Evolving Strategies in Venous Thromboembolism

Acute PE: Where, What, and How Long?

Victor F. Tapson, MD, FCCP, FRCP
Disclosures

• University Grant Monies
  – Actelion, Bayer, Gilead, Novartis, Pfizer, United Therapeutics

• Consultant Fee, Speaker Bureau, Advisory Committee, etc.
  – Actelion, Bayer, Gilead, United Therapeutics, Lung Biotechnology, Janssen, Daiichi
Objective

- Identify patients who may benefit from alternative therapies and outpatient based therapy
Nearly 20 Years of Outpatient DVT Therapy!

Acute DVT May Be Managed In The Outpatient Setting

- Controlled clinical trials suggest that outpatient management is at least as effective as inpatient management for acute DVT.
- Representative studies: 2000 - 2005

VTE Recurrence (%) and Major Bleeding (%)

<table>
<thead>
<tr>
<th>Study</th>
<th>VTE Recurrence (%)</th>
<th>Major Bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramacciotti et al, 2004</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Daskalopoulos et al, 2005</td>
<td>9.1</td>
<td>11.3</td>
</tr>
<tr>
<td>Chong et al, 2005</td>
<td>2.7</td>
<td>9.5</td>
</tr>
<tr>
<td>Boccalon et al, 2000</td>
<td>1.2</td>
<td>2</td>
</tr>
</tbody>
</table>

Shifting from Inpatient to Outpatient Treatment of Deep Vein Thrombosis in a Tertiary Care Center: A Cost-Minimization Analysis


Study Objective. To compare the cost of contemporary outpatient and historical inpatient management of proximal lower limb deep vein thrombosis (DVT) in adults.

Design. Prospective, observational study with historical inpatient cases as controls.

Setting. Ambulatory thrombosis clinic of a tertiary care teaching center in Canada.

Patients. Forty-nine inpatients with DVT from a previous study in 1996 at the same institution who would have been eligible for outpatient therapy if this option had been available, and 51 consecutive patients referred to the ambulatory clinic for DVT who were started on LMWH.

Mean cost/DVT case decreased from $2826 to $248. (CI $216 - $280; p<0.0005)

Outpatients received low-molecular-weight heparin (LMWH).

Measurements and Main Results. A cost-minimization analysis restricted to
WHAT ABOUT ACUTE PE?
DEFINITIONS

• Outpatient therapy – discharge in < 24 h
• Early discharge – discharge 24-72 h
• Thus, “standard” discharge = discharge after > 72 h

(ACCP definition of standard discharge is > 5 days)
What are the Potential Risks of Outpatient PE Therapy?

- Recurrence with the potential for death
- Bleeding with the potential for death
- Litigation

- **Are these concerns *different* in the inpatient setting?**
Which of the following would be the most acceptable scenario for outpatient acute PE therapy (patient diagnosed 2 hours ago)?

A. Bilateral, extensive acute PE with transient hypotension (RA O2 sat 93%)

B. Bilateral acute PE and unilateral iliofemoral DVT in a pregnant patient requiring no O2

C. Subdural hematoma occurring 12 months prior (trauma)

D. Small PE with normal RV, in 80 y-o patient with mild stable CHF and a creatinine of 3.0

E. Submassive PE in a comfortable appearing nursing home patient with Alzheimer’s
Acute VTE: Case Fatality Rates

Patients with PE treated in the hospital:
• 0.4% for fatal recurrent PE within the first 3 months
• 3% risk for nonfatal recurrent PE (1).

• 0.2% risk of fatal major bleeding within 3 months after PE
• 2.0% risk of nonfatal major bleed (1,2).

• Even in PEITHO (submassive PE), rates of recurrence, major bleeding and death were very low in anticoagulated patients...

Early vs Standard Discharge of Patients With Acute PE

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.

ACCP 2012
Meta-analyses and Systematic Reviews


Outpatient *versus* inpatient treatment in patients with pulmonary embolism: a meta-analysis

Wendy Zondag¹, Judith Kooiman¹, Frederikus A. Klok¹, Olaf M. Dekkers² and Menno V. Huisman¹

Affiliations:
¹Dept of Thrombosis and Haemostasis, LUMC, Leiden, and
²Dept of Epidemiology, LUMC, Leiden, The Netherlands.

Correspondence:
W. Zondag, Dept of Thrombosis and Haemostasis, Leiden University Medical Centre, Postbus 9600, 2300 RC Leiden, The Netherlands.
E-mail: W.Zondag@lumc.nl

ABSTRACT Our aim was to study the safety of outpatient treatment in low risk patients with acute pulmonary embolism compared with inpatient treatment, the current clinical standard.

We searched Medline, Web of Science, Cochrane and EMBASE databases and included studies on outpatient treatment of pulmonary embolism. The outcomes were 3-month recurrent venous thromboembolism, major bleeding and all-cause mortality. We identified 13 studies (1657 patients) with outpatients (discharge <24 h), three studies (256 patients) with early discharge patients (discharged within 72 h) and five studies (383 patients) with inpatients. The pooled incidence of recurrent venous thromboembolism was 1.7% (95% CI 0.92–3.1%) in outpatients, 1.1% (0.22–5.4%) in patients discharged early and 1.2% (0.16–8.1%) in inpatients. The pooled incidence of major bleeding was 0.97% (0.58–1.6%) in outpatients, 0.78% (0.16–3.7%) in early discharge patients and 1.0% (0.39–2.8%) in inpatients. The pooled incidence of mortality was 1.9% (0.79–4.6%) in outpatients, 2.3% (1.1–5.1%) in early discharge patients and 0.74% (0.04–11%) in inpatients.

Incidence of recurrent venous thromboembolism, major bleeding and, after correction for malignancies, mortality were comparable between outpatients, patients discharged early and inpatients. We conclude that home treatment or early discharge of selected low-risk patients with pulmonary embolism is as safe as inpatient treatment.
Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis

Wendy Zondag¹, Judith Kooiman¹, Frederikus A. Klok¹, Olaf M. Dekkers² and Menno V. Huisman¹

Outpatient/early d/c in most studies was ≤24 h. (A few were ≤72 h)

Only considered low-risk PE patients

Figure 1– Flow chart showing selection of studies.
Exclusion Criteria For Outpatient Therapy

- Hemodynamic instability
- Respiratory instability
- IV pain medication
- Bleeding risk
- Therapeutic oral anticoagulation
- Comorbidities
- Social reasons
- Pregnancy
- Renal impairment
- Contraindications to LMWH
The pooled incidence of recurrent VTE was:
- 1.7% (95% CI 0.92–3.1%) in outpatients (< 24 hours)
- 1.1% (0.22–5.4%) in patients discharged early (24 – 72 hours)
- 1.2% (0.16–8.1%) in inpatients

The pooled incidence of major bleeding was:
- 0.97% (0.58–1.6%) in outpatients
- 0.78% (0.16–3.7%) in early discharge patients
- 1.0% (0.39–2.8%) in inpatients
The pooled incidence of mortality was:

1.9% (0.79–4.6%) in outpatients
2.3% (1.1–5.1%) in early discharge patients
0.74% (0.04–11%) in inpatients

• Incidences of recurrent VTE, major bleeding and, after correction for malignancies, mortality were comparable between outpatients, patients discharged early and inpatients.
### PULMONARY VASCULAR DISEASE | W. ZONDAG ET AL.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cohort</th>
<th>Studies n</th>
<th>Patients n</th>
<th>Events n</th>
<th>Absolute risk % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>Home treatment</td>
<td>13</td>
<td>1657</td>
<td>33</td>
<td>1.70 (0.92–3.12)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>Early discharge</td>
<td>3</td>
<td>256</td>
<td>3</td>
<td>1.12 (0.22–5.43)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>Hospital treatment</td>
<td>4</td>
<td>329</td>
<td>6</td>
<td>1.18 (0.16–8.14)</td>
</tr>
<tr>
<td>Mortality</td>
<td>Home treatment</td>
<td>13</td>
<td>1657</td>
<td>49</td>
<td>1.94 (0.79–4.84)</td>
</tr>
<tr>
<td>Mortality</td>
<td>Early discharge</td>
<td>3</td>
<td>256</td>
<td>6</td>
<td>2.34 (1.06–5.12)</td>
</tr>
<tr>
<td>Mortality</td>
<td>Hospital treatment</td>
<td>5</td>
<td>383</td>
<td>8</td>
<td>0.74 (0.04–11.14)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Home treatment</td>
<td>12</td>
<td>1555</td>
<td>15</td>
<td>0.97 (0.58–1.59)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Early discharge</td>
<td>3</td>
<td>256</td>
<td>2</td>
<td>0.78 (0.16–3.73)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Hospital treatment</td>
<td>5</td>
<td>383</td>
<td>4</td>
<td>1.04 (0.39–2.75)</td>
</tr>
</tbody>
</table>

**FIGURE 2** Pooled incidences of clinical outcome after pulmonary embolism in patients treated at home, discharged early or treated as inpatients.
RESULTS

• Of the 1657 patients treated as outpatients, 49 died but none died of fatal PE (none died of PE in early d/c group either).
• Point estimates for mortality were higher in outpatient group (1.9% vs. 0.74%), but the CI were overlapping.
• After excluding studies with > 15% malignancy, the pooled mortality in outpatients decreased to 0.6% (vs 0.74% for inpatients).
• This significantly differed from the pooled mortality of 4.2% in the outpatients studies with a high proportion (>15%) of malignancies) (p=0.003).
Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis

Wendy Zondag¹, Judith Kooiman¹, Frederikus A. Klok¹, Olaf M. Dekkers² and Menno V. Huisman¹

Conclusions:
We conclude that home treatment or early discharge of selected low-risk patients with pulmonary embolism is as safe as inpatient treatment.

How should we risk stratify?
Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial

Prof Drahomír Aujesky MD a, Prof Pierre-Marie Roy MD b, Franck Verschuren MD c, Marc Righini MD d, Joseph Osterwalder MD e, Michael Egloff MD f, Bertrand Renaud MD g, Peter Verhamme MD h, Prof Roslyn A Stone PhD i, Catherine Legall MD j, Olivier Sanchez MD k, Nathan A Pugh BS l, Alfred N’gako MD m, Prof Jacques Cornuz MD n, Olivier Hugli MD o, Prof Hans-Jürg Beer MD f, Prof Arnaud Perrier MD d, Prof Michael J Fine MD i, Prof Donald M Yealy MD k

Summary

Background
Although practice guidelines recommend outpatient care for selected, haemodynamically stable patients with pulmonary embolism, most treatment is presently inpatient based. We aimed to assess non-inferiority of outpatient care compared with inpatient care.

The Lancet 2011; 378: (9785) Pages 41 – 48
Published Online: 23 June 2011
Outpatient Treatment May Be An Option For Patients With Low-risk PE

- **Methods**
  - Open-label, randomised non-inferiority trial at 19 EDs in Switzerland, France, Belgium, and the USA.
  - Acute, symptomatic PE and low risk of death (PESI risk class I or II)
  - Randomized to initial outpatient (ie, discharged from hospital ≤24 h after randomization) or inpatient treatment with SC enoxaparin (≥5 days) followed by oral anticoagulation (≥90 days).
  - Primary outcome was symptomatic, recurrent VTE within 90 days
  - Safety outcomes included major bleeding within 14 or 90 days and mortality within 90 days.
  - We used a non-inferiority margin of 4% for a difference between inpatient and outpatient groups.

Published Online: 23 June 2011
Outpatient Treatment May Be An Option For Patients With Low-risk PE

Results

• Between Feb, 2007, and June, 2010, 344 eligible patients enrolled.
• In primary analysis, one (0·6%) of 171 outpatients developed recurrent VTE within 90 d compared with none of 168 inpatients (95% upper CL 2·7%; p=0·011).
• One (0·6%) patient in each group died within 90 d (95% upper CL 2·1%; p=0·005).
• Two (1·2%) of 171 outpatients and no inpatients had major bleeding within 14 days (95% UCL 3·6%; p=0·031).
• By 90 days, three (1·8%) outpatients but no inpatients developed major bleeding (95% UCL 4·5%; p=0·086). Mean length of stay was 0·5 days (SD 1·0) for outpatients and 3·9 days (SD 3·1) for inpatients.

Published Online: 23 June 2011
The PESI\(^1\) and Simplified PESI\(^2\) Are Validated Tools to Identify Patients With Low-Risk PE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>sPESI</th>
<th>PESI</th>
<th>sPESI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&gt;80 years)</td>
<td>Age (years)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>10</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of cancer</td>
<td>30</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hx of heart failure</td>
<td>10</td>
<td></td>
<td>1(^*)</td>
<td></td>
</tr>
<tr>
<td>Hx of chronic lung disease</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse ≥110 bpm</td>
<td>20</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP &lt;100 mm Hg</td>
<td>30</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate ≥30 breaths/min</td>
<td>20</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature &lt;36°C</td>
<td>20</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered mental status(^†)</td>
<td>60</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SaO(_2) &lt;90%(^‡)</td>
<td>20</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Classification by Total Score

<table>
<thead>
<tr>
<th>PESI</th>
<th>sPESI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>≤65</td>
</tr>
<tr>
<td>Class II</td>
<td>66-85</td>
</tr>
<tr>
<td>Class III</td>
<td>86-105</td>
</tr>
<tr>
<td>Class IV</td>
<td>106-125</td>
</tr>
<tr>
<td>Class V</td>
<td>&gt;125</td>
</tr>
</tbody>
</table>

\(^1\)With or without the administration of supplemental oxygen.  
The PESI\(^1\) and Simplified PESI\(^2\) Are Validated Tools to Identify Patients With Low-Risk PE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>Classification by Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PESI</td>
<td>sPESI</td>
</tr>
<tr>
<td>Age &gt;80 years</td>
<td>Age (years)</td>
<td>1</td>
</tr>
<tr>
<td>Male sex</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>History of cancer</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Hx of heart failure</td>
<td>10</td>
<td>1*</td>
</tr>
<tr>
<td>Hx of chronic lung disease</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Pulse ≥110 bpm</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Systolic BP &lt;100 mm Hg</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory rate ≥30 breathes/min</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Temperature &lt;36°C</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Altered mental status(^†)</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>(\text{SaO}_2) &lt;90%(^‡)</td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>

\(\text{PESI}^1\) and \(\text{sPESI}^2\) Are Validated Tools to Identify Patients With Low-Risk PE

Outpatient Treatment May Be An Option For Patients With Low-risk PE

- Patients with low-risk PE (by PESI score) randomized to receive outpatient or inpatient treatment with enoxaparin / VKA

<table>
<thead>
<tr>
<th></th>
<th>Outcomes Within 14 days, n (%)</th>
<th>Outcomes Within 90 days, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outpatient (n=171)</td>
<td>Inpatient (n=168)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*P value for noninferiority.
†Patient died from accident-related trauma with resultant aortic rupture.
‡Patient died from pneumonia and lung cancer.

Derivation and Validation of Multimarker Prognostication for Normotensive Patients with Acute Symptomatic Pulmonary Embolism

David Jimenez1, Dita Kopecna1, Victor Tapson2, Beau Briese3, Donald Schreiber3, Jose´ Luis Lobo4, Mnuel Monreal5, Drahomir Aujesky6, Olivier Sanchez7, Guy Meyer7, Stavros Konstantinides8, and Roger D. Yusen9; on behalf of the PROTECT Investigators*

1Respiratory Department, Ramon y Cajal Hospital, IRYCIS, Madrid, Spain; 2Division of Pulmonary and Critical Care Medicine, Duke University Medical Center, Durham, NC; 3Division of Emergency Medicine, Stanford University School of Medicine, Palo Alto, CA; 4Respiratory Department, Txagorritxu Hospital, Vitoria, Spain; 5Medicine Department, Germans Trias I Pujol Hospital, Badalona, Spain; 6Division of General Internal Medicine, Bern University Hospital, Bern, Switzerland; 7Universite´ Paris Descartes, Sorbonne Paris Cite´, Division of Respiratory and Intensive Care Medicine, Hoˆpital Europe´ en Georges Pompidou, AP-HP, Paris, France; 8Center for Thrombosis and Hemostasis, University of Mainz, Germany; and 9Divisions of Pulmonary and Critical Care Medicine and General Medical Sciences, Washington University School of Medicine, St. Louis, MO.

Am J Respir Crit Care Med 2014;189:718–726 (Mar 15, 2014)
Copyright © 2014 by the American Thoracic Society
Table 3: Factors Associated with 30-Day Complicated Course in 848 Normotensive Patients with Acute Symptomatic PE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Troponin I &gt; 0.05 ng/ml</td>
<td>1.96 (1.06–3.63)</td>
<td>0.03</td>
</tr>
<tr>
<td>2. BNP &gt; 100 pg/ml</td>
<td>2.12 (1.13–3.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>3. DVT by US</td>
<td>2.08 (1.19–3.65)</td>
<td>0.01</td>
</tr>
<tr>
<td>4. Simplified PESI &gt;0</td>
<td>5.62 (2.19–14.45)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

We derived and validated a multimarker prognostic model consisting of sPESI, BNP, cTnI, and CCUS imaging for concomitant DVT for normotensive patients diagnosed with acute symptomatic PE in ED.

Combination of these 4 = 5-fold increase in adverse 30-day outcome.
AUC (c-statistic), 0.75; 95% CI, 0.69–0.80; P < 0.001.
50 year-old man with acute PE

- Two day history of mild dyspnea, pleuritic CP
- P- 70  RR- 18  BP 130/78
- Room air O2 sat 97%
- Exam unremarkable
- US of legs negative
- Rivaroxaban 15 mg q12h
- Discharged from ED after 12 hours
SUMMARY

• Patients with acute PE require stratification for early discharge / outpatient therapy to be considered.
• Experience, a solid infrastructure, and common sense should be employed.
• The sPESI score can also be incorporated.
Which of the following would be the most acceptable scenario for outpatient acute PE therapy (patient diagnosed 2 hours ago)?

A. Bilateral, extensive acute PE with transient hypotension (RA O2 sat 93%)

B. Bilateral acute PE and unilateral iliofemoral DVT in a pregnant patient requiring no O2

C. Subdural hematoma occurring 12 months prior (trauma)

D. Small PE with normal RV, in 80 y-o patient with mild stable CHF and a creatinine of 3.0

E. Submassive PE in a comfortable appearing nursing home patient with Alzheimer’s

Answer: C
The Holy Grail of Anticoagulation...

“The greatest unmet need in anticoagulation has been the replacement of warfarin with orally active agents that can be given in fixed doses without routine coagulation monitoring.”
Which drugs are currently FDA-approved for treatment of acute DVT / PE?

1. Dabigatran
2. Rivaroxaban
3. Apixaban
4. Both 1 and 2
5. All of the above
6. None of the above
## Comparative Pharmacology of NOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;a,c&lt;/sup&gt;</th>
<th>Edoxaban&lt;sup&gt;d-f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>IIa (thrombin)</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Hours to C&lt;sub&gt;max&lt;/sub&gt;</strong></td>
<td>1.25-3</td>
<td>2-4</td>
<td>3-4</td>
<td>1-2</td>
</tr>
<tr>
<td><strong>CYP metabolism</strong></td>
<td>None</td>
<td>32%</td>
<td>Minimal</td>
<td>&lt; 4%</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6%</td>
<td>80%</td>
<td>60%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Transporters</strong></td>
<td>P-gp</td>
<td>P-gp/BCRP</td>
<td>P-gp/BCRP</td>
<td>P-gp</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>35%</td>
<td>93%</td>
<td>87%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>14-17 h</td>
<td>7-11 h</td>
<td>8-15 h</td>
<td>8-10 h</td>
</tr>
<tr>
<td><strong>Renal elimination</strong></td>
<td>80%</td>
<td>35%</td>
<td>25%</td>
<td>50%</td>
</tr>
</tbody>
</table>

<sup>b</sup> Xarelto® PI 2011<sup>[15]</sup>;  
<sup>c</sup> Eliquis Summary of Product Characteristics. Bristol Myers Squibb/Pfizer EEIG, UK. 2012<sup>[16]</sup>;  
<sup>e</sup> Matsushima N, et al. AAPS 2011. Poster T2632<sup>[18]</sup>;  
## Acute VTE Treatment Trials

<table>
<thead>
<tr>
<th></th>
<th>RE-COVER(^a)</th>
<th>EINSTEIN(^{b,c})</th>
<th>AMPLIFY(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>5132</td>
<td>8282</td>
<td>5400</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Double-blind</td>
<td>PROBE</td>
<td>Double-blind</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>VTE</td>
<td>DVT or PE</td>
<td>VTE</td>
</tr>
<tr>
<td><strong>Heparin bridge</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Duration, mo</strong></td>
<td>6</td>
<td>3, 6, 12</td>
<td>6</td>
</tr>
</tbody>
</table>

# Efficacy of NOACs in Acute VTE

## Recurrent VTE

AT LEAST AS GOOD AS WARFARIN!

<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-COVER&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dabigatran</td>
<td>2.4</td>
<td>2.1</td>
<td>1.10 (0.65-1.84)</td>
</tr>
<tr>
<td>EINSTEIN-DVT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Rivaroxaban</td>
<td>2.1</td>
<td>3.0</td>
<td>0.68 (0.45-1.48)</td>
</tr>
<tr>
<td>EINSTEIN-PE&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Rivaroxaban</td>
<td>2.1</td>
<td>1.8</td>
<td>1.12 (0.75-1.68)</td>
</tr>
<tr>
<td>AMPLIFY&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Apixaban</td>
<td>2.3</td>
<td>2.7</td>
<td>0.84 (0.60-1.18)</td>
</tr>
</tbody>
</table>

---

# Safety of NOACs in Acute VTE Major Bleeding

## SAFER THAN WARFARIN?*

<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-COVER(^a)</td>
<td>Dabigatran</td>
<td>1.6</td>
<td>1.9</td>
<td>0.82 (0.45-1.48)</td>
</tr>
<tr>
<td>EINSTEIN-DVT(^b)</td>
<td>Rivaroxaban</td>
<td>0.8</td>
<td>1.2</td>
<td>0.65 (0.33-1.30)</td>
</tr>
<tr>
<td>EINSTEIN-PE(^c)</td>
<td>Rivaroxaban</td>
<td>1.1</td>
<td>2.2</td>
<td>0.49 (0.31-0.79) !!</td>
</tr>
<tr>
<td>AMPLIFY(^d)</td>
<td>Apixaban</td>
<td>0.6</td>
<td>1.8</td>
<td>0.31 (0.17-0.55) !!</td>
</tr>
</tbody>
</table>

*GI bleeding?

---

New Oral Anticoagulants Increase Risk for GI Bleeding: A Systematic Review and Meta-analysis

- 43 trials with a total of 151,578 patients
- Rivaroxaban - 15 studies reporting on 16 trials
- Apixaban - 12 trials
- Dabigatran - 10 trials
- Edoxaban - 4 trials
- Betrixaban - 1 trial

In conclusion, we have shown that the gastrointestinal bleeding risk associated with nOAC use might be higher compared with standard care.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Information</th>
</tr>
</thead>
</table>
| Rivaroxaban (Xarelto) | Concomitant use of rivaroxaban with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan) should be avoided.  
Concomitant use of rivaroxaban with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John’s wort should also be avoided. |
| Apixaban (Eliquis)    | If on strong dual CYP3A4 / P-gp inhibitors (e.g. ketoconazole, itraconazole, ritonavir, or clarithromycin):  
- If apixaban dose > 2.5 mg q12h, decrease dose by 50%  
- If apixaban dose 2.5 mg q12h, avoid coadministration  
If on strong dual CYP3A4 / P-gp inducers (e.g, rifampin, carbamazepine, phenytoin, St. John’s Wort) avoid use |
<p>| Dabigatran (Pradaxa)  | Concomitant P-gp inducers (e.g., rifampin) should not be used. |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Concomitant use of rivaroxaban with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan) should be avoided.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concomitant use of rivaroxaban with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John’s wort should also be avoided.</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td></td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
<td>If on strong dual CYP3A4 / P-gp inhibitors (e.g. ketoconazole, itraconazole, ritonavir, or clarithromycin):</td>
</tr>
<tr>
<td></td>
<td>- If apixaban dose &gt; 2.5 mg q12h, decrease dose by 50%</td>
</tr>
<tr>
<td></td>
<td>- If apixaban dose 2.5 mg q12h, avoid coadministration</td>
</tr>
<tr>
<td></td>
<td>If on strong dual CYP3A4 / P-gp inducers (e.g, rifampin, carbamazepine, phenytoin, St. John’s Wort) avoid use</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>Concomitant P-gp inducers (e.g., rifampin) should not be used.</td>
</tr>
<tr>
<td>Drug</td>
<td>Oral Dose</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| **Rivaroxaban (Xarelto)** | VTE: 15 mg q12h x 21 days, then 20 mg qd  
AF: 20 mg qd | **Acute VTE:** Do not use with CrCl < 30 mL/min  
**AF:** For CrCl 15 - 50 mL/min, 15 mg qd |
| **Apixaban (Eliquis)** | 10 mg q12h x 1 week, then 5 mg q12h.  
At 6 months, decrease to 2.5 mg qd | **Acute VTE:** No dose reduction (“use with caution”)  
**AF:** Decrease to 2.5 mg q12h if any two of the following are present:  
(1) creatinine ≥1.5 mg/dL  
(2) age ≥80 years, or  
(3) weight ≤60 kg  
ESRD on HD: 5 mg q12h; decrease to 2.5 mg q12h if age ≥80 yr or weight ≤60 kg |
| **Dabigatran (Pradaxa)** | 150 mg q12h | **All patients:**  
CrCl < 30 mL/min with concomitant use of P-gp inhibitors:  
Do not use  
P-gp inducers (e.g., rifampin): Do not use.  
HD patients: No dosing recommendations can be offered.  
**Acute VTE:**  
CrCl < 30 mL/min – Do not use.  
CrCl < 50 mL/min with concomitant use of P-gp inhibitors – Do not use.  
**AF:** CrCl 15-30 mL/min: 75 mg q12h  
CrCl 30 to 50 mL/min with concomitant use of P-gp inhibitors:  
• P-gp inhibitors dronedarone or ketoconazole: Consider 75 mg Q12h.  
• No dose adjustment when co-administered with other P-gp inhibitors |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Dose</th>
<th>Renal dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>VTE: 15 mg q12h x 21 days, then 20 mg qd</td>
<td><strong>Acute VTE:</strong> Do not use with CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td></td>
<td>AF: 20 mg qd</td>
<td><strong>AF:</strong> For CrCl 15 - 50 mL/min, 15 mg qd</td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
<td>10 mg q12h x 1 week, then 5 mg q12h.</td>
<td><strong>Acute VTE:</strong> No dose reduction (“use with caution”)</td>
</tr>
<tr>
<td></td>
<td>At 6 months, decrease to 2.5 mg qd</td>
<td><strong>AF:</strong> Decrease to 2.5 mg q12h if any two of the following are present: (1) creatinine ≥1.5 mg/dL (2) age ≥80 years, or (3) weight ≤60 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ESRD on HD: 5 mg q12h; decrease to 2.5 mg q12h if age ≥80 yr or weight ≤60 kg</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>150 mg q12h</td>
<td><strong>All patients:</strong> CrCl &lt; 30 mL/min with concomitant use of P-gp inhibitors: Do not use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P-gp inducers (e.g., rifampin): Do not use.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HD patients: No dosing recommendations can be offered.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Acute VTE:</strong> CrCl &lt; 30 mL/min – Do not use.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &lt; 50 mL/min with concomitant use of P-gp inhibitors – Do not use.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>AF:</strong> CrCl 15-30 mL/min: 75 mg q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl 30 to 50 mL/min with concomitant use of P-gp inhibitors:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• P-gp inhibitors dronedarone or ketoconazole: Consider 75 mg Q12h.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No dose adjustment when co-administered with other P-gp inhibitors</td>
</tr>
</tbody>
</table>
Discontinuation of NOACs for Surgery and Other Interventions: Recommendations

- Discontinue at least 24 hours prior to surgery with low risk of bleeding or where bleeding would be in a non-critical location and controllable.

- Discontinue at least 48 hours prior to surgery with a moderate or high risk of bleeding.
Reversal of NOACs

- Rarely necessary
- PCC 3 and 4 (only FDA-approved for warfarin)
- Andexanet – Factor Xa inhibitor reversal agent (not FDA-approved)
Which drugs are currently FDA-approved for treatment of acute DVT / PE?

A. Dabigatran  
B. Rivaroxaban  
C. Apixaban  
D. Both 1 and 2  
E. All of the above  
F. None of the above

Answer: E
<table>
<thead>
<tr>
<th>Drug</th>
<th>AFIB</th>
<th>THR / TKR PROPH</th>
<th>DVT/PE RX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Apixaban</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
</tbody>
</table>
56 year-old engineer with ankle fracture

DVT 3 days later...
How long should a patient with a reversible risk factor be treated for acute VTE?

A. 3 months
B. 6 months
C. 12 months
D. Indefinitely
Long-term Treatment of Patients With PE

In patients with PE provoked by a nonsurgical *transient* risk factor, we suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B).

Kearon, et al. ACCP Consensus Chest 2012
43 year-old man with acute unprovoked PE

• How long would you treat?
Risk of Recurrent VTE After Discontinuation of Anticoagulation

Bleeding Risk Factors

• Increasing age
• Prone to falling
• Hx of bleeding / GI bleeding, stroke, TIA
• Impaired renal function
• Thrombocytopenia
• Use of antiplatelet agents
Systematic Review: D-Dimer to Predict Recurrent Disease after Stopping Anticoagulant Therapy for Unprovoked Venous Thromboembolism

Madeleine Verhovsek, MD; James D. Douketis, MD; Qilong Yi, PhD; Sanjay Shrivastava, MBBS, MPH; R. Campbell Tait, MBChB; Trevor Baglin, PhD; Daniela Poli, MD; and Wendy Lim, MD, MSc

Background: The optimal duration of anticoagulation for a first episode of unprovoked venous thromboembolism (VTE) is uncertain. Methods for predicting risk for recurrence may identify low-risk patients who are less likely to benefit from prolonged anticoagulation.

Purpose: To synthesize evidence evaluating the value of d-dimer as a predictor of recurrent disease in patients who have stopped anticoagulant therapy after a first unprovoked VTE.

Data Sources: The MEDLINE, EMBASE, CINAHL, and Cochrane databases were searched until March 2008 without language restrictions. The strategy was supplemented with manual review of reference lists and contact with content experts.

Study Selection: Randomized, controlled trials or prospective cohort studies that measured d-dimer after anticoagulant therapy in patients who received at least 3 months of anticoagulant treatment of unprovoked VTE.

Data Extraction: Two authors independently reviewed articles and extracted data.

Data Synthesis: Seven studies, totaling 1888 patients with a first unprovoked VTE, were eligible for analysis. During 4500 person-years of follow up, annual rates of recurrent VTE differed statistically significantly: 8.9% (95% CI, 5.8% to 11.9%) in patients with positive d-dimer results and 3.5% (CI, 2.7% to 4.3%) in patients with negative d-dimer results.

Limitation: The duration of anticoagulation, timing of d-dimer testing, and d-dimer assay varied across studies.

Conclusion: In patients who have completed at least 3 months of anticoagulation for a first episode of unprovoked VTE and after approximately 2 years of follow-up, a negative d-dimer result was associated with a 3.5% annual risk for recurrent disease, whereas a positive d-dimer result was associated with an 8.9% annual risk for recurrence. These rates should inform decisions about the balance of risks and benefits of prolonging anticoagulation.

The optimal duration of anticoagulation for patients with a first episode of unprovoked venous thromboembolism (VTE), which occurs in the absence of a known risk factor, is uncertain (1, 2). At least 6 months of anticoagulation has been recommended because of presumed higher rates of recurrence with shorter durations of treatment (1, 3, 4). However, recent randomized trials indicate that the (or increased) d-dimer level may identify patients with a persistent prothrombotic tendency who, because they are at relatively high risk for recurrent VTE, warrant long-term anticoagulation. Prospective studies initially showed that d-dimer predicted recurrent VTE (7–9), and a subsequent trial found that patients with an elevated d-dimer level 1 month after stopping anticoagulant therapy had a VTE
### Table 4. Annualized Risk for Recurrence in Patients with Unprovoked Venous Thromboembolism

<table>
<thead>
<tr>
<th>Author, Year (Reference)</th>
<th>Patients, n</th>
<th>Person-Years</th>
<th>Recurrent Venous Thromboembolism, n</th>
<th>Annualized Risk (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with positive D-dimer result after anticoagulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palareti et al., 2003 (8)*</td>
<td>139</td>
<td>316</td>
<td>23</td>
<td>7.3 (4.3-10.3)</td>
</tr>
<tr>
<td>Eichinger et al., 2003 (9)*</td>
<td>401</td>
<td>1409</td>
<td>63</td>
<td>4.5 (3.4-5.6)</td>
</tr>
<tr>
<td>Palareti et al., 2006 (10)</td>
<td>120</td>
<td>166</td>
<td>18</td>
<td>10.9 (6.9-15.9)</td>
</tr>
<tr>
<td>Shrivastava et al., 2006 (14)</td>
<td>15</td>
<td>26.5</td>
<td>3</td>
<td>11.3 (0.0-24.1)</td>
</tr>
<tr>
<td>Tait et al., 2007 (46)</td>
<td>71</td>
<td>125</td>
<td>18</td>
<td>14.4 (7.7-21.1)</td>
</tr>
<tr>
<td>Baglin et al., 2008 (45)</td>
<td>91</td>
<td>261</td>
<td>23</td>
<td>8.8 (5.2-12.2)</td>
</tr>
<tr>
<td>Poli et al., 2008 (44)</td>
<td>70</td>
<td>158.1</td>
<td>17</td>
<td>10.8 (5.6-15.9)</td>
</tr>
<tr>
<td>Pooled</td>
<td>907</td>
<td>2461.6</td>
<td>165</td>
<td>8.9 (5.8-11.9)†</td>
</tr>
</tbody>
</table>

| Patients with negative D-dimer result after anticoagulation | | | | |
| Palareti et al., 2003 (8)* | 143 | 363 | 10 | 2.8 (1.0-4.5) |
| Eichinger et al., 2003 (9)* | 209 | 536 | 16 | 3.0 (1.5-4.4) |
| Palareti et al., 2006 (10) | 30 | 550 | 24 | 4.4 (2.6-6.1) |
| Shrivastava et al., 2006 (14) | 30 | 54.7 | 2 | 3.7 (0.0-8.7) |
| Tait et al., 2007 (46) | 58 | 104 | 4 | 3.8 (0.1-7.6) |
| Baglin et al., 2008 (45) | 51 | 167 | 8 | 4.8 (1.5-8.1) |
| Poli et al., 2008 (44) | 105 | 265.5 | 10 | 3.8 (1.4-6.1) |
| Pooled | 981 | 2040.2 | 74 | 3.5 (2.7-4.3)‡ |

* Person-years were estimated on the basis of survival curves.
† Heterogeneity test: chi-square = 23.8 ($I^2 = 75\%$; $P < 0.001$); therefore, a random-effects model was used to find the pooled rate.
‡ Heterogeneity test: chi-square = 2.81 ($I^2 = 0\%$; $P = 0.83$).

From: Systematic Review: D-Dimer Predicts Recurrence after Stopping Anticoagulant Therapy for Unprovoked VTE


From: Systematic Review: D-Dimer Predicts Recurrence after Stopping Anticoagulant Therapy for Unprovoked VTE


Funnel plot for positive post-treatment d-dimer result: annual risk.
### Duration Of Anticoagulation In Unprovoked PE: DASH

<table>
<thead>
<tr>
<th>Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>D – D-Dimer abnormal after stopping AC</td>
<td>+2</td>
</tr>
<tr>
<td>A – Age &lt;50yr</td>
<td>+1</td>
</tr>
<tr>
<td>S – Sex (male)</td>
<td>+1</td>
</tr>
<tr>
<td>H – No hormone use at time of VTE (women)</td>
<td>-2</td>
</tr>
</tbody>
</table>

- Unprovoked VTE – optimal duration of anticoagulation
- Risk of recurrence following unprovoked VTE
- 1,818 cases w/ at least 3 months of anticoagulation

- Score ≤ 1  Recurrence risk 3.1%
- Score = 2  Recurrence risk 6.4%
- Score ≥ 3  Recurrence risk 12.3%

Long-term Treatment of Patients With PE

• In patients with PE and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C).

• For patients with PE and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C).

This recommendation is pre-NOAC data…..

ACCP 2012
DVT Follow Up - Unresolved Questions

- **Ultrasound**
  - Variable definitions of residual venous obstruction
  - Variable patient populations
  - Variable timing of studies

- **D-Dimer**
  - Optimal timing of testing after stopping AC
  - Positive rates increase with time
  - Risk of recurrent VTE while awaiting testing
  - Role of repeat testing
  - Role of D-Dimer in other groups (Provoked VTE)
  - Limited positive predictive value
    - D-Dimer - PPV 15%
    - Idiopathic DVT history - 20%
## Role of Aspirin in VTE Management

### Outcome and Study

<table>
<thead>
<tr>
<th>VTE</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPIRE(^a)</td>
<td></td>
</tr>
<tr>
<td>WARFASA(^b)</td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major vascular events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPIRE</td>
<td></td>
</tr>
<tr>
<td>WARFASA</td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinically relevant bleeding</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPIRE</td>
<td></td>
</tr>
<tr>
<td>WARFASA</td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
</tr>
</tbody>
</table>

---

**ASPIRE + WARFASA:**
Reduction of 32% in the rate of recurrent VTE (p=0.007) and a reduction of 34% in the rate of major vascular events (p=0.002), with no excess risk of bleeding.

---

ASPIRIN?

ASPIRE + WARFASA: Reduction of 32% in the rate of recurrent VTE (p=0.007) and a reduction of 34% in the rate of major vascular events (p=0.002), with no excess risk of bleeding.

The bleeding rate with ASA is comparable to that of well-managed warfarin but lower than that of warfarin that is suboptimally managed.

ASA is much easier

ASA may be a reasonable choice for those with low to moderate risk of bleeding and/or those with low to moderate risk of recurrence.

The safety and efficacy of ASA for those at higher risks of bleeding and/or VTE recurrence, however, remains to be determined.
**Efficacy And Safety Of NOACs For Extended Treatment Of VTE: Systematic Review And Meta-analyses Of RCTs**

- **RESULTS:** Four RCTs included 7,877 participants.
  - NOACs significantly lowered risk of recurrent VTE or VTE-related death compared to placebo/warfarin (OR 0.25, 95% CI 0.07 - 0.86; NNT = 30).
  - All-cause mortality was significantly lower with NOACs compared to placebo (OR 0.38, 95% CI 0.18 - 0.80).
  - Risk of major bleeding was not different with NOACs compared to placebo/warfarin (OR 0.88, 95% CI 0.27 - 2.91).
  - NOACs caused significantly more major or clinically relevant bleeding compared to placebo (OR 2.69, 95% CI 1.25 - 5.77; NNH = 39).
  - All three NOACs individually significantly reduced recurrent VTE or VTE-related death compared to placebo. Major or clinically relevant bleeding was higher with dabigatran and rivaroxaban but not with apixaban.

Sardar P¹, Chatterjee S, Mukherjee D
How long should a patient with a reversible risk factor be treated for acute VTE?

A. 3 months
B. 6 months
C. 12 months
D. Indefinitely

Answer: A
Conclusions - Duration of Anticoagulation

- **Trials balance recurrent VTE and bleeding**
  - Unprovoked calf vein thrombosis – 3 months
  - Reversible risk factors – 3 months
  - Unprovoked VTE
    - 1\textsuperscript{st} episode – Assess risk / benefit after 6 months
    - 2\textsuperscript{nd} episode – Long-term treatment

- Consider D-Dimer to help guide AC duration

- Incomplete recanalization
  - Associated with, but may not predict recurrent VTE
  - Aspirin?
  - NOACs and low-dose NOACs
Comparison of the predictive accuracy of the 3 clinical probability assessment methods in patients with suspected PE, using clinical probability groups (low, moderate, and high).