Deep Vein Thrombosis and Pulmonary Embolism: Diagnosis and Management in the Family Medicine Setting

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On behalf of Thrombosis Canada
Conflict Disclosures

Pascal Bastien has received fees/honoraria from the following sources:

Sanofi-Canada

Bayer
Objectives

• Enable Safer and Simpler Management of DVT in the Outpatient Setting
• Review a Practical Approach to the Risk Stratification and Management of PE
• Outline New Treatment Options and Updates in the Management of VTE
Scope of the Problem

Venous thromboembolism
Disease Spectrum

Asymptomatic  SVT  Distal DVT  Proximal DVT  PE
• Epidemiology
  – Lifetime risk 5-10%
  – 1 VTE per 1000 individual per year
  – Case fatality of PE ~10%
• 3rd most common cardiovascular emergency after MI and stroke
• VTE Thromboprophylaxis now major factor in hospital accreditation
ACCP Guidelines
Case 1

• Ms. TC is a healthy 31 year-old woman
• Presents to family physician with a 24 hour history of pain and swelling in L leg
• Just returned from honeymoon in Paris yesterday
• Current medication: OCP
• Physical exam confirms moderate swelling of L calf, no redness, minimal tenderness
  – L calf 36cm vs. R calf 32cm
Audience Poll

• A) Send for CUS in coming days and start warfarin if results are positive
• B) Send to the ED for further assessment
• C) Assess pre-test probability and consider anticoagulation prior to further testing
• D) Check D-dimers and send to ER if “positive”
Ms. TC

Send to ER?!
Assessing VTE Risk
Virchow’s Triad

- Hypercoagulability
- Stasis
- Endothelial Injury
Epidemiology of VTE

- Malignancy
- Post-operative
- Unprovoked
- Medical/other
Effect of Age

VTE Incidence Rate per 100,000

0 20 40 60 80 100

0 200 400 600 800 1000 1200
Variable Risk Factors

- Obesity
  - RR 2-3
- OCP
  - RR 2-4
- Pregnancy
  - RR 2-4 (same throughout pregnancy)
- Post-partum (6-8 weeks)
  - RR 8-12
- Non-type O blood
  - RR 2
- Travel by air, car, train, bus (4 hours +)
  - RR 2
Individual Inherent Risk

- VTE Risk
  - Variable propensity
  - Wild-type

Age
Effect of Transient Risk Factor

- Baseline
- Transient effect

VTE Risk vs. Age
Take Home Points

• VTE is common
• DVT and PE are manifestations of a single disease
• Virchow’s triad for risk factors
• Individual VTE risk is influenced by inherent and transient factors
A Practical Approach to DVT
Signs and Symptoms of DVT

• Unilateral leg swelling
• Palpable cord
• Leg pain
• Warmth
• Leg erythema

Broad differential:
- Cellulitis?
- Superficial thrombophlebitis?
- Ruptured baker’s cyst?
- Venous insufficiency?
- Knee effusion/bursitis?
- MSK injury?
- Drug effect?
Pre-test Probability Assessment

- Clinical Expertise
- Wells
- Geneva
Take Home Points

• The differential diagnosis of DVT is relatively benign
• Wells’ Criteria for DVT can be used to standardize clinical probability assessment
D-dimer
Venous US
Outpatient Diagnosis of DVT

Low Clinical Probability Assessment:
- No empiric anticoagulation unless delay > 24h
- hs D-dimer
  - Negative: DVT excluded
  - Positive: hs D-dimer +/- repeat CUS in 5-7 days

High Clinical Probability Assessment:
- Initiate anticoagulation if any delay
- Proximal CUS
  - Negative: DVT excluded
  - Positive: TREAT
Take Home Points

• Do not delay treatment in patients at moderate-to-high risk of DVT
• D-dimers are NOT used to rule out disease in patients with high clinical probability of DVT
• Proximal CUS is not a definitive test
Treatment of DVT
Tried, Tested and True

LMWH
Minimum 5 days

Warfarin
Minimum 3 months
2 NOACs Approved by Health Canada for Acute VTE Monotherapy

- Rivaroxaban
  - 15mg po bid for 3 weeks
  - 20mg po daily

- Apixaban
  - 10 mg po bid for 7 days
  - 5 mg po bid
  - Secondary prevention (after 6 months) 2.5 mg po bid
# Summary of NOAC Acute VTE Trials

<table>
<thead>
<tr>
<th></th>
<th>RE-COVER I(^1) &amp; II(^2)</th>
<th>AMPLIFY(^3)</th>
<th>EINSTEIN DVT(^4) &amp; PE(^5)</th>
<th>Hokusai(^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Dabigatran</td>
<td>Apixaban</td>
<td>Rivaroxaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>150 mg BID</td>
<td>10 mg BID x 10d then 5 mg BID</td>
<td>15 mg BID x 3 weeks then 20 mg OD</td>
<td>60 mg OD</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Warfarin</td>
<td>LMWH + Warfarin</td>
<td>Warfarin</td>
<td>Warfarin</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Non-inferiority, double blind RCT</td>
<td>Non-inferiority, open label RCT</td>
<td>Non-inferiority DB RCT</td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy endpoint</strong></td>
<td>Recurrent VTE and related death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety endpoint</strong></td>
<td>Major bleeding</td>
<td>Major or significant non-major bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Enrolled patients</strong></td>
<td>5107</td>
<td>5395</td>
<td>8281</td>
<td>8292</td>
</tr>
</tbody>
</table>

Buller HR. *Blood*. 2012;120: Abstract 20
About NOACs, DOACs or TSOACs

• Pros
  – Greatly facilitates outpatient management: first dose can be given in office!
  – Less Major Bleeding
    • See pooled analysis EINSTEIN-PE and EINSTEIN-DVT
  – Fast on, fast off – analogous to LMWH
  – Adequately tested in extensive disease
  – Cost no more prohibitive than LMWH to warfarin
About NOACs, DOACs or TSOACs

• Cons
  – Caution with dosing – simpler (but different) in VTE than AF
  – Renal function must be monitored
  – Not standard-of-care in patients with cancer
  – Not tested in pregnancy or breastfeeding
  – Not tested in upper extremity DVT, splanchnic or cortical vein thrombosis, or superficial phlebitis
Outpatient Diagnosis of DVT

Clinical Probability Assessment

LOW: No empiric anticoagulation unless delay > 24h

MOD-HIGH: Start Rivaroxaban or Apixaban

D-dimer

- POSITIVE
  - Repeat CUS in 5-7 days
- NEGATIVE
  - DVT EXCLUDED

Proximal CUS

- NEGATIVE
  - DVT EXCLUDED
- POSITIVE
  - Continue Rivaroxaban or Apixaban
Take Home Points

- Rivaroxaban and Apixaban are approved by Health Canada for monotherapy in acute VTE
- Compared to standard therapy, NOAC efficacy and safety are equal or better
2.7. In patients with acute DVT of the leg and whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital (Grade 1B).
Which DVT to admit?

- Phlegmasia or venous ischemia
- Need for IV analgesia
- Severe CKD (CrCl <25)
- High bleeding risk
Teaching Point

- Most patients with DVT should be managed in the outpatient setting.
Case 1 solved

• I can just start her on Rivaroxaban 15mg po bid
• I’ll send her for an elective duplex US that will be done this week
• I’ll see her back after the US and continue or stop
A Practical Approach to PE
Signs and Symptoms of PE

- Pleuritic chest pain
- Sudden onset shortness of breath
- Hemoptysis
- Palpitations
- Low grade fever
- Pre/syncope
- Hypotension/shock
- Sudden death

Broad differential:

- ACS?
- Pneumonia?
- Malignancy?
- Esophageal spasm?
- Reactive airways?
- Sepsis?
- Pericarditis?
- Pleuritis?
- Pneumothorax?
Take Home Points

• When PE is considered clinically, an emergent workup is necessary.
• The differential diagnosis of PE includes numerous dangerous etiologies
Case 2

- Mr. OB is a 42 year-old man
- PMH obesity (125kg)
- Presents to ED with pleuritic chest pain. SpO2 93% RA, HR 92. BP 120/80. CXR normal.
- hs-d-dimer 2453. Trop negative. eGFR > 60. CTPA segmental PE RLL, and radiologist comments on normal sized RV.
Audience Poll

- A) Inpatient management
- B) Outpatient management
## ESC Risk stratification in PE

<table>
<thead>
<tr>
<th>PE-related early MORTALITY RISK</th>
<th>RISK MARKERS</th>
<th>Potential treatment implications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CLINICAL (shock or hypotension)</td>
<td>RV dysfunction</td>
</tr>
<tr>
<td>HIGH &gt;15%</td>
<td>+</td>
<td>(+)(^a)</td>
</tr>
<tr>
<td>NON HIGH 3–15%</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Low &lt;1%</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Risk Stratification in PE

Pulmonary Embolism Severity Index (PESI)
Predicts 30-day outcome of patients with pulmonary embolism using 11 clinical criteria.

- Age (years) (+1 per year) 42
- Male Patient (+10)
- History of Cancer (+30)
- History of heart failure (+10)
- History of chronic lung disease (+10)
- Heart Rate ≥ 110 (+20)
- Systolic Blood Pressure < 100 mmHg (+30)
- Respiratory Rate ≥ 30/min (+20)
- Temperature < 36°C (96.8°F) (+20)
- Altered Mental Status (disorientation, lethargy, stupor, or coma) (+40)
- $O_2$ Saturation < 90% on Room Air (+20)

Score 52

Class I, Very Low Risk: 0-1.6% 30-day mortality in this group.
Risk Stratification in PE

Table 1 Hestia criteria

<table>
<thead>
<tr>
<th>Hestia criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hemodynamically unstable?*</td>
</tr>
<tr>
<td>2. Thrombolysis or embolectomy necessary?</td>
</tr>
<tr>
<td>3. Active bleeding or high risk of bleeding?†</td>
</tr>
<tr>
<td>4. Oxygen supply to maintain oxygen saturation &gt; 90% &gt; 24 h?</td>
</tr>
<tr>
<td>5. Pulmonary embolism diagnosed during anticoagulant treatment?</td>
</tr>
<tr>
<td>6. Intravenous pain medication &gt; 24 h?</td>
</tr>
<tr>
<td>7. Medical or social reason for treatment in the hospital &gt; 24 h?</td>
</tr>
<tr>
<td>8. Creatinine clearance of less than 30 mL/min?‡</td>
</tr>
<tr>
<td>9. Severe liver impairment?§</td>
</tr>
<tr>
<td>10. Pregnant?</td>
</tr>
<tr>
<td>11. Documented history of heparin-induced thrombocytopenia?</td>
</tr>
</tbody>
</table>

If one of the questions is answered with YES, The patient can NOT be treated at home.
Which PE to admit!?

- High risk PE
- Need for IV analgesia
- Need for O2
- Severe CKD (CrCl <25)
- High bleeding risk
- Significant co-morbid disease
5.5. In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (e.g., after the first 5 days of treatment) (Grade 2 B).
Teaching Point

- Not all patients with PE need to be admitted and as many as 50% can be managed safely as outpatients, including those with signs of RV dysfunction
Case 2 solved

• Mr. OB is anticoagulated
  – i.e. apixaban 10 mg po bid
• Given acetaminophen and low-dose morphine prn for analgesia
• Discharged from ED with short-term f/u
Case 2-B

• Mr. OB is a 42 year-old man
• PMH obesity (105kg)
• Presents to ED with pleuritic chest pain. SpO2 93% RA, HR 112. BP 120/80. CXR normal.
• hs-d-dimer 2453. Troponin positive. CTPA extensive bilateral PE, with enlarged RV, RV/LV ratio of 1.2.
Audience Poll

• A) Thrombolyse
• B) Do Not Thrombolyse
Management: High Risk

• “It is uncertain whether the benefits of more-rapid resolution of PE outweigh the risk of increased bleeding associated with thrombolytic therapy...Patients with the most severe presentations who have the highest risk of dying from an acute PE have the most to gain from thrombolysis.”
# PEITHO Primary Outcome

<table>
<thead>
<tr>
<th></th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td>n</td>
</tr>
<tr>
<td>All-cause mortality or hemodynamic collapse within 7 days of randomization</td>
<td>13 (2.6)</td>
<td>28 (5.6)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

**Thrombolysis superior**
## PEITHO Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality within 7 days</td>
<td>n=6 (1.2)</td>
<td>n=9 (1.8)</td>
<td>0.43</td>
</tr>
<tr>
<td>Hemodynamic collapse within 7 days</td>
<td>8 (1.6)</td>
<td>25 (5.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Need for CPR</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Hypotension / blood pressure drop</td>
<td>8</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Catecholamines</td>
<td>3</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Resulted in death</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Open-label thrombolysis</td>
<td>4 (0.8)</td>
<td>23 (4.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Steps to Thrombolysis

Assess hemodynamic stability

SBP <90*

Yes
CTPA immediately available & patient stable for test

No

Positive
CTPA

PE Confirmed
Initiate treatment with consideration for thrombolysis

Negative
Cardiac Echo

PE excluded

Positive***
PE Likely
Initiate treatment with consideration for thrombolysis
Teaching Point

• The only indication for thrombolysis in PE is hemodynamic instability

• There is no data that supports “prophylactic” thrombolysis, even in the highest risk patients without hemodynamic instability
Case 2-B solved

• Mr. OB is started on anticoagulation and admitted for observation
  – We may treat with LMWH of choice (or NOAC, or UH)
  – No LMWH dose capping!
  – Discharged after 48 hours of observation
    • HR normalized to 80 bpm
    • O2 95% RA
Summary

• DVT and PE are manifestations of a single disease
• The diagnosis of DVT relies on the judicious use of clinical risk assessment, hs D-dimers and CUS
• Rivaroxaban and Apixaban are approved by Health Canada for monotherapy in acute VTE
Summary

• VTE is largely an outpatient disease, both DVT and even many PE

• Clinical assessments such as the Hestia criteria allow the identification of patients with DVT and PE that can be safely managed in the outpatient setting

• The only indication for thrombolysis in PE is hemodynamic instability
Thrombosis Canada

• **Our Mission:**
  – To further education and research in the prevention and treatment of thrombotic vascular disease.

• **Who are we?**
  – An organization of internationally recognized thrombosis experts
  – Our membership is comprised of thrombosis experts from many disciplines across Canada, including internal medicine, hematology, stroke neurology, cardiology, pharmacy, laboratory medicine, emergency medicine and primary care
Our Focus

• Engage Young Investigators: *Research fellowship*

• Offer point of care solutions for primary care: *Clinical Guides, Quality Improvement Program*

• Collaborate with like-minded groups: *e.g., College of Family Physicians of Canada, Canadian Cardiovascular Society*

• Provide patient and family education: *Support groups, information for patients, children and families*
Thrombosis Canada Clinical Guides

- Point-of-care guides that summarize evidence and help clinicians make informed decisions
  - Evidence-based
  - Patient-centred
  - A broad range of topics
  - Peer reviewed, up-to-date and concise
  - Developed by Thrombosis Canada members
Thrombosis Canada Tools

- Anticoagulant Dosing in Atrial Fibrillation
- Perioperative Anticoagulant Management Algorithm
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Anticoagulant and Antithrombotic Drugs

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