Pulmonary Embolism Literature Review: What is New?

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• I have no conflicts of interest to report.
VTE Pathogenesis

- Virchow’s triad (stasis, endothelial injury, hypercoagulability)

- Acute Death (for PE):
  - 10% sudden death
  - untreated -> 20-30% mortality

- (DVT) - Clot propagation, Embolization: 15%

- Recurrence

- Post-phlebitic syndrome, CTEPH
Epidemiology of venous thromboembolism

John A. Heit

Primary prevention and treatment of venous thromboembolic events in patients with gastrointestinal cancers - Review

300,000+ cases annually in the United States
2016: 272 articles

2017: 185 articles

Since 2000: > 3,500 articles
VTE Overview

• Diagnosis
• Classifying Disease
• Treatment
  • Medical +/- Invasive
• Secondary Prevention
Diagnostic Approach for Suspected PE in a Stable Patient

Symptoms/History/Exam

- no suspicion → NO treatment
- low pre-test → Quant D Dimer
- high pre-test

- Quant D Dimer
  - negative → NO treatment
  - positive → CT scan (or VQ scan)

- treatment

- negative
The concept of “pre-test probability” is not entirely consistent among providers.

Many ongoing efforts to improve our ability to estimate probability of PE or outcome prior to expensive or harmful testing.
• clinical signs of DVT?
• hemoptysis?
• PE is the most likely diagnosis?

Zero items and D-dimer less than 1000 ng/mL
OR
≥1 items and D-dimer less than 500 ng/mL = PE excluded

Outcome = #VTE in 3 months of follow-up

Secondary outcome was the number of required CTPA compared with the Wells’ diagnostic
- clinical signs of DVT?
- hemoptysis?
- PE is the most likely diagnosis?

- 13% of patients had PE in this cohort.

- 2946 (85%) ruled out:
  - 18 patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up, with an incidence of 0.61%
  - The incidence of fatal pulmonary embolism was 0.20%

- 14% reduction in CTPA compared to Well’s criteria
PERC: Pulmonary Embolism Rule-Out Criteria

- New onset SOB/chest pain
- Low Risk PE (gestalt < 15%)
- Excluded if obvious alternative DX, shock/resp failure, contraindication to w/u, already anti-coagulated

- O2 Sat: 94%
- Pulse 100
- Age 50
- Unilateral leg swelling
- Hemoptysis
- Recent trauma/surgery
- Prior VTE
- Exogenous Estrogen

Frend et al. JAMA 2018;319 (6): 559-566
Table 3. Main Outcomes in the Study of Pulmonary Embolism Rule-Out Criteria

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
<th>Mean Difference, % (95% CI)</th>
<th>Number Needed to Treat</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intention-to-treat population, No.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolic event at 3 mo (primary outcome)</td>
<td></td>
<td></td>
<td></td>
<td>.12</td>
</tr>
<tr>
<td>PERC</td>
<td>962</td>
<td>32 (3)</td>
<td>0.2 (−∞ to 1.6)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>954</td>
<td>29 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTVA performed</td>
<td>129 (13)</td>
<td>220 (23)</td>
<td>9.7 (6.1 to 13.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of ED stay, median (IQR), h:min</td>
<td>4:36 (3:16 to 6:21)</td>
<td>5:14 (3:50 to 7:18)</td>
<td>−00:36 (−1:08 to −0:04)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>121 (13)</td>
<td>152 (16)</td>
<td>3.3 (0.1 to 6.6)</td>
<td>.04</td>
</tr>
<tr>
<td>Anticoagulation therapy introduced</td>
<td>21 (2)</td>
<td>33 (3)</td>
<td>1.3 (0.3 to 2.9)</td>
<td>.09</td>
</tr>
<tr>
<td>Hospital readmission at 3 mo</td>
<td>43 (4)</td>
<td>62 (7)</td>
<td>2.1 (−0.1 to 4.3)</td>
<td>.051</td>
</tr>
<tr>
<td>All-cause death at 3 mo</td>
<td>3 (0.3)</td>
<td>2 (0.2)</td>
<td>0.1 (−0.5 to 0.7)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td><strong>Per-protocol population, No.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolic event at 3 mo (primary outcome)</td>
<td></td>
<td></td>
<td></td>
<td>.09</td>
</tr>
<tr>
<td>PERC</td>
<td>847</td>
<td>1 (0.1)</td>
<td>0.1 (−∞ to 0.8)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>902</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTVA performed</td>
<td>114 (14)</td>
<td>211 (23)</td>
<td>9.9 (6.2 to 13.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of ED stay, median (IQR), h:min</td>
<td>4:34 (3:12 to 6:14)</td>
<td>5:12 (3:50 to 7:17)</td>
<td>−00:37 (−1:11 to −0:02)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>101 (12)</td>
<td>139 (15)</td>
<td>3.5 (0.2 to 6.8)</td>
<td>.03</td>
</tr>
<tr>
<td>Anticoagulation therapy introduced</td>
<td>19 (2)</td>
<td>28 (3)</td>
<td>0.8 (−0.8 to 2.5)</td>
<td>.27</td>
</tr>
<tr>
<td>Hospital readmission at 3 mo</td>
<td>38 (4)</td>
<td>62 (7)</td>
<td>2.4 (0.1 to 4.7)</td>
<td>.03</td>
</tr>
<tr>
<td>All-cause death at 3 mo</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>0.01 (−0.4 to 0.4)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>
Performance of the age-adjusted cut-off for D-dimer in patients with cancer and suspected pulmonary embolism.

**RESULTS:** Of 3324 patients with suspected PE, 429 (12.9%) patients had cancer. The prevalence of PE was 25.2% in cancer patients and 18% in patients without cancer (p<0.001). Among cancer patients with an unlikely CDR, 9.9% had a DD <500μg/L as compared with 19.7% using the age-adjusted cutoff. In patients without cancer, these rates were 30.1% and 41.9%. The proportion of cancer patients in whom PE could be excluded by CDR and DD doubled from 6.3% to 12.6%. No VTE occurred during three-month follow-up (failure rate 0.0% (95% CI 0.0-6.9%)).

**CONCLUSION:** Compared with the conventional cutoff, the age-adjusted D-dimer cutoff doubles the proportion of patients with cancer in whom PE can be safely excluded by CDR and DD without imaging.

- Age Adjusted D-dimer valid in multiple populations
- Safely “rules out” PE and decreases unnecessary testing
PE Acute Therapeutic Approach

- Anticoagulation
- EKOS, directed thrombolysis
- Anticoag + Systemic Thrombolysis
- Monitor?
- Stable
- RV dys
- Dying

Elevated bleeding risk
- Filter?
- Surgical/mech thrombectomy?
Rates by Severity

- **Massive**: 5%
  - Large Clot Burden, Shock
- **Sub-massive**: 40%
  - Evidence of Right Ventricular Strain without Shock
- **Stable PE**: 55%
  - Clinically stable No evidence of RV strain
Overall mortality = ~5-20%
Arrest on Presentation = ~90%
Mech Vent = ~80%
Lytics = ~30%
PESI very high = ~20%
PESI medium = ~5%
PESI low = ~1%
subseg = ~0%
Many variables inform Risk from the disease:

Informs risk tolerance of treatment.
Should we treat Submassive PE differently?

- RV/LV ratio > 0.9 is an independent risk factor for mortality

- Persistent RV dysfunction at d/c:
  - 8 fold risk of recurrent, symptomatic PE
  - 4 fold risk of mortality

Quiroz, Circ 2004; 109:2401-2404
Frémont, Chest 2008; 133:558-362
Schoef, Circ 2004; 110:3276-3280
Kucher, Arch Intern Med 2005; 165:1777-1781
Systemic Thrombolysis

- Obstructive Shock is a widely accepted indication for systemic thrombolysis. (ACCP Guidelines)

- Has been proposed for:
  - RV dysfunction
  - Respiratory Failure
  - Extensive Clot Burden
  - RA or RV thrombus
  - Patent Foramen Ovale

*22. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1B).

*23. In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).
Catheter Directed Thrombolysis

• Superior hemodynamic response versus anticoagulation alone

• Significantly lower dose of TPA (15mg to 40mg versus 50mg-100mg) over a longer period of time (12 hours versus 2 hours)

• Potential for lower risk of adverse events and improved efficacy.
Catheter Directed Thrombolysis

- Literature often combines techniques: masseration, angioplasty, wire agitation, rheolytic: all with or without local thrombolytic delivery.

- RCT data proves a lower risk of long-term pulmonary HTN, but the NNT for this is very high.

- RCT data (PEITHO) has also shown that lysis in sub-massive PE prevents hemodynamic compromise, but at a risk of bleeding. Can CDT provide the hemodynamic benefit without the bleeding risk?

- CDT Registry data and RCTs have suggests major bleeding rates of 5-10%: not substantially different than anticoagulation alone.

- Based on safety data and emerging data on benefit, will see this performed more frequently in select patients at capable centers.
Anticoagulation

• If high suspicion of PE in a sick patient, anticoagulate while figuring it out.

• For lobar or $>1$ PEs, all patients who can be anticoagulated should be.

• If hemodynamically stable (no RV strain) and no clot in transition, then anticoagulation alone is sufficient.
PE (unprovoked) Chronic Therapeutic Approach

- Anticoagulation
  - DOACs
  - Warfarin
  - LMWH

ASA?

For at least 3 months. Stop if reversible cause. Consider indefinite if low bleeding risk.
For VTE without an associated cancer diagnosis, all direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, or edoxaban) are recommended over vitamin K antagonist (VKA) therapy (all Grade 2B) and VKA therapy is recommended over low molecular weight heparin (LMWH; Grade 2C).

Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report

Clive Kearon MD, PhD a, Elie A. Akl MD, MPH, PhD a, b, c, Joseph Ornelas PhD c, Allen Blaivas DO, FCCP d, David Jimenez MD, PhD, FCCP e, Henri Bounnameaux MD f, Menno Huisman MD, PhD g, Christopher S. King MD, FCCP h, Timothy A. Morris MD, FCCP i, Namita Sood MD, FCCP j, Scott M. Stevens MD k, Janine R.E. Vintch MD, FCCP l, Philip Wells MD m, Scott C. Woller MD k, COL Lisa Moores MD, FCCP n
Secondary Prevention of VTE in Malignancy

- Recurrent VTE 11% with warfarin and 7% with low-molecular-weight heparin.

- Subgroup analyses of DOAC studies showed that DOACs at least as effective and safe as warfarin therapy among patients with cancer who have venous thromboembolism.
Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Riaskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segera, M.D., et al., for the Hokusai VTE Cancer Investigators

![Graph showing the comparison of Dalteparin and Edoxaban over time]
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Compliance (12 month) in edoxaban group vs. dalteparin group (38.3% vs. 29.4%).
Secondary Prevention of VTE in Malignancy

• SELECT-D Trial with similar preliminary results. (Rivaroxaban vs. Dalteparin)

• Consider in patients without a high bleeding risk.

• Avoided if Cr clearance of less than 30 ml/min
Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

Jeffrey I. Weitz, M.D., Anthonie W.A. Lensing, M.D., Ph.D., Martin H. Prins, M.D., Ph.D., Rupert Bauersachs, M.D., Jan Beyer-Westendorf, M.D., Henri Bounameaux, M.D., Timothy A. Brighton, M.D., Alexander T. Cohen, M.D., Bruce L. Davidson, M.D., M.P.H., Hervé Decousus, M.D., Maria C.S. Freitas, M.D., Ph.D., Gerlin Holberg, V.D., Ph.D., et al., for the EINSTEIN CHOICE Investigators
Summary

• For any severity of PE: Disease risk, treatment efficacy, and treatment risk inform treatment.

• For most PEs, anticoagulation alone is sufficient.

• Lytics appear to have a role in submassive/massive PE

• CDT has a role. *Patient selection is critical.*