Introduction

• Venous thromboembolism (VTE) is the third most common cardiovascular disease after MI and stroke
• Current standard of treatment: heparin/vitamin K antagonist (VKA)
• New oral anticoagulants with and without heparin are effective and safe in the treatment of VTE
Pulmonary Embolism

Global Trends

STATE-OF-THE-ART REVIEW

Management of Pulmonary Embolism
An Update

Stavros V. Constantinides, MD, PhD,² Stefano Barco, MD,² Mareike Lankeit, MD,² Guy Meyer, MD²

PRE-TEST CLINICAL ASSESSMENT

- Revised Geneva score
- Wells rule
- Empirical assessment

DIAGNOSIS

- Age-adjusted D-dimers
- CTPA
- V/Q scan
- Echocardiography
- CUS

ACUTE RISK STRATIFICATION

- FESI and iPEIS
- Biochemical markers
- RV dysfunction
- RV enlargement (CTPA)

TREATMENT

- Parenteral anticoagulants
- Oral anticoagulants
- Fibrinolysis
- Catheter-directed techniques
- Surgical embolectomy
- Venous filters

LONG-TERM CLINICAL COURSE

- Recanalization
- Repeat VTE recurrence
- Increased risk of CTEPH

(J Am Coll Cardiol 2016;67:976-90)
Goals of VTE treatment

Initial Treatment
- Acute Clot:
  - Stop propagation
  - Prevent embolism
  - Protect pulmonary circulation
  - Restore venous return

Long-term Prevention
- Prevent Recurrent VTE
- Postthrombotic syndrome
- CTEPH

Minimize Bleeding Risk

CTEPH = chronic thromboembolic pulmonary hypertension

New concepts in anticoagulation therapy

Conventional therapy
- Heparin plus VKA

New therapy
- Single drug approach
- Higher initial dose

www.escardio.org
Acute VTE Treatment Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>RE-COVER</th>
<th>EINSTEINbc</th>
<th>AMPLIFYd</th>
<th>Hokusaie</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2589</td>
<td>8281</td>
<td>5395</td>
<td>8240</td>
</tr>
<tr>
<td>Design</td>
<td>2 x blind</td>
<td>PROBE</td>
<td>2 x blind</td>
<td>2 x blind</td>
</tr>
<tr>
<td>Indication</td>
<td>VTE</td>
<td>DVT or PE</td>
<td>VTE</td>
<td>VTE</td>
</tr>
<tr>
<td>Heparin bridge</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration, mo</td>
<td>6</td>
<td>3, 6, 12</td>
<td>6</td>
<td>3-12</td>
</tr>
</tbody>
</table>


RE-COVER II
Study Design

- Primary efficacy outcomes: Symptomatic recurrent VTE and related death
- Principal safety outcome: Major bleeding

**RE-COVER II**

*Results*

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>2.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Safety</td>
<td>1.2</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*P < .001 (for noninferiority)*


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**EINSTEIN DVT/PE**

*Study Designs*

- Open-label, noninferiority study

**EINSTEIN-DVT:** Objectively confirmed VTE without PE

N = 3449

Rivaroxaban 15 mg twice daily for 21 days, plus VKA INR 2.0 to 3.0

- Primary efficacy outcome: Symptomatic recurrent VTE
- Principal safety outcome: Major or nonmajor clinically relevant bleeding

**EINSTEIN-PE:** Objectively confirmed PE ± DVT

N = 4832

Day 1

Rivaroxaban 20 mg once daily for 3, 6, or 12 months


EINSTEIN DVT/PE

Result - Efficacy

Cumulative event rate for primary efficacy outcome (%)

- ENOXAPARIN-VKA (n=1718)
- RIVAROXABAN (n=1731)

P < 0.001 FOR NONINFERIORITY

DAYS

EINSTEIN-DVT and EINSTEIN-PE
Pooled analysis: Major bleeding

First major bleeding

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>Enoxaparin/VKA</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40/4130 (1.0)</td>
<td>72/4116 (1.7)</td>
<td>0.54 (0.37–0.79)</td>
<td>p=0.002</td>
</tr>
</tbody>
</table>

Cumulative event rate (%)

Time to event (days)

Number of patients at risk:
- Rivaroxaban: 4130, 3921, 3862, 3611, 3479, 3433, 3433, 2074, 1135, 1095, 1025, 989, 947, 496
- Enoxaparin/VKA: 4116, 3868, 3784, 3525, 3394, 3348, 1835, 1109, 1065, 990, 956, 916, 409

**EINSTEIN Pooled Data**

**Fragile Patients**

- Elderly (>75 years)
- Body weight ≤ 50 kg
- Renal failure (Cr Cl < 50 mL/min)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban, % (n = 791)</th>
<th>Enoxaparin/VKA, % (n = 782)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence of thromboembolism</td>
<td>2.7</td>
<td>3.8</td>
<td>0.68 (0.39-1.18)</td>
<td>--</td>
</tr>
<tr>
<td>Overall</td>
<td>2.1</td>
<td>2.3</td>
<td>0.89 (0.66-1.19)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.3</td>
<td>4.5</td>
<td>0.27 (0.13-0.54)</td>
<td>--</td>
</tr>
<tr>
<td>Overall</td>
<td>1.0</td>
<td>1.7</td>
<td>0.54 (0.37-0.79)</td>
<td>.002</td>
</tr>
</tbody>
</table>


**AMPLIFY**

**Study Design**

- Patients with DVT or PE ± DVT
- N = 5395
- Apixaban 10 mg twice daily for 7 days
- Apixaban 5 mg twice daily
- Enoxaparin every 12 hours for 5 or more days and warfarin to INR 2.0 to 3.0
- Follow-up at 6 months

- Primary efficacy outcome: Symptomatic recurrent VTE or VTE-related death
- Principal safety outcome: Major bleeding

**AMPLIFY Results**

**Efficacy**

- **Recurrent VTE**
  - **Apixaban**: 2.3
  - **Conventional Therapy**: 2.7

- **P < .001 (noninferiority)**

**Safety**

- **Major Bleeding**
  - **Apixaban**: 0.8
  - **Conventional Therapy**: 1.8

- **CRNM Bleeding**
  - **Apixaban**: 3.8
  - **Conventional Therapy**: 8

- **Major or CRNM Bleeding**
  - **Apixaban**: 4.3
  - **Conventional Therapy**: 9.7

- **P < .001 (superiority)**

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**Hokusai-VTE Study Design**

- **Maximum treatment period of 12 months**

**Day 1**

- **Symptomatic DVT and/or PE**
  - LMWH/UFH (at least 5 days) + edoxaban 60 mg once daily
  - LMWH/UFH (at least 5 days) + warfarin (INR, 2.0-3.0)

**Edoxaban**

- **Standard therapy**

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- **Primary efficacy outcome:**
  - Symptomatic recurrent VTE or VTE-related death

- **Principal safety outcome:**
  - Major or CRNM bleeding during treatment

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*References*

**Hokusai-VTE Results**

- **Efficacy**
  - Edoxaban: 3.2%
  - Warfarin: 3.5%

- **Safety**
  - P = 0.004 (superiority)
  - P < 0.001 (noninferiority)


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**Treatment of acute DVT/PE: NOACs non-inferior to warfarin for prevention of recurrent DVT/PE in Phase III trials**

- RE-COVER™/RE-COVER™ II: Dabigatran
- EINSTEIN-DVT/EINSTEIN-PET: Rivaroxaban
- AMPLIFY: Apixaban
- Hokusai-VTE: Edoxaban

**Patients (%)**

<table>
<thead>
<tr>
<th>Study</th>
<th>HR</th>
<th>CI</th>
<th>NOAC</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER™/II</td>
<td>1.09</td>
<td>(0.78–1.57)</td>
<td>2.4%</td>
<td>2.2%</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>0.89</td>
<td>(0.66–1.19)</td>
<td>2.1%</td>
<td>2.3%</td>
</tr>
<tr>
<td>EINSTEIN-PET</td>
<td>0.84</td>
<td>(0.66–1.18)</td>
<td>2.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>0.82</td>
<td>(0.66–1.14)</td>
<td>1.6%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Direct comparisons cannot be made as no head-to-head data are available.

Treatment of acute DVT/PE: NOACs associated with less major bleeding than warfarin in Phase III trials

Direct comparisons cannot be made as no head-to-head data are available
*Statistically significant reductions for dabigatran, rivaroxaban, and apixaban vs warfarin, numerical reduction for edoxaban vs warfarin. 1Pooled data from RE-COVERTM and RE-COVERTM II oral drug treatment period only. 2Pooled analysis. 3On treatment

Phase 3 Secondary Prevention (Extension) Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Oral Agent Tested</th>
<th>Comparator</th>
<th>N*</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-MEDY</td>
<td>Dabigatran etexilate 150 mg BID</td>
<td>Warfarin PRN (INR 2.0-3.0) (All patients received 3-6 months of anticoagulation for symptomatic acute VTE before randomization)</td>
<td>2700</td>
<td>18 months</td>
</tr>
<tr>
<td>RE-SONATE</td>
<td>Dabigatran etexilate 150 mg BID</td>
<td>Placebo (All patients received 6-18 months of VKA for symptomatic acute VTE before randomization)</td>
<td>1462</td>
<td>6 months</td>
</tr>
<tr>
<td>AMPLIFY-EXT</td>
<td>Apixaban 2.5 mg BID 5.0 mg BID</td>
<td>Placebo (All patients completed intended treatment for DVT or PE before randomization)</td>
<td>2430</td>
<td>12 months</td>
</tr>
<tr>
<td>EINSTEIN-EXT</td>
<td>Rivaroxaban 20 mg QD</td>
<td>Placebo (All patients received 6-12 months of anticoagulant treatment for symptomatic acute VTE before randomization)</td>
<td>1197</td>
<td>6-12 months</td>
</tr>
</tbody>
</table>
**RE-MEDY Study Design**

Anticoagulant therapy 3 to 12 months and “increased risk of recurrence”

Confirmed VTE

Screening/baseline

0 to 7 days until INR ≤ 2.3

Dabigatran etexilate 150 mg twice daily

Warfarin (INR, 2.0-3.0)

Follow-up every 30 days to 6 months, then every 90 days to end of treatment

Up to 36 months End of treatment


**RE-SONONATE Study Design**

Anticoagulant (VKA) therapy 6 to 18 months

Confirmed VTE

Screening

0 to 7 days until INR ≤ 2.3

Dabigatran etexilate 150 mg twice daily

Placebo

Follow-up 30 days

Extended follow-up 11 months

6 months End of treatment

7 months End of study follow-up

18 months End of extension follow-up

RE-MEDY, RE-SONATE

Results

Efficacy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RE-MEDY</th>
<th>RE-SONATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.3</td>
<td>10.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.4</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Safety

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RE-MEDY</th>
<th>RE-SONATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>0.9</td>
<td>0</td>
</tr>
<tr>
<td>Major/CR Bleeding</td>
<td>1.8</td>
<td>1.8</td>
</tr>
</tbody>
</table>


EINSTEIN-Extension

Study Design

Equipoise: Should treatment be continued or not?

Patients in EINSTEIN-DVT who had completed 6 to 12 months of therapy

N = 1197

Rivaroxaban 20 mg once daily

Additional 6 to 12 months of treatment

- Primary efficacy outcome: Symptomatic recurrent VTE
- Principal safety outcome: Major bleeding

**EINSTEIN-Extension**

### Results

#### Recurrent VTE

<table>
<thead>
<tr>
<th></th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>1.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.1</td>
</tr>
</tbody>
</table>

\[ P < .001 \]

#### Safety

<table>
<thead>
<tr>
<th></th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>0.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.2</td>
</tr>
</tbody>
</table>

\[ P < .001 \]


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**AMPLIFY-EXT**

### Study Design

**Equipoise:** Should treatment be continued or not?

- Clinical diagnosis of DVT or PE, anticoagulation treatment 6 to 12 months, no recurrence

- Apixaban 2.5 mg twice daily
- Apixaban 5 mg twice daily
- Follow-up at 12 months

N = 2482

- Primary endpoint: VTE recurrence or death
- Secondary outcome measures: Major bleeding

AMPLIFY-EXT

Results


Recurrent VTE in Extension VTE Trials

Incidence of Recurrent VTE

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>NOAC, %</th>
<th>Warfarin, %</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-MEDY</td>
<td>Dabigatran</td>
<td>1.8</td>
<td>1.3</td>
<td>1.44 (0.78-2.64)</td>
</tr>
<tr>
<td>RE-SONATE</td>
<td>Dabigatran</td>
<td>0.4</td>
<td>5.6</td>
<td>0.08 (0.02-0.25)</td>
</tr>
<tr>
<td>EINSTEIN-EXT</td>
<td>Rivaroxaban</td>
<td>1.3</td>
<td>7.1</td>
<td>0.18 (0.09-0.39)</td>
</tr>
<tr>
<td>AMPLIFY-EXT</td>
<td>Apixaban 2.5 mg</td>
<td>1.7</td>
<td>8.8</td>
<td>0.19 (0.11-0.33)</td>
</tr>
<tr>
<td></td>
<td>Apixaban 5 mg</td>
<td>1.7</td>
<td>8.8</td>
<td>0.20 (0.11-0.34)</td>
</tr>
</tbody>
</table>

## Major Bleeding in Extension VTE Trials

### Incidence of Major Bleeding

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>NOAC, %</th>
<th>Warfarin, %</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-MEDYa</td>
<td>Dabigatran</td>
<td>0.9</td>
<td>1.8</td>
<td>0.52 (0.27-1.02)</td>
</tr>
<tr>
<td>RE-SONATEa</td>
<td>Dabigatran</td>
<td>0.3</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>EINSTEIN-EXTb</td>
<td>Rivaroxaban</td>
<td>0.7</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>AMPLIFY-EXTc</td>
<td>Apixaban 2.5 mg</td>
<td>0.2</td>
<td>0.5</td>
<td>0.49 (0.09-2.64)</td>
</tr>
<tr>
<td></td>
<td>Apixaban 5 mg</td>
<td>0.1</td>
<td>0.5</td>
<td>0.25 (0.03-2.24)</td>
</tr>
</tbody>
</table>

Current standard of care

- LMWH + warfarin > 5 d
  - Warfarin daily (INR 2-3)
  - Warfarin daily (INR 2-3)

LMWH initially then switch:

- LMWH 5 d
  - Dabigatran (150 mg BD)
  - Dabigatran (150 mg BD)

- LMWH 5 d
  - Edoxaban daily (60 mg or 30 mg)
  - No data currently

Single oral agent:

- Apixaban 10 mg BD 1 wk
  - Apixaban (5 mg BD)
  - Apixaban (2.5 mg BD)

- Rivaroxaban 15 mg BD 3 wk
  - Rivaroxaban (20 mg daily)
  - Rivaroxaban (20 mg daily)

Initial treatment: Acute/long term treatment (3 mo) Extended treatment (12 mo)

### Assessment of pre-test probability

#### Clinical prediction rules for pulmonary embolism

<table>
<thead>
<tr>
<th>Wells rule</th>
<th>Clinical decision rule points</th>
</tr>
</thead>
<tbody>
<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>Haemophysis</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

<table>
<thead>
<tr>
<th>Three-level score</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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Two-level score</th>
<th>PE unlikely</th>
<th>PE likely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-4</td>
<td>2-5</td>
</tr>
</tbody>
</table>

---

### Assessment of pre-test probability (cont’d)

#### Clinical prediction rules for pulmonary embolism (cont.)

<table>
<thead>
<tr>
<th>Revised Geneva score</th>
<th>Clinical decision rule points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous DVT or PE</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate</td>
<td>3</td>
</tr>
<tr>
<td>75-94 b.p.m.</td>
<td>5</td>
</tr>
<tr>
<td>≥95 b.p.m.</td>
<td>2</td>
</tr>
<tr>
<td>Surgery or fracture within the past month</td>
<td>2</td>
</tr>
<tr>
<td>Haemophysis</td>
<td>2</td>
</tr>
<tr>
<td>Active cancer</td>
<td>2</td>
</tr>
<tr>
<td>Unilateral lower limb pain</td>
<td>3</td>
</tr>
<tr>
<td>Pain on lower limb deep venous palpation and unilateral oedema</td>
<td>4</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>1</td>
</tr>
</tbody>
</table>

#### Clinical probability

<table>
<thead>
<tr>
<th>Three-level score</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-3</td>
<td>4-10</td>
<td>≥11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Two-level score</th>
<th>PE unlikely</th>
<th>PE likely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-5</td>
<td>2-6</td>
</tr>
</tbody>
</table>
### Classification of early mortality risk

<table>
<thead>
<tr>
<th>Early mortality risk</th>
<th>Shock or hypotension</th>
<th>PESI Class III-V or sPESI $\geq 1$</th>
<th>Signs of RV dysfunction on an imaging test</th>
<th>Cardiac laboratory biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>Intermediate</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</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>-</td>
<td>-</td>
<td>Assessment optional; if assessed, both negative</td>
<td></td>
</tr>
</tbody>
</table>

---

### Original and simplified pulmonary embolism severity index (PESI)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Original version</th>
<th>Simplified version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age in years</td>
<td>1 point (if age $\geq 80$ years)</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10</td>
<td>-</td>
</tr>
<tr>
<td>Cancer</td>
<td>+30</td>
<td>1</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>+10</td>
<td>1</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>+10</td>
<td>1</td>
</tr>
<tr>
<td>Pulse rate $\geq 110$ b.p.m.</td>
<td>+20</td>
<td>1</td>
</tr>
<tr>
<td>Systolic blood pressure $&lt;100$ mmHg</td>
<td>+30</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory rate $&gt;30$ breaths per minute</td>
<td>+20</td>
<td>-</td>
</tr>
<tr>
<td>Temperature $&lt;36^\circ$C</td>
<td>+20</td>
<td>-</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60</td>
<td>-</td>
</tr>
<tr>
<td>Arterial oxygen saturation $&lt;90$%</td>
<td>+20</td>
<td>1</td>
</tr>
</tbody>
</table>
**Original and simplified pulmonary embolism severity index (PESI)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Original version</th>
<th>Simplified version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk strata</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I: ≤65 points</td>
<td>very low 30-day mortality risk (0-1.6%)</td>
<td>0 points = 30-day mortality risk 1.0% (95% CI 0.0%-2.1%)</td>
</tr>
<tr>
<td>Class II: 66-85 points</td>
<td>low mortality risk (1.7-3.5%)</td>
<td></td>
</tr>
<tr>
<td>Class III: 86-105 points</td>
<td>moderate mortality risk (3.2-7.1%)</td>
<td>≥1 point(s) = 30-day mortality risk 10.9% (95% CI 8.5%-13.2%)</td>
</tr>
<tr>
<td>Class IV: 106-125 points</td>
<td>high mortality risk (4.0-11.4%)</td>
<td></td>
</tr>
<tr>
<td>Class V: &gt;125 points</td>
<td>very high mortality risk (10.0-24.5%)</td>
<td></td>
</tr>
</tbody>
</table>

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**Risk-adjusted management algorithm**

- **Clinical suspicion of PE**
  - Shock / Hypotension?
    - Yes
      - Diagnostic algorithm as for suspected high-risk PE
      - PE confirmed
    - No
      - Diagnostic algorithm as for suspected not high-risk PE
      - PE confirmed
        - Intermediate risk
          - RV function (echo or CT) Laboratory testing
            - Both positive / Both negative
              - Low risk
                - AIC: consider early discharge and home treatment, if feasible
              - One positive / One negative
                - Intermediate-low risk
                  - AIC: hospitalization
              - One positive / Both negative
                - Intermediate-high risk
                  - AIC: monitoring consider rescue reperfusion
              - Both positive
                - High risk
                  - Primary reperfusion
      - PE confirmed
        - Intermediate-low risk
          - RV function (echo or CT) Laboratory testing
            - Both positive / Both negative
              - Low risk
                - AIC: consider early discharge and home treatment, if feasible
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                - AIC: hospitalization
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          - AIC: monitoring consider rescue reperfusion
      - Both positive
        - High risk
          - Primary reperfusion
  - Low risk
    - AIC: consider early discharge and home treatment, if feasible
# Thrombolytic treatment of PE

<table>
<thead>
<tr>
<th>Approved thrombolytic regimen for pulmonary embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Streptokinase</strong></td>
</tr>
<tr>
<td>250,000 IU as a loading dose over 30 minutes, followed by 100,000 IU/h over 12-24 hours.</td>
</tr>
<tr>
<td>Accelerated regimen: 1.5 million IU over 2 hours.</td>
</tr>
<tr>
<td><strong>Urokinase</strong></td>
</tr>
<tr>
<td>4400 IU/kg as a loading dose over 10 min., followed by 4400 IU/kg per hour over 12-24 hours.</td>
</tr>
<tr>
<td>Accelerated regimen: 3 million IU over 2 hours.</td>
</tr>
<tr>
<td><strong>rtPA</strong></td>
</tr>
<tr>
<td>100 mg over 2 hours; or</td>
</tr>
<tr>
<td>0.6 mg/kg over 15 minutes (maximum dose 50 mg).</td>
</tr>
</tbody>
</table>