</tr>
<tr>
<td>75–94 beats/min</td>
<td>+3</td>
</tr>
<tr>
<td>≥95 beats/min</td>
<td>+5</td>
</tr>
<tr>
<td>Pain on lower limb deep vein at palpation and unilateral oedema</td>
<td>+4</td>
</tr>
</tbody>
</table>

### Wells score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predisposing factors</td>
<td></td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>+1.5</td>
</tr>
<tr>
<td>Recent surgery or immobilization</td>
<td>+1.5</td>
</tr>
<tr>
<td>Cancer</td>
<td>+1</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>+1</td>
</tr>
<tr>
<td>Clinical signs</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
</tr>
<tr>
<td>&gt;=100 beats/min</td>
<td>+1.5</td>
</tr>
<tr>
<td>Clinical signs of DVT</td>
<td>+3</td>
</tr>
</tbody>
</table>

Clinical judgement

Alternative diagnosis less likely than PE | +3

### Clinical probability

- **Total**: 0–3
  - Low
  - Intermediate: 4–10
  - High: ≥11

### Clinical probability (3 levels)

- **Total**: 0–1
  - Low
  - Intermediate: 2–6
  - High: ≥7

### Clinical probability (2 levels)

- **Total**: 0–4
  - PE unlikely
  - PE likely: >4

From Torbicki. *Eur Heart J* 2008
D-dimer

- Plasma D-dimer degradation product of crosslinked fibrin
- Useful in ruling out clot
  - High negative predictive value (NPV)
- Fibrin present in many other disorders
  - Low positive predictive value (PPV)
- ELISA-derived assays have highest sensitivity
  - Latex-derived & whole-blood agglutination assays have lower sensitivity
Negative D-dimer safely excludes PE in patients with **low** clinical probability

<table>
<thead>
<tr>
<th>Series</th>
<th>Clinical probability</th>
<th>Patients (n)</th>
<th>D-dimer &lt;500 μg/L [n (%)]</th>
<th>3-month thromboembolic risk [% (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vidas D-dimer $^{63,67,77-79}$</td>
<td>Low or moderate$^a$</td>
<td>3367</td>
<td>1184 (33%)</td>
<td>0.1 (0–0.5)</td>
</tr>
<tr>
<td>Tinaquant $^{67,80}$</td>
<td>Low$^a$</td>
<td>2071</td>
<td>857 (32%)</td>
<td>0.6 (0.2–1.4)</td>
</tr>
<tr>
<td>SimpliRED $^{68}$</td>
<td>Low</td>
<td>930</td>
<td>437 (47%)</td>
<td>0.2 (0–1.3)</td>
</tr>
</tbody>
</table>

From Torbicki. *Eur Heart J* 2008
Pulmonary vascular disease: pulmonary thromboembolism and pulmonary hypertension

Rachel Davies, Luke Howard

Medicine
Volume 40, Issue 4, April 2012, Pages 214–220
Techniques for diagnosis of PE

- EKG
- Chest Radiographs
- Echocardiogram
- V/Q Scans
- Helical CT
- MRI
EKG Findings of Pulmonary Embolism

- Tachycardia
- T-wave changes
- ST-segment changes
- Right axis deviation
- S1-Q3-T3
- RBBB
- p-pulmonale
Sinus tachycardia, rate 119. Normal P axis, rate >= 100
High QRS voltage
Inferior infarct, age indeterminate
Q's & neg T's in II, III, aVF
Anterior infarct
2 Q waves in V2-V4

--AXIS--
P 36
QRS 57
T -7

- ABNORMAL ECG -

PRELIMINARY-MD MUST REVIEW
Chest Radiography

- Valuable in excluding other diagnoses
  - Pneumothorax, Pneumonia, CHF, tumor, rib fx
- Aids in interpreting V/Q scan
- Radiographic signs suggest PE:
  - Hampton’s hump
  - Westermark sign
  - Fleischner sign
Westermark’s Sign
Fleischner sign
Echocardiogram

- Useful for rapid triage of pts
- Assess right and left ventricular function
- Diagnostic of PE if hemodynamics by echo are consistent with clinical hx
Echocardiogram

- TEE more sensitive than TTE
- Demonstrate intracardiac clot or signs of right ventricular failure
- Emboli observed = 42-50% mortality rate
- Indirect evidence
  - right ventricular dilation
  - dilated pulmonary artery
  - abnl right ventricular wall motion
  - dilated vena cava
Right Ventricular Dysfunction

- Progressive right heart failure is the usual immediate cause of death from PE
- As pulmonary vascular resistance increases, right ventricular wall tension rises and perpetuates further right ventricle dilation and dysfunction
- Interventricular septum bulges into and compresses the normal left ventricle
Echocardiogram suggesting a PE. Diastole on the left, systole on the right
MORTALITY with RV DYSFUNCTION

Ventilation-Perfusion (V/Q) Scans
V/Q with Large Defect

**Lung Ventilation**
- 15 sec Breath hold
- Equilibrium
- LPO
- RPO
- Posterior
- Xe 133

**Lung Perfusion**
- Rt Lat
- Anterior
- Lt Lat
- LPO
- Posterior
- RPO
V/Q with Multiple Defects

Lung Ventilation

Breath hold
15 sec

Equilibrium

LPO

RPO

Lung Perfusion

Rt Lat

Anterior

Lt Lat

LPO

Posterior

RPO
High Probability V/Q Scan

**Lung Perfusion**
- Rt Lat
- Anterior
- Lt Lat
- LPO
- Posterior
- RPO

**Lung Ventilation**
- Breath hold 15 sec
- Equilibrium
- LPO
- RPO
V/Q with Subsegmental Defects

Lung Ventilation

15 sec Breath hold  Equilibrium

LPO  RPO  Posterior

Xe 133

Posterior

Lung Perfusion

Rt Lat  Anterior  Lt Lat

LPO  Posterior  RPO

07/09/90
V/Q Lung Scan

- Normal V/Q Sensitivity 99%
  - Rules *out* PE
- High Prob V/Q Specificity 96%
  - Rules *in* PE
- But, >60% nondiagnostic
- Takes >2 hr to perform
- Not available at all times
CT Pulmonary Angiogram

- Identifies proximal PE (which are the ones usually hemodynamically important)
- Not as accurate with peripheral PE
Spiral CT for Dx PE
Spiral CT for Dx PE
Pulmonary Embolism by CT
Pulmonary Angiogram

- Most specific test available for diagnosis of PE
- Can detect emboli as small as 1-2 mm
- Most useful when the clinical likelihood of PE differs substantially from the lung scan or CTPA results
# Pulmonary Angiography

## Diagnostic Findings

<table>
<thead>
<tr>
<th>Diagnostic Findings</th>
<th>Intraluminal filling defects</th>
<th>Vascular Cutoffs</th>
</tr>
</thead>
</table>

0.5% Mortality       1% Major Morbidity
Pulmonary angiogram
Pulmonary angiogram
Initial Treatment of Pulmonary Embolism

• Anticoagulant treatment should be administered to all patients with high or intermediate clinical probability of acute PE, without awaiting definitive confirmation by imaging procedures.
Initial Treatment of Pulmonary Embolism

- Unfractionated heparin is the preferred mode of initial anticoagulation for patients with severe renal impairment (creatinine clearance <20–30 mL/min)
- for those at high risk of bleeding
- for high-risk hypotensive patients
- as a rule, for extremely overweight, underweight, or old patients
Initial Treatment of Pulmonary Embolism

• With the exception of these circumstances
• LMWH or fondaparinux is given subcutaneously at weight-adjusted doses
• Anticoagulation with unfractionated heparin or LMWH/fondaparinux should be continued for at least 5 days
Initial Treatment of Pulmonary Embolism

• Oral anticoagulants (vitamin K antagonists) should be initiated as soon as possible in haemodynamically stable patients, preferably on the same day as heparin.

• Parenteral anticoagulation can be stopped as soon as the international normalized ratio (INR) has been in the therapeutic range (between 2.0 and 3.0) on 2 consecutive days.
## Newer Strategies for Treatment

### Overlapping

<table>
<thead>
<tr>
<th>Current standard of care</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH or Fonda s.c.*</td>
<td></td>
</tr>
<tr>
<td>VKA</td>
<td></td>
</tr>
</tbody>
</table>

- **Day 1**
- **Days 5–11**
- **At least 3 months**

### Switching

<table>
<thead>
<tr>
<th>RE-COVER (published)†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HOKUSAI-VTE (NCT00986154—ongoing)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LMWH s.c.</th>
<th>dabigatran b.i.d. / edoxaban o.d.</th>
</tr>
</thead>
</table>

- **Day 1**
- **Days 5–11**
- **At least 3 months**

### Single oral drug

<table>
<thead>
<tr>
<th>EINSTEIN-DVT/PE (published)‡</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY (NCT006432001—ongoing)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rivaroxaban 15 mg b.i.d. for 3 weeks, then 20 o.d.</th>
</tr>
</thead>
</table>

- **Day 1**
- **At least 3 months**

Source: Eur Heart J © 2012 Oxford University Press
Recurrence rates for DVT and PE after anticoagulation is stopped

Duration of Anticoagulation

• First event with reversible risk factors, warfarin therapy for at least 3 months
• First event – idiopathic – 3 months and reassess
• unprovoked pulmonary embolism should undergo a risk-to-benefit evaluation to determine if long-term therapy is needed (grade 1C)
Duration of Anticoagulation

• Patients who have pulmonary embolism and preexisting irreversible risk factors, such as deficiency of antithrombin III, protein S and C, factor V Leiden mutation, or the presence of antiphospholipid antibodies, should be placed on long-term anticoagulation.
Thrombolytic Therapy

- Thrombolytic therapy is clearly indicated for hemodynamically unstable patient who lack contraindication.

- In only one randomized thrombolysis trial with clinical endpoints, early thrombolytic treatment given to normotensive patients with evidence of RV dysfunction significantly reduced the need for emergency escalation of therapy during the hospital stay.

Thrombolytic Therapy

- Overall, >90% of patients with PE appear to respond favourably to thrombolysis as indicated by clinical and echocardiographic improvement within the first 36 h.
- The greatest benefit is observed when treatment is initiated within 48 h of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for 6–14 days.


The current eighth edition of the American College of Chest Physicians (ACCP) guidelines for antithrombotic and thrombolytic therapy are summarized as follows:

All patients with pulmonary embolism require rapid risk stratification (grade 1C).

Thrombolytic therapy should be used in patients with evidence of hemodynamic compromise, except in the face of major contraindications due to bleeding risks (grade 1B).

Do not delay thrombolysis in this population, owing to the potential for the development of irreversible cardiogenic shock.

Thrombolytic therapy is suggested in select high-risk patients who do not have hypotension and are at low risk for bleeding (grade 2B).

Assessment of pulmonary embolism severity, prognosis, and risk of bleeding dictate whether thrombolytic therapy should be started. Thrombolytic therapy is not recommended for most patients (grade 1B).
# Thrombolysis for pulmonary embolism

## Agents and regimens

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose and Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase(^a)</td>
<td>250,000 U as a loading dose over 30 min, followed by 100,000 U/h over 12–24 h</td>
</tr>
<tr>
<td></td>
<td>Accelerated regimen: 1.5 million IU over 2 h(^b)</td>
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<tr>
<td>Urokinase(^a,c)</td>
<td>4400 U per kg of body weight as a loading dose over 10 min, followed by 4400 U/kg/h over 12–24 h</td>
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<tr>
<td></td>
<td>Accelerated regimen: 3 million U over 2 h(^b)</td>
</tr>
<tr>
<td>Alteplase(^a)</td>
<td>100 mg over 2 h(^d)</td>
</tr>
<tr>
<td></td>
<td>Accelerated regimen: 0.6 mg/kg for 15 min</td>
</tr>
<tr>
<td>Retepase(^a,e)</td>
<td>Two bolus injections of 10 U 30 min apart</td>
</tr>
<tr>
<td>Tenecteplase(^f)</td>
<td>30–50 mg bolus for 5–10 s adjusted for body weight</td>
</tr>
<tr>
<td></td>
<td>&lt; 60 kg: 30 mg</td>
</tr>
<tr>
<td></td>
<td>≥ 60 to &lt; 70 kg: 35 mg</td>
</tr>
<tr>
<td></td>
<td>≥ 70 to &lt; 80 kg: 40 mg</td>
</tr>
<tr>
<td></td>
<td>≥ 80 to &lt; 90 kg: 45 mg</td>
</tr>
<tr>
<td></td>
<td>≥ 90 kg: 50 mg</td>
</tr>
</tbody>
</table>

## Contraindications

### Absolute
- History of haemorrhagic stroke or stroke of unknown origin
- Ischaemic stroke in previous 6 months
- Central nervous system neoplasms
- Major trauma, surgery, or head injury in previous 3 weeks

### Relative
- Transient ischaemic attack in previous 6 months
- Oral anticoagulation
- Pregnancy or first postpartum week
- Non-compressible puncture sites
- Traumatic resuscitation
- Refractory hypertension (systolic blood pressure > 180 mmHg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer
Indications for Vena Caval Interruption

1. Contraindication to anticoagulation
2. Recurrent emboli on adequate Tx
3. Serious bleeding on anticoagulation
4. Massive pulmonary embolism
5. Psychosocial reasons
Surgical Treatment

- Pulmonary embolectomy is a recommended therapeutic option in patients with high-risk PE in whom there are absolute contraindications to thrombolysis, or if thrombolysis has failed.[5,53]

- Recent technical advances in transportable extracorporeal assist systems, and particularly the timely early involvement of the cardiac surgeon as part of an interdisciplinary approach to high-risk PE before haemodynamic collapse, have contributed to improved postoperative outcomes and case fatality rates as low as 23%.[58]
Interventional Treatment

In case of absolute contraindications to thrombolysis:

- thrombus fragmentation
- rheolytic thrombectomy
- suction thrombectomy
- rotational thrombectomy
A 57-year-old woman presented in extremis from massive bilateral PE. The patient was referred to the Interventional Radiology Department when there was no response to IV infusion of 100 mg of tPA. Both lungs were treated emergently with CDI, including 20 mg of local TNK. Pulmonary angiograms of the left lung, before and after CDI, are shown. Top, a: left pulmonary angiogram demonstrates a persistent massive PE, despite treatment with systemic TPA, and flow into the left lung is severely compromised. Bottom, b: following CDI, left lung perfusion is improved. Similar maneuvers were performed in the right lung (not shown) with good results and resolution of shock. Reproduced with permission from Sze et al.¹³
Outpatient Tx for PE

• Normotensive patients without serious comorbidity or signs of (right) heart failure belong to a low-risk group which could be treated out of hospital.[65–67]


Outpatient Tx for PE

- A randomized study reported that low-risk patients as defined by the PE severity index can safely be discharged within 24 h and treated as outpatients.[23

In a randomized, open-label, event-driven, noninferiority trial involving 4832 patients who had acute symptomatic pulmonary embolism with or without deep-vein thrombosis, we compared rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with standard therapy with enoxaparin followed by an adjusted-dose vitamin K antagonist for 3, 6, or 12 months. The primary efficacy outcome was symptomatic recurrent venous thromboembolism. The principal safety outcome was major or clinically relevant nonmajor bleeding.
Cumulative Rates of the Primary Efficacy and Safety Outcomes and Rates of Major Bleeding.

"Hmmm... Sounds grave, very grave. We'll know more after the autopsy!"