Venous Thromboembolic Disease Update

Benjamin Bell, MD FRCPC

James Douketis, MD FRCPC

On Behalf of Thrombosis Canada
Conflict Disclosures
The speaker has received fees/honoraria from the following sources:
sanofi-aventis, BMS/Pfizer, Bayer

Some of the drugs, devices, or treatment modalities mentioned in this presentation are:
dabigatran, rivaroxaban, apixaban, edoxaban, warfarin, tenecteplase, ASA
• Engage young investigators: Research fellowship

• Offer point of care solutions for healthcare providers: Clinical guides, clinical tools, quality improvement program

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

• Provide patient and family education: Support groups, information for patients, children and families
Is there an app for that?

Bleeding Risk
- Low (minor non-dental procedure), e.g.
  - Minor eye procedure (cataract extraction)
  - Minor dermatologic procedure (e.g. biopsy)
  - Endoscopic procedures not involving biopsy
- Low (minor dental procedure), e.g.
  - Up to 2 tooth extractions
  - Biopsies
  - Peridontal surgery
  - Root canal
  - Subgingival scaling

Summary
- Bleeding Risk: Moderate (2-day risk of major bleed 0-2%)
- Anticoagulant: Warfarin
- CrCl: 98.2 mL/min
- Indication For Antithrombotic: Mechanical valve
- Thromboembolic Risk: High

Preoperative Recommendations
- Bridging anticoagulant therapy warranted. Stop warfarin 5 days before surgery. Provide morning therapeutic doses of LMWH (e.g. dalteparin 200 IU/kg SC OD, enoxaparin 1.5 mg/kg SC OD) on preoperative days 3 and 2, and on the day before surgery administer half of the
Objectives

• Acute management
  – assess risk of individual patients with acute VTE to aid in disposition decisions
  – utilize up-to-date and evidence based therapies for the treatment of VTE

• Chronic management
  – Identify patients who require long term secondary prophylaxis for VTE using the most appropriate agent
Tried, Tested and True

(LMW)H

Warfarin

Minimum 5 days

Minimum 3 months
Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines
Vignette

• 42 yr obese (105 kg) male presents to ER with pleuritic chest pain.

• SpO2 93% RA, HR = 92, BP = 120/80, CXR normal, D-dimer positive (2453 ng/mL), troponin negative, eGFR >60 mL/min.

• CTPA: segmental PE RLL; radiologist comments on normal sized RV.

• ER physician administers 200 IU/kg dalteparin and refers.
Decision number 1

A) Admit
B) Discharge
## 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>Intermediate 3–15%</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Low &lt;1%</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

<1%  
~50%  
~50%
# Risk Stratification in PE

The Pulmonary Embolism Severity Index (PESI) tool is used to predict the 30-day outcome of patients with pulmonary embolism using 11 clinical criteria:

- Age (years) (+1 per year)
- 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) (+60)
- O₂ Saturation < 90% on Room Air (+20)

### Score

**97**

Class III, Intermediate Risk: 3.2-7.1% 30-day mortality in this group.
5.5. In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (eg, after the first 5 days of treatment) (Grade 2 B).

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).
Teaching Point Number 1

• 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

• Most patients with DVT should be managed in the outpatient setting
Decision number 2

Case of idiopathic low-risk PE in young male

A) Continue LMWH and start warfarin
B) Continue LMWH and start dabigatran after 5 days
C) Discontinue LMWH and start rivaroxaban/apixaban
D) Any of the above
Treatment Options in 2014

- **Bridge**
  - (LMW)H
  - Warfarin

- **Single agent** (LMWH/rivaroxaban/apixaban*)
  - NOAC

- **Switch** (dabigatran/edoxaban*)
  - LMWH
  - NOAC

*when HC approved
NOAC and Acute VTE Caveats

• Majority of patients had CrCl >50 mL/min
• Most patients <75 years old
• Caution at extremes of weight
• Very few patients with cancer
• Not tested in upper extremity/distal DVT, splanchnic thrombosis, or superficial phlebitis
• Cost

• Adequately tested in extensive disease
Teaching Point Number 2

• Rivaroxaban is a Health Canada approved alternative to LMWH/warfarin for acute & long-term management DVT and PE, without the need for an LMWH bridge

• Dabigatran is also Health Canada approved and requires a 5 day LMWH lead-in
Vignette

• 42 yr old obese male presents to ER with pleuritic chest pain.

• SpO2 = 89% (RA), HR = 112, BP = 120/80. CXR normal.

• Troponin positive. CTPA: extensive bilateral PE with enlarged RV (RV-to-LV ratio = 1.2).

• ER physician asks if thrombolytic therapy should be given.
Decision Number 3

What is the optimal management of this PE?

A) Thrombolysis
B) Do Not Thrombolysis
### PEITHO Trial: Primary Outcome

<table>
<thead>
<tr>
<th>Condition</th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<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>

**Odds ratio: 0.88 (95% CI: 0.44 - 2.33)**

*Thrombolysis superior*
# PEITHO Trial: Secondary Outcomes

<table>
<thead>
<tr>
<th>All-cause mortality within 7 days</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>n (%)</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality within 7 days</td>
<td>6 (1.2)</td>
<td>9 (1.8)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemodynamic collapse within 7 days</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>n (%)</td>
<td></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>0.002</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>
</tbody>
</table>

| Open-label thrombolysis             | 4 (0.8)              | 23 (4.6)        | <0.001  |
Teaching Point Number 3

• 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
Decision Number 4a

High risk PE without contraindication to anticoagulation. CUS finds proximal clot in left leg

A) Insert IVC filter
B) Do Not Insert IVC filter

Decision Number 4b

High risk PE without contraindication to anticoagulation. CUS finds proximal clot in left leg

A) Recommend compression stockings to prevent PTS
B) Do not recommend compression stockings to prevent PTS
Permanent Vena
embolism

Pulmonary embolism (%)

Deep-vein thrombosis (%)

Survival probability

Year(s) after index deep-vein thrombosis

Hazard ratio, 0.97
P = 0.83
<table>
<thead>
<tr>
<th></th>
<th>Filter n=200</th>
<th>No Filter n=199</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>6 (3%)</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>DVT</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>8 (4%)</td>
<td>10 (5%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>15 (7.5%)</td>
<td>12 (6.0%)</td>
</tr>
<tr>
<td>Retrieved</td>
<td>152 (92.1%)</td>
<td>--</td>
</tr>
</tbody>
</table>
SOX Trial

Cumulative incidence of post-thrombotic syndrome (%)

Time since randomisation (days)

Active ECS
Placebo ECS

Lancet 2014; 383: 880-88
Teaching Point Number 4

• The only indication for an IVC filter in a patient with acute VTE is a contraindication to anticoagulation

• Compression socks don’t prevent the post phlebitic syndrome but can be considered for symptomatic edema
Summary: Acute Management

- Most patients with DVT and up to 50% of patients with PE can be safely treated at home
- LMWH/warfarin or NOACs are both viable options for the acute treatment of VTE
- Thrombolysis should be reserved for patients with hemodynamic instability
- IVC filters should be reserved for patients with contraindications to anticoagulation
- Compression socks don’t prevent PTS
Objectives

• Acute management
  – Assess risk of individual patients with acute VTE to aid in disposition decisions
  – Utilize up-to-date and evidence based therapies for the treatment of VTE

• Chronic management
  – Identify patients who require long term secondary prophylaxis for VTE using the most appropriate agent
Vignette

• 48 yr female with PE following laparoscopic cholecystectomy 1 month ago and put on warfarin.

• Mother had blood clot in her leg many years ago and is still on warfarin.

• Referred to an internist for duration of anticoagulation.
Decision Number 5

A) Discontinue warfarin after 3 months treatment
B) Discontinue warfarin at 3 months then switch to ASA
C) Recommend indefinite warfarin therapy
D) Thrombophilia screening to aid in decision making
Influence of Preceding Length of Anticoagulation

Acute therapy too short → Higher risk of recurrent VTE

Beyond adequate course → Longer isn’t safer when stopped
Provoked* vs. Unprovoked

3.1.2. In patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), and (iii) extended therapy if there is a high bleeding risk (Grade 1B). We suggest treatment with therapy risk.

6.2. In patients with PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), and (iii) extended therapy if there is a high bleeding risk (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B).
*Acceptable transient provoking factors*

- Surgery
- Immobilization ≥ 3 days
- Lower extremity plaster cast
- Admission to hospital
- Pregnancy and puerperium
- Estrogen therapy

- Annual risk of recurrence ~1-3%
  - Case fatality rate ~10%

- Annual risk of anticoagulant induced hemorrhage ~3-5%
  - Case fatality rate ~10%
Teaching Point Number 5

• The management of an acute VTE is 3 months

• Extended therapy corresponds to secondary prevention / thromboprophylaxis

• Transient provocative risk factors include surgery, hospitalization, immobilization and pregnancy
Vignette

• 35 yr old obese (BMI 35) female with PE following transatlantic flight 1 month ago and is put on rivaroxaban.

• Only regular medication is OCP. Mother had a blood clot in her leg many years ago and is still on warfarin.

• Referred to internist for duration of anticoagulation.
Decision Number 6
(assuming OCP discontinued)

A) Discontinue rivaroxaban after 3 months
B) Discontinue rivaroxaban at 3 months then switch to ASA
C) Continue rivaroxaban indefinitely
D) Thrombophilia screening to aid in decision making
E) Other
3.1.4.1. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B).

6.3.1. In patients with a first VTE that is an unprovoked PE and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B).
Predicting Recurrence in VTE

- Provoking factor
- Extent of venous thrombosis
- Sex
- Hormonal therapy
- Age
- Thrombophilia
- Ethnicity
- D-dimer levels
- Post-phlebitic syndrome
Extent of thrombosis
## Incidence of Recurrent VTE: events per patient year

<table>
<thead>
<tr>
<th>Time after OAC stopped</th>
<th>Men with unprovoked VTE</th>
<th>Women with unprovoked VTE (HRT-associated)</th>
<th>Women with unprovoked VTE (non HRT-associated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>10.4</td>
<td>5.6</td>
<td>6.7</td>
</tr>
<tr>
<td>2 years</td>
<td>15.8</td>
<td>8.3</td>
<td>10.6</td>
</tr>
<tr>
<td>3 years</td>
<td>22.5</td>
<td>9.1</td>
<td>10.6</td>
</tr>
<tr>
<td>5 years</td>
<td>43.1</td>
<td>11.5</td>
<td>12.2</td>
</tr>
</tbody>
</table>
Thrombophilia and Recurrence

Figure 2: Number of risk factors identified by laboratory screening for thrombophilia in 158 patients without cancer with two episodes of unprovoked venous thrombosis. 3 weeks after the incident event, patients were screened for deficiency of antithrombin, protein C, or protein S; presence of lupus anticoagulant, factor V Leiden, factor II G20210A; and high concentrations of homocysteine, factor VIII, or factor IX.
# Thrombophilia and Recurrence

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Prevalence among patients with 1\textsuperscript{st} VTE</th>
<th>Risk of recurrent VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>2%</td>
<td>RR 2.5</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>1%</td>
<td>RR 1.8</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>6%</td>
<td>RR 1.0</td>
</tr>
<tr>
<td>APC resistance</td>
<td>16%</td>
<td>HR 1.3</td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>4%</td>
<td>HR 1.7</td>
</tr>
</tbody>
</table>
Effect of d-dimer

Ann Intern Med. 2010;153:523-531
HERDOO-2 Score

Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy

- Women with 0-1 risk factor: annual recurrence risk **1.6%**
- Women with ≥ 2 risk factors: annual recurrence risk **14.1%**
- No combination of factors predicted low risk in men
- Post-thrombotic signs (hyperpigmentation, edema or redness)
- **D-dimers ≥ 250μg/L**
- **BMI ≥ 30 (obesity)**
- **Age ≥ 65 (old)**
DASH Score

Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH)

- +2 for D-dimer ≥ 500 ng/mL post anticoag
- +1 for age ≤ 50 years
- +1 for male sex
- -2 for HRT at time of initial VTE
The Bottom Line: Secondary Prevention

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban 2.5</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial</strong></td>
<td>RE-MEDY</td>
<td>RE-SONATE</td>
<td>EINSTEIN-EXT</td>
<td>AMPLIFY-EXT</td>
<td>INSPIRE</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Warfarin</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>150 mg BID</td>
<td>150 mg BID</td>
<td>20 mg OD</td>
<td>2.5 mg BID</td>
<td>100 mg OD</td>
</tr>
<tr>
<td><strong>Intensity</strong></td>
<td>Therapeutic</td>
<td>Therapeutic</td>
<td>Therapeutic</td>
<td>Prophylactic</td>
<td>--</td>
</tr>
<tr>
<td><strong>Efficacy†</strong></td>
<td>1.8% vs 1.3%</td>
<td>0.4% vs 5.6%*</td>
<td>1.3% vs 7.1%*</td>
<td>1.7% vs 8.8%*</td>
<td>5.1% vs 7.5%*</td>
</tr>
<tr>
<td><strong>NNT</strong></td>
<td>--</td>
<td>19</td>
<td>17</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td><strong>Safety‡</strong></td>
<td>5.6% vs 10.2%*</td>
<td>5.3% vs. 1.8%*</td>
<td>6.0% vs 1.2%*</td>
<td>3.2% vs 2.7%</td>
<td>1.1% vs 0.7%</td>
</tr>
<tr>
<td><strong>NNH</strong></td>
<td>--</td>
<td>29</td>
<td>21</td>
<td>200</td>
<td>250</td>
</tr>
</tbody>
</table>

* statistical difference
† annual rate of VTE or VTE related death
‡ annual rate of composite of major and clinically relevant nonmajor bleeding

Teaching Point Number 6

- **Routine** screening for thrombophilia should not be done
- All men and women with elevated D-dimer 1 month after OAC discontinuation are at increased risk for recurrence
- VTE recurrence scores exist and may assist in decision making but need validation before clinical utilization
- No compelling reason to switch from one agent to another for long term secondary prevention
- ASA considered in those with high bleeding risk
We’ve come a long way