Evolution in Thrombosis Management
CCCEP Accreditation

Evolution in Thrombosis Management

• Accredited for 1.5 CEU
• Program Accredited January 23rd, 2014
• Program Accreditation Expires January 23rd, 2015
Program Objectives

After attending this session, participants will be better able to:

• Implement strategies for the management of acute DVT and for the prevention of DVT/PE recurrence
• Utilize guideline based strategies for stroke prevention in atrial fibrillation
• Appropriately use anticoagulant therapy for the treatment of thrombosis
Evolution in Thrombosis Management

MODULE 1: Stroke Prevention in Atrial Fibrillation
MODULE 2: Clinical Challenges in the Treatment of Venous Thromboembolism
Faculty/Presenter Disclosure

- Faculty Name: Dr Claudia Bucci
- Relationships with commercial interests:
  - Consulting Fees/Honoraria: Astra Zeneca, BMS/Pfizer, Bayer
  - Officer, Director, Or In Any Other Fiduciary Role: None
  - Clinical Trials: None
  - Ownership/Partnership/Principal: None
  - Intellectual Property Rights: None
  - Other Financial Benefit: None
Disclosure of Commercial Support

- This program has received financial support from Bayer Canada in the form of an educational grant.
- This program has been created solely by Thrombosis Canada without the input of any commercial or non-commercial organization.

Potential for conflict(s) of interest:

- Bayer Canada benefits from the sale of a product(s) that will be discussed in this program: Xarelto (rivaroxaban)
Mitigating Potential Bias

- This program has been created solely by Thrombosis Canada, a registered non-profit, non-commercial organization.

- This program has been peer reviewed by Thrombosis Canada and the College of Family Physicians of Canada.

- No commercial or other non-commercial organization have had any input to the content of this program.

- No commercial or other non-commercial organization have been present at or privy to any discussions, meetings, or other activities related to the content of this program.
Module 1: Learning Objectives

After attending this session, participants will be better able to:

• Understand the risk of atrial fibrillation associated stroke;

• Identify patients with atrial fibrillation requiring anticoagulation based on stroke risk stratification;

• Use the most appropriate therapy to prevent stroke in patients with atrial fibrillation;

• Minimize bleeding risk in patients with atrial fibrillation requiring anticoagulation.
Atrial Fibrillation accounts for what percentage of all strokes?

A. 5 - 10%
B. 10 - 15%
C. 15 - 20%
D. 20 - 30%
E. 30 - 40%
An 84 year old female with AF, type 2 diabetes, hypertension, a remote history of GI bleeding and 2 falls in the past year should not be anticoagulated due to her high risk of bleeding.

A. True
B. False
Which of the following anticoagulants should be used for an AF patient with a Creatinine Clearance of 22?

A. Dabigatran 150 mg bid
B. Dabigatran 110 mg bid
C. Rivaroxaban 20 mg od
D. Rivaroxaban 15 mg od
E. Apixaban 5 mg bid
F. Apixaban 2.5 mg bid
G. Warfarin titrated to INR of 2 – 3
H. Warfarin or any of the NOACs at the reduced dose
All novel oral anticoagulants are contraindicated in a patient with moderate aortic stenosis.

A. True
B. False
The Canadian Cardiovascular Society recommends warfarin and the novel oral anticoagulants equally for stroke prevention in atrial fibrillation.

A. True
B. False
STROKE: INCIDENCE AND ETIOLOGY
The Impact of Stroke

- **Globally**:  
  - The 3rd most common cause of death in developed countries  
  - 15 million strokes annually  
    - 5 million deaths  
    - 5 million people permanently disabled

- **Each year in Canada**:  
  - 50,000 people have a stroke – one every 10 minutes  
  - 14,000 people die from stroke – the 3rd leading cause of death

- **Stroke costs the Canadian economy $2.7 billion annually**

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1. World Health Organization. 2004  
3. Canadian Stroke Network.
The Most Frequent Sites of Arterial and Cardiac Abnormalities Causing Ischemic Stroke

- Intracranial Atherosclerosis
- Carotid Plaque with Arteriogenic Emboli
- Aortic Arch Plaque
- Cardiogenic Emboli
- Penetrating Artery Disease
- Flow Reducing Carotid Stenosis
- Atrial Fibrillation
- Valve Disease
- Left Ventricular Thrombi

Stroke Types and Incidence

Ischemic stroke 88%

- Hemorrhagic stroke 12%
- Cryptogenic 30%
- Cardiogenic embolism 20%
- Atherosclerotic cerebrovascular disease 20%
- Small vessel disease “lacunes” 25%
- Other 5%

Albers GW et al. Chest. 2004; 126(3 Suppl):438S-512S.
ATRIAL FIBRILLATION RATES AND STROKE ASSOCIATION
Atrial fibrillation affects approximately 350,000 Canadians
Atrial Fibrillation
Major Risk Factor for Stroke

- Increases the risk of stroke by 5-fold\(^1,2,3\)
- Accounts for approximately 15-20\% of all strokes nationally\(^1,4\)
  - Associated with a 50-90\% increase in mortality risk after adjustment for co-existing cardiovascular conditions\(^2\)
  - Risk of stroke in atrial fibrillation patients who do not receive anticoagulation averages \sim 5\% per year
- Risk of stroke in atrial fibrillation patients by age group
  - 1.5\% in 50-59 year olds
  - 23.5\% in 80-89 year olds

Atrial Fibrillation
An Age Related Disease


Prevalence of Diagnosed Atrial Fibrillation Stratified by Age and Sex

Age, y

Prevalence, (%)

No. Women Men

<55 530 1259
55 - 59 310 634
60 - 64 566 934
65 - 69 896 1426
70 - 74 1498 1907
75 - 79 1572 1886
80 - 84 1291 1374
≥85 1132 759

Women Men
Atrial Fibrillation
A Growing Burden

Projected Number of Adults With Atrial Fibrillation in the United States Between 1995 and 2050

Upper and lower curves represent the upper and lower scenarios based on sensitivity analyses.

Attributable Risk of Stroke


<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Percentage (%)</th>
<th>Atrial fibrillation prevalence</th>
<th>Strokes attributable to atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-89</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Age-Related Increase in Attributable Risk of Stroke for Atrial Fibrillation

The Framingham Heart Study

Attributable risk of stroke for hypertension, coronary heart disease, cardiac failure and atrial fibrillation.

<table>
<thead>
<tr>
<th>Cardiovascular condition</th>
<th>50-59 yr</th>
<th>60-69 yr</th>
<th>70-79 yr</th>
<th>80-89 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>48.8%</td>
<td>53.2%</td>
<td>48.6%</td>
<td>33.4%</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>11.1%</td>
<td>12.4%</td>
<td>12.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2.3%</td>
<td>3.1%</td>
<td>5.6%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Atrial fibrillation*</td>
<td>1.5%</td>
<td>2.8%</td>
<td>9.9%</td>
<td>23.5%</td>
</tr>
</tbody>
</table>

*Significant increase with age, $p < 0.01$

Wolf PA et al. Stroke. 1991; 22(8):983-8
Atrial Fibrillation is a Progressive Disease

Incidence of Stroke or Non-Central Nervous System (CNS) Systemic Embolism According to Type of Atrial Fibrillation


<table>
<thead>
<tr>
<th></th>
<th>Paroxysmal</th>
<th>Sustained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk</td>
<td>1,199</td>
<td>5,499</td>
</tr>
<tr>
<td></td>
<td>1,121</td>
<td>5,264</td>
</tr>
<tr>
<td></td>
<td>862</td>
<td>4,006</td>
</tr>
<tr>
<td></td>
<td>304</td>
<td>1,560</td>
</tr>
</tbody>
</table>

Cumulative hazard rates

Years

0 0.01
0.5 0.02
1.0 0.03
1.5 0.04

Paroxysmal

Sustained

Atrial Fibrillation Patients Have Increased Post-Stroke Mortality and Morbidity

Dulli DA. et al. Neuroepidemiology. 2003; 22(2):118-23
Thromboembolic Events in Control Patients in Nonvalvular Atrial Fibrillation (NVAF) Trials

Cerebral* 49 (91%†)

Systemic* 5 (9%)

* Number of events (% of total of 54 events in control patients); † Range in the studies: 81 to 94% Combined data for AFASAK, SPAF, and BAATAF shown.

ATRIAL FIBRILLATION RELATED STROKE: RISK ASSESSMENT AND GUIDELINES
### CHADS<sub>2</sub> Risk Factor Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/Thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Maximum Score</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients (n = 1733)</th>
<th>Adjusted Stroke Rate (%/yr) 95% CI</th>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>1.9 (1.2 to 3.0)</td>
<td>0</td>
</tr>
<tr>
<td>463</td>
<td>2.8 (2.0 to 3.8)</td>
<td>1</td>
</tr>
<tr>
<td>523</td>
<td>4.0 (3.1 to 5.1)</td>
<td>2</td>
</tr>
<tr>
<td>337</td>
<td>5.9 (4.6 to 7.3)</td>
<td>3</td>
</tr>
<tr>
<td>220</td>
<td>8.5 (6.3 to 11.1)</td>
<td>4</td>
</tr>
<tr>
<td>65</td>
<td>12.5 (8.2 to 17.5)</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>18.2 (10.5 to 27.4)</td>
<td>6</td>
</tr>
</tbody>
</table>
# Predictive Index for Stroke

## CHADS<sub>2</sub> Risk Factor Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/Thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td><strong>Maximum Score</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

## CHA<sub>2</sub>DS<sub>2</sub>-VASc Risk Factor Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA Thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td><strong>Maximum Score</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>

# Bleeding Risk–HAS-BLED Score

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal Liver or Renal Function / 1 point each</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (age &gt; 65 yr)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or Alcohol / 1 point each</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Maximum 9 points

Bleeding Risk Management

• Address reversible risk factors:
  ▪ Falling – provide mobility aid
  ▪ Hypertension – treat BP to target
  ▪ Alcohol – encourage abstinence
  ▪ Labile INR – use NOAC
  ▪ Drugs – replace NSAID with other analgesic, avoid ASA unless clearly indicated for secondary prevention
  ▪ GI bleeding – use PPI

Do not withhold anticoagulation unless bleeding risk extreme
Risks of a Fall While on Coumadin

So...
- Would need to fall 295 times a year to outweigh the benefits of warfarin *regardless of age/baseline stroke risk*
- Average # of falls in a “fall risk”
  - 1.4
- RR of subdural hematoma in faller on warfarin vs faller not on warfarin:
  - 3.3
Overview of Stroke Management

Assess Thromboembolic Risk (CHADS₂)

- **CHADS₂ = 0**
  - No anti-thrombotic
  - No additional risk factors for stroke

- **CHADS₂ = 1**
  - ASA
  - Either female sex or vascular disease

- **CHADS₂ ≥ 2**
  - OAC*
  - Age ≥ 65 or combination of female sex and vascular disease

*ASA is a reasonable alternative in selected patients as indicated by risk/benefit

Increasing stroke risk

2012 Update
Assessing the Risk of Stroke

- > Age 65?
- Anticoagulant indicated
  - Yes
  - No
  - Any other risk factor for stroke?
    - Yes
    - No
    - Prior stroke?
      - Yes
      - No
      - Diabetes?
        - Yes
        - No
        - Hypertension?
          - Yes
          - No
          - Female with vascular disease?
            - Yes
            - No
            - Heart Failure?
              - Yes
              - No

We recommend that all patients with AF or AFL (paroxysmal, persistent or permanent), should be stratified using a predictive index for stroke (e.g. CHADS²) and for the risk of bleeding (e.g. HAS-BLED), and that most patients should receive either an oral anticoagulant or ASA. (Strong Recommendation, High Quality Evidence)

We suggest, that when OAC therapy is indicated, most patients should receive dabigatran or rivaroxaban or apixaban* in preference to warfarin. (Conditional recommendation, High Quality Evidence). *Once approved by Health Canada.

Values and Preferences - This recommendation places a relatively high value on comparisons to warfarin showing that dabigatran and apixaban have greater efficacy and rivaroxaban has similar efficacy for stroke prevention; dabigatran and rivaroxaban have no more major bleeding and apixaban has less; dabigatran, rivaroxaban and apixaban have less intracranial haemorrhage; and all three new OACs are much simpler to use. The recommendation places less value on these features of warfarin: long experience with clinical use, availability of a specific antidote and a simple and standardized test for intensity of anticoagulant effect. The preference for one of the new OACs over warfarin is less marked among patients already receiving warfarin with stable INRs and no bleeding complications.
STROKE PREVENTION IN AF CARE GAP
Atrial Fibrillation

Warfarin Benefit

Warfarin reduces the risk of AF related stroke by about 2/3

64% RRR

38% RRR

Warfarin vs. Placebo

Favours Warfarin

Favours Comparator

Treatment on Admission With Stroke


All High-Risk Atrial Fibrillation Patients

- No antithrombotics: 10%
- Dual antiplatelets: 25%
- Single antiplatelet: 29%
- Warfarin: therapeutic: 29%
- Warfarin: sub-therapeutic: 2%

High-Risk Atrial Fibrillation Patients with Previous Stroke or Transient Ischemic Attack

- No antithrombotics: 15%
- Dual antiplatelets: 29%
- Single antiplatelet: 18%
- Warfarin: therapeutic: 3%
- Warfarin: sub-therapeutic: 39%

<table>
<thead>
<tr>
<th>Year published</th>
<th>Study</th>
<th>Population</th>
<th>% Treated with Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Gage BF et al. Stroke</td>
<td>597 US Medicare pts</td>
<td>34</td>
</tr>
<tr>
<td>2005</td>
<td>NABOR. Waldo AL et al. J Am Coll Cardiol</td>
<td>945 US pts</td>
<td>55 (high-risk)</td>
</tr>
<tr>
<td>2006</td>
<td>Hylek EM et al. Stroke</td>
<td>402 US patients, ≥65 years</td>
<td>51</td>
</tr>
<tr>
<td>2006</td>
<td>Birman-Deych E et al. Stroke</td>
<td>17,272 US Medicare pts</td>
<td>49</td>
</tr>
<tr>
<td>2006</td>
<td>Friberg L et al. Eur Heart J</td>
<td>2,796 Swedish pts</td>
<td>54</td>
</tr>
<tr>
<td>2006</td>
<td>Monte S et al. Eur Heart J</td>
<td>1,812 elderly Italian pts discharged with AF</td>
<td>34 (high-risk)</td>
</tr>
</tbody>
</table>
Oral Anticoagulant Use by CHADS$_2$ Score

Oral anticoagulant therapy use declines in patient with higher CHADS$_2$ scores (CHADS$_2$ ≥ 2).

Bell AD. Canadian Cardiovascular Congress 2012 Poster Presentation.
1 Million Preventable Strokes

15 million strokes annually worldwide

20% of strokes due to atrial fibrillation

3 million are due to atrial fibrillation

Relative risk reduction (RRR) of 64% with warfarin

2 million are preventable with warfarin therapy

50% of eligible patients treated with warfarin

1 million strokes could have been prevented

NOVEL ORAL ANTICOAGULANTS FOR SPAF
# Novel Oral Anticoagulants

## Pharmacological Properties

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor IIa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dosing</td>
<td>BID</td>
<td>OD</td>
<td>BID</td>
</tr>
<tr>
<td>Bioavailability, %</td>
<td>6.5%</td>
<td>80-100%*</td>
<td>50%</td>
</tr>
<tr>
<td>Half-life</td>
<td>12-14 h</td>
<td>5-13h</td>
<td>8-15 h</td>
</tr>
<tr>
<td>Renal clearance (unchanged bioavailable drug)</td>
<td>85%</td>
<td>~33%</td>
<td>27%†</td>
</tr>
<tr>
<td>Cmax</td>
<td>1-2 h</td>
<td>2-4 h</td>
<td>3-4 h</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>P-gp inhibitors</td>
<td>Strong inhibitors of both CYP3A4 and P-gp</td>
<td>Strong inhibitors of both CYP3A4 and P-gp</td>
</tr>
</tbody>
</table>

* When the 15mg and 20mg dose is taken with food
† Factoring in the absolute bioavailability of apixaban, ~ 50% of the systemically available dose is eliminated in urine

1. Xarelto® PM, June 2013;
2. Pradaxa® PM November, 2012;
3. Eliquis® PM November, 2012;
4. FDA Eliquis Drug Approval Package, Clinical Pharmacology/Biopharmaceutics Review
# Trials Comparing New Oral Anticoagulants vs Warfarin

<table>
<thead>
<tr>
<th></th>
<th>RE-LY&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ROCKET AF&lt;sup&gt;2&lt;/sup&gt;</th>
<th>ARISTOTLE&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Non-inferiority, open label</td>
<td>Non-inferiority, double blind</td>
<td>Non-inferiority, double blind</td>
</tr>
<tr>
<td><strong>Study drugs</strong></td>
<td>Dabigatran (2 doses, blinded)</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>Open-label warfarin (INR 2–3)</td>
<td>Double-blind warfarin (INR 2–3)</td>
<td>Double-blind warfarin (INR 2–3)</td>
</tr>
<tr>
<td><strong>Primary Dose(s) Studied</strong></td>
<td><strong>110 mg BID and 150 mg BID</strong></td>
<td><strong>20 mg OD</strong></td>
<td><strong>5 mg BID</strong></td>
</tr>
<tr>
<td><strong>Adjusted Dose Studied</strong></td>
<td>None</td>
<td><strong>15 mg OD</strong></td>
<td>2.5 mg BID</td>
</tr>
</tbody>
</table>

*For patients with any two of the following:*  
- Age $\geq$ 80 years  
- Body weight $\leq$ 60 kg  
- Serum creatinine $\geq$ 1.5 mg/dl (133 $\mu$mol/l)

Dabigatran: RE-LY Design

- 18,113 patients randomized to dabigatran (110 or 150 mg BID) vs warfarin (INR 2-3)
- Followed for 2+ years (RELY-ABLE extension)
- Primary outcome: stroke/systemic embolism
- Safety outcome: major hemorrhage
- Patients with AF plus ≥1 CHADS$_2$ risk
- Excluded: valvular AF, “increased hemorrhage risk”, CrCl <30, liver disease, recent stroke

Dabigatran: RE-LY Primary Outcome

Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

150 mg RR = 0.55 (95% CI 0.53-0.82)
  $p < 0.001$ (superiority)
  $p < 0.001$ (non-inferiority)

110 mg RR = 0.91 (95% CI 0.74-1.11)
  $p = 0.34$ (superiority)
  $p < 0.001$ (non-inferiority)

Dabigatran: RE-LY Bleeding

<table>
<thead>
<tr>
<th>Event</th>
<th>Dabigatran, 110 mg, vs. Warfarin</th>
<th>Dabigatran, 150 mg, vs. Warfarin</th>
<th>Dabigatran, 150 mg vs. 110 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risk (95% CI)</td>
<td>P Value</td>
<td>Relative Risk (95% CI)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.80 (0.69–0.93)</td>
<td>0.003</td>
<td>0.93 (0.81–1.07)</td>
</tr>
<tr>
<td>Life threatening</td>
<td>0.68 (0.55–0.83)</td>
<td>&lt;0.001</td>
<td>0.81 (0.66–0.99)</td>
</tr>
<tr>
<td>Non–life threatening</td>
<td>0.94 (0.78–1.15)</td>
<td>0.56</td>
<td>1.07 (0.89–1.29)</td>
</tr>
<tr>
<td>Gastrointestinal†</td>
<td>1.10 (0.86–1.41)</td>
<td>0.43</td>
<td>1.50 (1.19–1.89)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>0.79 (0.74–0.84)</td>
<td>&lt;0.001</td>
<td>0.91 (0.85–0.97)</td>
</tr>
<tr>
<td>Major or minor bleeding</td>
<td>0.78 (0.74–0.83)</td>
<td>&lt;0.001</td>
<td>0.91 (0.86–0.97)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.31 (0.20–0.47)</td>
<td>&lt;0.001</td>
<td>0.40 (0.27–0.60)</td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td>0.94 (0.80–1.10)</td>
<td>0.45</td>
<td>1.07 (0.92–1.25)</td>
</tr>
<tr>
<td>Net clinical benefit outcome‡</td>
<td>0.92 (0.84–1.02)</td>
<td>0.10</td>
<td>0.91 (0.82–1.00)</td>
</tr>
</tbody>
</table>

## Newly Identified Events in the RE-LY Trial

**Table 1. Published and Revised Data for Primary Efficacy and Safety Outcomes and Myocardial Infarction, According to Treatment Group.**

<table>
<thead>
<tr>
<th>Event</th>
<th>Dabigatran, 110 mg (N = 6015)</th>
<th>Dabigatran, 150 mg (N = 6076)</th>
<th>Warfarin (N = 6022)</th>
<th>Dabigatran, 110 mg, vs. Warfarin</th>
<th>Dabigatran, 150 mg, vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients %/yr</td>
<td>no. of patients %/yr</td>
<td>no. of patients %/yr</td>
<td>Relative Risk (95% CI) P Value</td>
<td>Relative Risk (95% CI) P Value</td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Published</td>
<td>182 1.53</td>
<td>134 1.11</td>
<td>199 1.69</td>
<td>0.91 (0.74–1.11) 0.34</td>
<td>0.66 (0.53–0.82) &lt;0.001</td>
</tr>
<tr>
<td>Revised</td>
<td>183 1.54</td>
<td>134 1.11</td>
<td>202 1.71</td>
<td>0.90 (0.74–1.10) 0.30</td>
<td>0.65 (0.52–0.81) &lt;0.001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Published</td>
<td>322 2.71</td>
<td>375 3.11</td>
<td>397 3.36</td>
<td>0.80 (0.69–0.93) 0.003</td>
<td>0.93 (0.81–1.07) 0.31</td>
</tr>
<tr>
<td>Revised</td>
<td>342 2.87</td>
<td>399 3.32</td>
<td>421 3.57</td>
<td>0.80 (0.70–0.93) 0.003</td>
<td>0.93 (0.81–1.07) 0.32</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Published</td>
<td>86 0.72</td>
<td>89 0.74</td>
<td>63 0.53</td>
<td>1.35 (0.98–1.87) 0.07</td>
<td>1.38 (1.00–1.91) 0.048</td>
</tr>
<tr>
<td>Revised</td>
<td>98 0.82</td>
<td>97 0.81</td>
<td>75 0.64</td>
<td>1.29 (0.96–1.75) 0.09</td>
<td>1.27 (0.94–1.71) 0.12</td>
</tr>
</tbody>
</table>
Dabigatran Association With Higher Risk of Acute Coronary Events

Meta-analysis of Noninferiority Randomized Controlled Trials

Ken Uchino, MD; Adrian V. Hernandez, MD, PhD

<table>
<thead>
<tr>
<th>Study, y</th>
<th>Dabigatran, No.</th>
<th>Control, No.</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACEv</td>
<td>No Event</td>
<td>ACEv</td>
</tr>
<tr>
<td>RE-NOVATE,10 2007</td>
<td>13</td>
<td>2296</td>
<td>9</td>
</tr>
<tr>
<td>RE-MODEL,11 2007</td>
<td>10</td>
<td>1372</td>
<td>4</td>
</tr>
<tr>
<td>PETRO,12 2007</td>
<td>2</td>
<td>443</td>
<td>0</td>
</tr>
<tr>
<td>RE-LY original,23 2009</td>
<td>175</td>
<td>11916</td>
<td>63</td>
</tr>
<tr>
<td>RE-COVER,13 2009</td>
<td>4</td>
<td>1269</td>
<td>2</td>
</tr>
<tr>
<td>RE-DEEM,14 2011</td>
<td>32</td>
<td>1458</td>
<td>4</td>
</tr>
<tr>
<td>RE-NOVATE II,15 2011</td>
<td>1</td>
<td>1009</td>
<td>1</td>
</tr>
<tr>
<td>FE model</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Post Market Dabigatran Registry Data

#### Warfarin vs dabigatran 110mg

<table>
<thead>
<tr>
<th>Outcome / Model</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>0.79 (0.59; 1.03)</td>
<td>0.23</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.73 (0.54; 1.00)</td>
<td>0.092</td>
</tr>
<tr>
<td><strong>Systemic embolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>0.74 (0.72; 0.78)</td>
<td>0.70</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.60 (0.19; 1.60)</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.02 (0.87; 1.20)</td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.79 (0.65; 0.95)</td>
<td></td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>0.41 (0.26; 0.62)</td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.30 (0.18; 0.49)</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary embolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>0.42 (0.18; 0.87)</td>
<td>0.011</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.33 (0.12; 0.74)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Intracranial bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>0.30 (0.12; 0.63)</td>
<td>0.005</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.24 (0.08; 0.56)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Gastrointestinal bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>0.67 (0.43; 0.99)</td>
<td>0.12</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.60 (0.37; 0.93)</td>
<td>0.075</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>0.88 (0.66; 1.14)</td>
<td>0.043</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.82 (0.59; 1.12)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Hospitalization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>0.51 (0.48; 0.55)</td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.53 (0.49; 0.57)</td>
<td></td>
</tr>
</tbody>
</table>

---

Rivaroxaban:  
**ROCKET-AF Design**

- 14,264 patients randomized to rivaroxaban (20 mg OD or 15 mg OD if CrCl 30-50) or DA warfarin (INR 2-3)
- Double blind with sham INRs
- Followed for average 707 days
- Primary outcome: stroke/systemic embolism
- Safety outcome: major & clinically relevant bleeding
- Patients with AF plus ≥ 2 CHADS$_2$ risk
- Excluded: valvular AF, CrCl <30, hemorrhagic criteria

Rivaroxaban:
ROCKET-AF Primary Outcome

ITT Analysis HR = 0.88 (95% CI 0.75-1.03)
*p < 0.001 (non-inferiority)
*p = 0.12 (superiority)

## Rivaroxaban: 
*ROCKET-AF* Bleeding

### Table 3. Rates of Bleeding Events.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rivaroxaban (N=7111)</th>
<th>Warfarin (N=7125)</th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events no. (%)</td>
<td>Event Rate no./100 patient-yr</td>
<td>Events no. (%)</td>
<td>Event Rate no./100 patient-yr</td>
</tr>
<tr>
<td>Principal safety end point: major and nonmajor clinically relevant bleeding‡</td>
<td>1475 (20.7) 14.9</td>
<td>1449 (20.3) 14.5</td>
<td>1.03 (0.96–1.11)</td>
<td>0.44</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>395 (5.6) 3.6</td>
<td>386 (5.4) 3.4</td>
<td>1.04 (0.90–1.20)</td>
<td>0.58</td>
</tr>
<tr>
<td>Decrease in hemoglobin ≥2 g/dl</td>
<td>305 (4.3) 2.8</td>
<td>254 (3.6) 2.3</td>
<td>1.22 (1.03–1.44)</td>
<td>0.02</td>
</tr>
<tr>
<td>Transfusion</td>
<td>183 (2.6) 1.6</td>
<td>149 (2.1) 1.3</td>
<td>1.25 (1.01–1.55)</td>
<td>0.04</td>
</tr>
<tr>
<td>Critical bleeding¶</td>
<td>91 (1.3) 0.8</td>
<td>133 (1.9) 1.2</td>
<td>0.69 (0.53–0.91)</td>
<td>0.007</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>27 (0.4) 0.2</td>
<td>55 (0.8) 0.5</td>
<td>0.50 (0.31–0.79)</td>
<td>0.003</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>55 (0.8) 0.5</td>
<td>84 (1.2) 0.7</td>
<td>0.67 (0.47–0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Nonmajor clinically relevant bleeding</td>
<td>1185 (16.7) 11.8</td>
<td>1151 (16.2) 11.4</td>
<td>1.04 (0.96–1.13)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Apixaban: ARISTOTLE Design

- 18,201 patients randomized to apixaban (5 mg BID or 2.5 mg BID) or DA warfarin (INR 2-3)
- Followed for 1.8 years
- Double blind with sham INRs
- Primary outcome: stroke/systemic embolism
- Safety outcome: ISTH major bleeding
- Patients with AF plus $\geq 1$ CHADS$_2$ risk
- Excluded: valvular AF, another indication for anticoag, CrCl <25, concurrent ASA + clopidogrel use

Apixaban: ARISTOTLE Primary Outcome

Hazard ratio, 0.79 (95% CI, 0.66 - 0.95)
P = 0.01

## Table 3. Bleeding Outcomes and Net Clinical Outcomes,*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban Group (N=9088)</th>
<th>Warfarin Group (N=9052)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with Event no.</td>
<td>Event Rate %/yr</td>
<td>Patients with Event no.</td>
<td>Event Rate %/yr</td>
</tr>
<tr>
<td>Primary safety outcome: ISTH major bleeding†</td>
<td>327</td>
<td>2.13</td>
<td>462</td>
<td>3.09</td>
</tr>
<tr>
<td>Intracranial</td>
<td>52</td>
<td>0.33</td>
<td>122</td>
<td>0.80</td>
</tr>
<tr>
<td>Other location</td>
<td>275</td>
<td>1.79</td>
<td>340</td>
<td>2.27</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>105</td>
<td>0.76</td>
<td>119</td>
<td>0.86</td>
</tr>
<tr>
<td>Major or clinically relevant nonmajor bleeding</td>
<td>613</td>
<td>4.07</td>
<td>877</td>
<td>6.01</td>
</tr>
<tr>
<td>GUSTO severe bleeding</td>
<td>80</td>
<td>0.52</td>
<td>172</td>
<td>1.13</td>
</tr>
<tr>
<td>GUSTO moderate or severe bleeding</td>
<td>199</td>
<td>1.29</td>
<td>328</td>
<td>2.18</td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>148</td>
<td>0.96</td>
<td>256</td>
<td>1.69</td>
</tr>
<tr>
<td>TIMI major or minor bleeding</td>
<td>239</td>
<td>1.55</td>
<td>370</td>
<td>2.46</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>2356</td>
<td>18.1</td>
<td>3060</td>
<td>25.8</td>
</tr>
<tr>
<td><strong>Net clinical outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke, systemic embolism, or major bleeding</td>
<td>521</td>
<td>3.17</td>
<td>666</td>
<td>4.11</td>
</tr>
<tr>
<td>Stroke, systemic embolism, major bleeding, or death from any cause</td>
<td>1009</td>
<td>6.13</td>
<td>1168</td>
<td>7.20</td>
</tr>
</tbody>
</table>

Apixaban & Bleeding: Interesting Results from AVERROES

- 55% reduction in the risk stroke and systemic embolism
- Comparable risk of major bleeding

Mean CHADS$_2$ Score in ROCKET AF, RE-LY, ARISTOTLE and ENGAGE AF Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mean CHADS$_2$ Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET AF$_1$</td>
<td>3.5</td>
</tr>
<tr>
<td>RE-LY$_2$</td>
<td>2.1</td>
</tr>
<tr>
<td>ARISTOTLE$_3$</td>
<td>2.1</td>
</tr>
<tr>
<td>ENGAGE AF</td>
<td>2.8</td>
</tr>
</tbody>
</table>

1. Patel MR et al, 2011;
2. Connolly SJ et al, 2009;

Not intended as cross-trial comparison
Absolute Reduction in Stroke/SE†

Hart analysis* vs placebo vs warfarin
-10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0

ROCKET AF vs placebo vs warfarin
ARISTOTLE* vs placebo vs warfarin
RELY 110 vs placebo vs warfarin
RELY 150* vs placebo vs warfarin

† Not intended as cross-trial comparison
* Statistically Significant

Rivaroxaban, Dabigatran, Apixaban and Warfarin All Have Excellent Efficacy For the Prevention of Stroke in Atrial Fibrillation Patients

Subjects without Stroke and Systemic Embolism (% per year)*

ROCKET AF\textsuperscript{1}

RE-LY\textsuperscript{2}

ARISTOTLE\textsuperscript{3}

*All event rates from ITT analyses

1. Adapted from Patel et al., *N Engl J Med.* 2011;
2. Adapted from Connolly et al., *N Engl J Med.* 2009;361:
3. Adapted from Granger et al., *N Engl J Med.* 2011
Reversibility

No known antidote is available for NOAC

But…

- NOAC anticoagulant effect reverses quickly when drug is withdrawn
- Warfarin induced intracranial bleeding is unlikely to benefit from reversing agents
  - Best approach to ICH is prevention with use of NOAC over warfarin
- GI and other major bleeds are most effectively treated by fluid replacement and mechanical hemostasis
Despite an Antidote for Warfarin, No Mortality Benefit Is Observed

Data obtained from intention-to-treat analysis

Xarelto® PM, June 2013, 2012; Eliquis® PM November, 2012; Pradaxa® PM November, 2012
NOVEL ORAL ANTICOAGULANTS
FOR SPAF DOSING
Recommended dose

Dose can be considered

Figure adapted from Huisman et al. Thromb Haemost 2012: 107: 838-847., Pradaxa © PM November, 2012;
Canadian Dosing Recommendations for Stroke Prevention in AF

Patient has risk factor for stroke

Estimate CrCl

<30 mL/min

Not recommended

30-49 mL/min

15 mg OD

>50 mL/min

20 mg OD

Rivaroxaban

*Rivaroxaban 15mg and 20mg should be taken with food

Figure adapted from Huisman et al. Thromb Haemost 2012: 107: 838-847.
Xarelto® PM, June 2013
Canadian Dosing Recommendations for Stroke Prevention in AF

**Apixaban**

Patient has risk factor for stroke

- Estimate CrCl
  - <15 mL/min: Not recommended
  - ≥25 mL/min: No dosing recommendation can be made*
  - 24 mL/min: Check Age, Check Weight, Check Serum Creatinine
    - ≥ 80 years: If ≥ 2 features
    - ≤ 60 kg: If ≤ 1 feature

*In patients with eCrCL 15 - 24 mL/min, no dosing recommendation can be made as clinical data are very limited

---

**Rivaroxaban**

**Dabigatran**

*Figure adapted from Huisman et al. Thromb Haemost 2012: 107: 838-847, Eliquis® PM November, 2012;*
### Antithrombotic Algorithm for Atrial Fibrillation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure History</td>
<td>☐</td>
</tr>
<tr>
<td>Hypertension History</td>
<td>☑</td>
</tr>
<tr>
<td>Diabetes Mellitus History</td>
<td>☐</td>
</tr>
<tr>
<td>Stroke symptoms previously or TIA?</td>
<td>☑</td>
</tr>
<tr>
<td>Macrovascular Disease History (peripheral vascular disease, coronary artery disease)</td>
<td>☐</td>
</tr>
<tr>
<td>Female Patient</td>
<td>☐</td>
</tr>
</tbody>
</table>

#### Patient Information

- **Age (years):** 65
- **Weight (kg):** 73
- **Serum Creatinine (μmol/L):** 132

#### Score

**Score (CHADS2, eGFR):** 3, 50.9

- Dabigatran 150 mg twice daily or
- Rivaroxaban 20 mg once daily or
- Apixaban 5 mg twice daily or
- Warfarin to achieve INR between 2-3. Creatinine clearance should be checked yearly and drug selection and dose should be reassessed accordingly.

The Canadian Cardiovascular Society recommends a novel oral anticoagulant over warfarin (High-Quality Evidence).
Appropriate Candidates for Warfarin

- Severe renal impairment (CrCl < 25 mL/min)
- Patients with mechanical valve, rheumatic mitral valve disease
- Stable INR
- Patient preference
- Drug cost: may impact some patients

Take-home Messages

- Atrial fibrillation is the most common significant cardiac rhythm disorder
- Atrial fibrillation is a major independent risk factor for ischemic stroke
- Current stroke prevention management in atrial fibrillation is poor
- Although warfarin is an effective agent to prevent AF stroke NOACs offer significant advantages in efficacy, safety and convenience
Atrial Fibrillation Strokes are NOT Cerebrovascular “ACCIDENTS”

They are PREDICTABLE and PREVENTABLE Events
Please indicate how well this program met the stated learning objectives.

After attending this session, participants will be better able to:

- Understand the risk of atrial fibrillation associated stroke;
- Identify patients with atrial fibrillation requiring anticoagulation based on stroke risk stratification;
- Use the most appropriate therapy to prevent stroke in patients with atrial fibrillation;
- Minimize bleeding risk in patients with atrial fibrillation requiring anticoagulation.

A. Exceeded
B. Met
C. Poorly Met
D. Did Not Meet
Please rate Dr Claudia Bucci on her presentation.

A. Excellent
B. Good
C. Fair
D. Poor
Was this program free of industry bias?

A. Yes
B. No
Do you feel this program complied with RX&D/Mainpro Code of Ethics?

A. Yes
B. No
MODULE 2
Clinical Challenges in the Treatment of Venous Thromboembolism

James Douketis, MD, FRCPC
Specialty: Internal Medicine
Professor, Department of Medicine, McMaster University
Staff, General Internal Medicine and Vascular Medicine,
St. Joseph's Health Care, Hamilton, ON
Thrombosis Canada President
Faculty/Presenter Disclosure

- Faculty Name: Dr James Douketis
- Relationships with commercial interests:
  - Consulting Fees/Honoraria: Scientific advisor for Bristol-Myers Squibb-Pfizer, Bayer, Boehringer-Ingelheim, Biotie, Medicine.ca
  - Officer, Director, Or In Any Other Fiduciary Role: None
  - Clinical Trials: NIH, CIMR, HSF, Portola Pharmaceuticals
  - Ownership/Partnership/Principal: None
  - Intellectual Property Rights: None
  - Other Financial Benefit: None
Disclosure of Commercial Support

- This program has received financial support from Bayer Canada in the form of an educational grant.
- This program has been created solely by Thrombosis Canada without the input of any commercial or non-commercial organization.

Potential for conflict(s) of interest:
- Bayer Canada benefits from the sale of a product(s) that will be discussed in this program: Xarelto (rivaroxaban)
Mitigating Potential Bias

- This program has been created solely by Thrombosis Canada, a registered non-profit, non-commercial organization.

- This program has been peer reviewed by Thrombosis Canada and the College of Family Physicians of Canada.

- No commercial or other non-commercial organization have had any input to the content of this program.

- No commercial or other non-commercial organization have been present at or privy to any discussions, meetings, or other activities related to the content of this program.
Module 2: Learning Objectives

After attending this session, participants will be better able to:

• Use the most appropriate therapy to treat deep vein thrombosis (DVT) and pulmonary embolism (PE)
  ▪ “Uncomplicated” DVT in the setting of a transient risk factor
  ▪ Unprovoked DVT
  ▪ Provoked PE – stable and unstable patients
  ▪ Challenging clinical situations, including superficial thrombophlebitis, cancer-associated venous thromboembolism (VTE), pregnancy-associated VTE, splanchnic thrombosis, upper extremity DVT

• Evaluate the risks and benefits of novel and traditional anticoagulants in patients with DVT and PE
Case #1: Deep Vein Thrombosis in a Surgical Inpatient

- A 75 year old, otherwise healthy man falls and sustains an intertrochanteric left hip fracture. He waits in hospital for 4 days before undergoing an open reduction internal fixation

- On postoperative day #2, nursing staff note that his left leg is swollen, erythematous and tender

- A duplex ultrasound confirms an occlusive deep vein thrombosis extending from the popliteal vein to the common femoral vein
Case #1: 
*Deep Vein Thrombosis in a Surgical Inpatient*

What treatment options will you offer in the short and medium terms?
45,000 Canadians are affected by DVT each year. Why do we treat it?

- Prevent embolization
- Prevent extension
- Prevent recurrence

Systematic Review: Recurrent VTE in First 3 Months on Anticoagulants

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pts with any VTE*</th>
<th>Pts with DVT</th>
<th>Pts with PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>19 027</td>
<td>10 050</td>
<td>3 422</td>
</tr>
<tr>
<td>Recurrent fatal VTE (95% confidence interval (CI)), %</td>
<td>0.4 (0.3 – 0.6)</td>
<td>0.3 (0.2 – 0.5)</td>
<td>1.3 (0.9 – 1.7)</td>
</tr>
<tr>
<td>Recurrent PE (95% confidence interval), %</td>
<td>1.6 (1.3 – 2.0)</td>
<td>1.3 (1.0 – 1.7)</td>
<td>3.0 (2.5 – 3.7)</td>
</tr>
<tr>
<td>Recurrent VTE (95% confidence interval), %</td>
<td>3.4 (2.9 – 4.0)</td>
<td>3.2 (2.4 – 4.1)</td>
<td>3.6 (2.3 – 5.0)</td>
</tr>
</tbody>
</table>

*Patients presenting with DVT, PE or both or patients whose initial presentation was not specified in original study reports

Systematic Review:
*Bleeding in First 3 Months on Anticoagulants*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients with any VTE*</th>
<th>Patients with DVT</th>
<th>Patients with PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>19 027</td>
<td>10 050</td>
<td>3 422</td>
</tr>
<tr>
<td>Fatal major bleeding event (95% CI), %</td>
<td>0.2 (0.1 – 0.3)</td>
<td>0.2 (0.1 – 0.3)</td>
<td>0.2 (0.1 – 0.4)</td>
</tr>
<tr>
<td>Major bleeding event (95% CI), %</td>
<td>1.6 (1.3 – 2.0)</td>
<td>1.6 (1.2 – 2.1)</td>
<td>1.8 (1.1 – 2.6)</td>
</tr>
</tbody>
</table>

*Patients presenting with DVT, PE or both or patients whose initial presentation was not specified in original study reports

Initial Pharmacologic Therapy of “Uncomplicated” DVT

- Unfractionated heparin (UFH)
- Low molecular weight heparin (LMWH)
- Fondaparinux
- Oral factor Xa inhibitors
  - Rivaroxaban
  - Apixaban
- Oral direct thrombin inhibitors
  - Dabigatran

DISCLAIMER: dabigatran and apixaban not yet approved by Health Canada for treatment of VTE
Traditional Anticoagulants: Pros and Cons

- **Unfractionated Heparin**
  - Use is complicated by narrow therapeutic range, inter-individual variation in anticoagulant effect, and increased risk of heparin induced thrombocytopenia (HIT).
  - Ideal in patients with:
    - severe renal insufficiency (creatinine clearance (CrCl) < 30 mL/min)
    - patients at increased risk for bleeding, in whom rapid reversal of the anticoagulant effect may be needed
    - patients who receive thrombolytic therapy
  - Initial treatment with UFH is generally a segue to therapeutic dose warfarin (INR 2-3)
Traditional Anticoagulants: 
Pros and Cons

• **LMWH**
  - Use is complicated by inconvenient route of administration (subcutaneous), cost
  - When compared to UFH, it is more bioavailable, has predictable dosing, has longer duration of effect, has lower risk of HIT, has less effect on bone metabolism, and no requirement for monitoring
  - Ideal in patients with:
    - Cancer who require long-term anticoagulation
  - Initial treatment with LMWH is generally a segue to therapeutic dose warfarin (INR 2-3)
Traditional Anticoagulants: 
Pros and Cons

• Fondaparinux
  ▪ Has many of the same advantages and disadvantages of LMWH
  ▪ Double-blind, randomized MATISSE trial randomized 2205 patients with acute symptomatic DVT to:
    • Fondaparinux (5, 7.5, or 10 mg subcutaneously once daily for weights of <50, 50 to 100, or >100 kg, respectively)
    • Enoxaparin (1 mg/kg subcutaneously twice daily) for at least five days, and until vitamin K antagonists were therapeutic with INR > 2
  ▪ Fondaparinux is at least as effective and safe as enoxaparin for initial treatment of DVT
### Novel Oral Anticoagulants (NOACs)
#### Pharmacological Properties

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Dabigatran&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Factor Xa</td>
<td>Factor IIa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>OD</td>
<td>BID</td>
<td>BID</td>
</tr>
<tr>
<td><strong>Bioavailability, %</strong></td>
<td>80-100%&lt;sup&gt;*&lt;/sup&gt;</td>
<td>6.5%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>5-13h</td>
<td>12-14 h</td>
<td>8-15 h</td>
</tr>
<tr>
<td><strong>Renal clearance</strong></td>
<td>~33%</td>
<td>85%</td>
<td>27%†</td>
</tr>
<tr>
<td>(unchanged bioavailable drug)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cmax</strong></td>
<td>2-4 h</td>
<td>1-2 h</td>
<td>3-4 h</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Strong inhibitors of both CYP3A4 and P-gp</td>
<td>P-gp inhibitors</td>
<td>Strong inhibitors of both CYP3A4 and P-gp</td>
</tr>
</tbody>
</table>

* When the 15mg and 20mg dose is taken with food
† Factoring in the absolute bioavailability of apixaban, ~ 50% of the systemically available dose is eliminated in urine

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1. Xarelto® PM, June 2013;
2. Pradaxa © PM November, 2012;
3. Eliquis® PM November, 2012;
4. FDA Eliquis Drug Approval Package, Clinical Pharmacology/Biopharmaceutics Review
## Major Trials Comparing NOACs to Warfarin in VTE

<table>
<thead>
<tr>
<th></th>
<th>EINSTEIN-DVT&lt;sup&gt;1&lt;/sup&gt;</th>
<th>EINSTEIN-PE&lt;sup&gt;2&lt;/sup&gt;</th>
<th>AMPLIFY&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>3 449 (acute, symptomatic DVT)</td>
<td>4 832 (acute, symptomatic PE with or without DVT)</td>
<td>5 395 (acute VTE)</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Non-inferiority, open label</td>
<td>Non-inferiority, open label</td>
<td>Non-inferiority, double blind</td>
</tr>
<tr>
<td><strong>Study Drug</strong></td>
<td>Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily</td>
<td>Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily</td>
<td>Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>Subcutaneous enoxaparin followed by a VKA (warfarin or acenocoumarol)</td>
<td>Subcutaneous enoxaparin followed by a VKA (warfarin or acenocoumarol)</td>
<td>Subcutaneous enoxaparin for 5 days followed by warfarin</td>
</tr>
<tr>
<td><strong>Primary efficacy outcomes</strong></td>
<td>Recurrent VTE</td>
<td>Recurrent VTE</td>
<td>Recurrent symptomatic VTE or death related to VTE</td>
</tr>
<tr>
<td><strong>Primary safety outcomes</strong></td>
<td>Major bleeding or clinically relevant non-major bleeding</td>
<td>Major bleeding or clinically relevant non-major bleeding</td>
<td>Major bleeding or clinically relevant non-major bleeding</td>
</tr>
</tbody>
</table>

## Major Trials Comparing NOACs to Warfarin in VTE

<table>
<thead>
<tr>
<th></th>
<th>RE-COVER⁴</th>
<th>HOKUSAI-VTE⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>2,539 (acute PE)</td>
<td>4,832 (acute, symptomatic PE with or without DVT)</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Non-inferiority, double blind</td>
<td>Non-inferiority, double blind</td>
</tr>
<tr>
<td><strong>Study Drug</strong></td>
<td>Dabigatran 150 mg bid</td>
<td>Heparin (enoxaparin or UFH) followed by edoxaban 60 mg daily (or 30 mg daily if CrCl 30-50 mL/min or wt &lt; 60 kg)</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>Double-blind warfarin (INR 2–3)</td>
<td>Heparin (enoxaparin or UFH) followed by warfarin</td>
</tr>
<tr>
<td><strong>Primary efficacy outcomes</strong></td>
<td>Recurrent symptomatic, VTE and related deaths</td>
<td>Recurrent symptomatic VTE</td>
</tr>
<tr>
<td><strong>Primary safety outcomes</strong></td>
<td>Bleeding events, acute coronary syndromes, other adverse events, results of liver-function tests</td>
<td>Major bleeding or clinically relevant non-major bleeding</td>
</tr>
</tbody>
</table>

How Do NOACs Stack Up to Warfarin?

- 2012 Meta-analysis of 9 randomized trials concluded:
  - Compared with vitamin K antagonists (VKAs), NOACs had similar risk of recurrence of acute VTE and all cause mortality, though rivaroxaban was associated with a reduced risk of bleeding
  - Compared with each other, no one NOAC was superior to any other in terms of recurrent VTE, mortality or major bleeding

- Subsequent studies suggest apixaban and edoxaban also associated with a reduced risk of bleeding

- Further trials and postmarketing surveillance are needed for all of the NOACs

### Relative Risk for Recurrent VTE with Novel Oral Anticoagulants vs Vitamin K Antagonists

<table>
<thead>
<tr>
<th>Study</th>
<th>Novel oral anticoagulants</th>
<th>Vitamin K antagonists</th>
<th>Risk ratio (95% CI)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>36/1731</td>
<td>51/1718</td>
<td>0.70 (0.46 to 1.07)</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>50/2419</td>
<td>44/2413</td>
<td>1.13 (0.76 to 1.69)</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DOSE</td>
<td>3/115</td>
<td>7/101</td>
<td>0.38 (0.10 to 1.42)</td>
<td></td>
</tr>
<tr>
<td>OXIDa</td>
<td>2/100</td>
<td>1/112</td>
<td>2.24 (0.21 to 24.33)</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>91/4365</td>
<td>103/4344</td>
<td>0.85 (0.55 to 1.31)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity I² = 38%, P = 0.185</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botticelli-DVT</td>
<td>3/130</td>
<td>3/128</td>
<td>0.98 (0.20 to 4.79)</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>3/130</td>
<td>3/128</td>
<td>0.98 (0.20 to 4.79)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity I² = NA, P = 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECOVER</td>
<td>30/1274</td>
<td>27/1265</td>
<td>1.10 (0.66 to 1.84)</td>
<td></td>
</tr>
<tr>
<td>RECOVER II</td>
<td>30/1279</td>
<td>28/1289</td>
<td>1.08 (0.65 to 1.80)</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>60/2553</td>
<td>55/2554</td>
<td>1.09 (0.76 to 1.57)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity I² = 0%, P = 0.954</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ximelagatran</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THRIVE II</td>
<td>26/1240</td>
<td>24/1249</td>
<td>1.09 (0.63 to 1.89)</td>
<td></td>
</tr>
<tr>
<td>THRIVE I</td>
<td>1/65</td>
<td>2/73</td>
<td>0.56 (0.05 to 6.05)</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>27/1305</td>
<td>26/1322</td>
<td>1.06 (0.62 to 1.80)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity I² = 0%, P = 0.594</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative Risk for Major Bleeding with NOACs vs VKAs

<table>
<thead>
<tr>
<th>Study</th>
<th>NOACs Events</th>
<th>NOACs Total</th>
<th>Vitamin K Antagonists Events</th>
<th>Vitamin K Antagonists Total</th>
<th>Risk Ratio (95% CI) NOACs vs Vitamin K Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>14/1718</td>
<td>20/1711</td>
<td></td>
<td></td>
<td>0.70 (0.35 to 1.38)</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>26/2412</td>
<td>52/2405</td>
<td></td>
<td></td>
<td>0.50 (0.31 to 0.80)</td>
</tr>
<tr>
<td>EINSTEIN-DOSE</td>
<td>1/135</td>
<td>2/137</td>
<td></td>
<td></td>
<td>0.51 (0.05 to 5.53)</td>
</tr>
<tr>
<td>OXIDa</td>
<td>2/117</td>
<td>0/126</td>
<td></td>
<td></td>
<td>5.38 (0.26 to 110.96)</td>
</tr>
<tr>
<td>Random effects model</td>
<td>43/4382</td>
<td>74/4379</td>
<td></td>
<td></td>
<td>0.57 (0.39 to 0.84)</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity $I^2 = 0%$, $P = 0.426$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botticelli-DVT</td>
<td>1/128</td>
<td>0/126</td>
<td></td>
<td></td>
<td>2.95 (0.12 to 71.82)</td>
</tr>
<tr>
<td>Random effects model</td>
<td>1/128</td>
<td>0/126</td>
<td></td>
<td></td>
<td>2.95 (0.12 to 71.82)</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity $I^2 = NA$, $P = 1$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECOVER I</td>
<td>20/1274</td>
<td>24/1265</td>
<td></td>
<td></td>
<td>0.83 (0.46 to 1.49)</td>
</tr>
<tr>
<td>RECOVER II</td>
<td>15/1279</td>
<td>22/1289</td>
<td></td>
<td></td>
<td>0.69 (0.36 to 1.32)</td>
</tr>
<tr>
<td>Random effects model</td>
<td>35/2553</td>
<td>46/2554</td>
<td></td>
<td></td>
<td>0.76 (0.49 to 1.18)</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity $I^2 = 0%$, $P = 0.678$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ximelagatran</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THRIVE II/V</td>
<td>14/1240</td>
<td>26/1249</td>
<td></td>
<td></td>
<td>0.54 (0.28 to 1.03)</td>
</tr>
<tr>
<td>THRIVE I</td>
<td>0/62</td>
<td>0/73</td>
<td></td>
<td></td>
<td>0.54 (0.28 to 1.03)</td>
</tr>
<tr>
<td>Random effects model</td>
<td>14/1305</td>
<td>26/1322</td>
<td></td>
<td></td>
<td>0.54 (0.28 to 1.03)</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity $I^2 = NA$, $P = 1$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative Risk for All-Cause Mortality with NOACs vs VKAs

<table>
<thead>
<tr>
<th>Study</th>
<th>NOACs Events</th>
<th>NOACs Total</th>
<th>Vitamin K Antagonists Events</th>
<th>Vitamin K Antagonists Total</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>38/1718</td>
<td>49/1711</td>
<td></td>
<td></td>
<td>0.77 (0.51 to 1.17)</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>58/2412</td>
<td>50/2405</td>
<td></td>
<td></td>
<td>1.16 (0.80 to 1.68)</td>
</tr>
<tr>
<td>EINSTEIN-DOSE</td>
<td>4/135</td>
<td>5/137</td>
<td></td>
<td></td>
<td>0.81 (0.22 to 2.96)</td>
</tr>
<tr>
<td>OXIDa</td>
<td>0/117</td>
<td>0/126</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>100/4382</td>
<td>104/4379</td>
<td></td>
<td></td>
<td>0.96 (0.72 to 1.27)</td>
</tr>
<tr>
<td>Heterogeneity $I^2 = 2.7%$, $P = 0.358$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botticelli-DVT</td>
<td>3/128</td>
<td>0/126</td>
<td></td>
<td></td>
<td>6.89 (0.36 to 132.06)</td>
</tr>
<tr>
<td>Random effects model</td>
<td>3/128</td>
<td>0/126</td>
<td></td>
<td></td>
<td>6.89 (0.36 to 132.06)</td>
</tr>
<tr>
<td>Heterogeneity $I^2 = NA$, $P = 1$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECOVER I</td>
<td>21/1274</td>
<td>21/1265</td>
<td></td>
<td></td>
<td>0.99 (0.56 to 1.81)</td>
</tr>
<tr>
<td>RECOVER II</td>
<td>25/1279</td>
<td>25/1289</td>
<td></td>
<td></td>
<td>1.01 (0.58 to 1.74)</td>
</tr>
<tr>
<td>Random effects model</td>
<td>46/2553</td>
<td>46/2554</td>
<td></td>
<td></td>
<td>1.00 (0.67 to 1.50)</td>
</tr>
<tr>
<td>Heterogeneity $I^2 = 0%$, $P = 0.971$</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Ximelagatran</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THRIVE II/V1</td>
<td>28/1240</td>
<td>42/1249</td>
<td></td>
<td></td>
<td>0.67 (0.42 to 1.08)</td>
</tr>
<tr>
<td>THRIVE I</td>
<td>0/65</td>
<td>0/73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>28/1305</td>
<td>42/1322</td>
<td></td>
<td></td>
<td>0.67 (0.42 to 1.08)</td>
</tr>
</tbody>
</table>
Pros and Cons of NOACs

Pros:
- Rapid onset
- Predictable effect
- Specific target
- Few food / drug interactions
- Renal elimination
- Difficult to monitor
- Potential for overuse
- High cost
- Short half-life
- No antidote

Cons:
- Rapid onset
- Predictable effect
- Specific target
- Few food / drug interactions
Which Agent to Choose?

- **Consider patient's values and preferences**
  - Risk tolerance for bleeding versus clotting
  - Ability to afford drug
  - Ability to get lab work done
  - Need to affiliate closely with healthcare providers

- **Consider patient's bleeding risk factors**
  - Age, previous bleeding, cancer, renal failure, liver failure, thrombocytopenia, anemia, previous stroke, diabetes, antiplatelet therapy, poor anticoagulant control, co-morbidity and reduced functional capacity, recent surgery, frequent falls, alcohol abuse
Drug Interactions Still Exist

• Serious effects…
  ▪ Highly active antiretroviral therapy (HAART) and antifungal azoles – increase levels of all NOACs
  ▪ Rifampicin, St. John's wort, carbamazepine, phenytoin, and phenobarbital – decrease levels of dabigatran and apixaban
  ▪ Dronedarone – increases levels of dabigatran and rivaroxaban

• Moderate effects…
  ▪ Quinidine, verapamil – increases levels of dabigatran and rivaroxaban
  ▪ Amiodarone – increases levels of dabigatran

If You Choose a NOAC for VTE

**Rivaroxaban**
- Health Canada approved for treatment of DVT without symptomatic PE and for treatment of PE
  - Recommended dosing is 15 mg twice daily for first 21 days, followed by 20 mg once daily for duration of treatment
  - Overlap with a parenteral agent not needed
  - Should not be used in women who are pregnant or breast-feeding

**Dabigatran**
- Not Health Canada approved for treatment of DVT or PE
Rivaroxaban: Only Currently Approved NOAC for VTE Treatment

- Straightforward oral treatment option for DVT and PE
- Ideal for primary care physicians managing uncomplicated VTE, who...
  - Are not comfortable with the use of LMWH
  - Do not have the necessary time and resources to teach patients self-injection
- Benefits of Rivaroxaban in treatment of VTE
  - Stable patients can be treated in the primary care setting, without referral to emergency rooms
  - More rapid treatment initiation
  - No overlap with LMWH or UFH required
  - Greater convenience for patient and physician
  - Potentially reduced health care costs
Case #2: Deep Vein Thrombosis In an Outpatient

- A 45 year old man with a past history of hypertension and seasonal allergies presents to his family doctor with a swollen, erythematous and tender left leg. He reports no recent changes in his health or activities. He is on hydrochlorothiazide and cetirizine.

- The nearest lab is closed, so a duplex ultrasound is not available.
Case #2: Deep Vein Thrombosis In an Outpatient

What treatment options will you offer?

If an ultrasound is not rapidly available...

... patients with moderate to high suspicion of DVT, and a low to moderate risk of bleeding, should start therapy before the diagnosis is confirmed!
Case #2: Deep Vein Thrombosis In an Outpatient

• The patient returns for an ultrasound the following morning. A duplex ultrasound confirms an occlusive deep vein thrombosis extending from the popliteal vein to the common femoral vein.
Case #2: Deep Vein Thrombosis In an Outpatient

What treatment options will you offer?

What duration of treatment is required?
# Duration of Therapy

<table>
<thead>
<tr>
<th>Categories of VTE</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated distal DVT, DVT or PE provoked by a transient risk factor</td>
<td>3 months</td>
</tr>
<tr>
<td>First unprovoked DVT or PE</td>
<td>Minimum of 3 months and then reassess. For patients with no or only minor risk factors for bleeding, long-term therapy with annual review can be offered. Decision to continue anticoagulation should consider patient’s values and preferences.</td>
</tr>
<tr>
<td>Second unprovoked DVT or PE</td>
<td>Minimum of 3 months and then reassess. For patients with no or only minor risk factors for bleeding, long-term therapy with annual review should be encouraged. Decision to continue anticoagulation should consider patient’s values and preferences.</td>
</tr>
<tr>
<td>Cancer-associated VTE</td>
<td>Minimum of 3 months and then reassess. Continue if active cancer (overt evidence of cancer) or continuing to receive anti-cancer therapy.</td>
</tr>
</tbody>
</table>

Decisions About Duration of Therapy Must Consider Bleeding and Thrombosis Risk, as well as Patient’s Values and Preferences

- **Transient risk factors include:**
  - Surgery, hospitalization or plaster cast immobilization, all within 3 months, lesser leg injuries or immobilizations more recently (e.g. within 6 weeks), estrogen therapy or pregnancy, prolonged travel (e.g. > 8 hours)

- **Bleeding risk factors include:**
  - Age, previous bleeding, cancer, renal failure, liver failure, thrombocytopenia, anemia, previous stroke, diabetes, antiplatelet therapy, poor anticoagulant control, co-morbidity and reduced functional capacity, recent surgery, frequent falls, alcohol abuse
Long-term Therapy with NOACs

• **EINSTEIN-EXTENSION**: compared to placebo, rivaroxaban associated with less recurrent DVT, more clinically relevant non-major bleeding, and similar nonfatal major bleeding after 6 to 12 months of therapy

• **AMPLIFY-EXT**: compared to placebo, apixaban (prophylactic or therapeutic dose) associated with less recurrent VTE after 6 months of therapy

• **RE-MEDY**: compared to warfarin, dabigatran associated with similar rate of recurrent VTE, less major or clinically relevant bleeding, and more acute coronary syndrome after at least 3 months of therapy

• **RE-SONATE**: compared to placebo, dabigatran associated with less recurrent VTE, and more major or clinically relevant bleeding after at least 3 months of therapy
Rivaroxaban: An Approved NOAC for Long-term VTE Treatment

- At this time, Rivaroxaban can be used for long-term treatment of both DVT and PE
- EINSTEIN-EXTENSION trial provides supporting evidence
- Patients should be counselled on increased risk of clinically relevant non-major bleeding
What about acetylsalicylic acid (ASA) for long-term therapy?

- Two studies compared 100 mg ASA to placebo in patients with first unprovoked DVT who completed 6-18 months of anticoagulation.

- Pooled analysis showed that patients on ASA had:
  - 32% reduction in VTE recurrence (p=0.007)
  - 34% reduction in other major vascular events (e.g., ACS, stroke) (p=0.002)
  - No significant increase in major or clinically significant bleeding

- ASA should not be used for initial treatment of DVT

- ASA likely provides less benefit than continued anticoagulation for extended treatment!

Case #3: *Pulmonary Embolism in an Outpatient*

- A 25 year old woman with a past history of mild asthma presents to the emergency room with sharp chest pain, worsened on deep inspiration. Vital signs are stable, and peripheral oxygen saturations are 99% on room air. Her D-dimer is markedly elevated (>3000). She reports starting a combined oral contraceptive pill 30 days ago.

- CT-PA shows bilateral pulmonary emboli.
Case #3: *Pulmonary Embolism in an Outpatient*

- What treatment options will you offer?
- What duration of treatment is required?
- Can this patient be sent home?
Case #3: Pulmonary Embolism in an Outpatient

What treatment options will you offer?
- Rivaroxaban
- Warfarin (with initial overlap with subcut LMWH or IV UFH, until INR > 2)

What duration of treatment is required?
- PE in the setting of a transient risk factor
- Must treat for a minimum of 3 months
- Can discontinue anticoagulation at 3 months if patient discontinues estrogen-containing products

Can this patient be sent home?
- YES!
Do I need to consider thrombolytic therapy?

- Paucity of evidence
- Patients with acute PE and signs of hemodynamic compromise suggesting right heart failure are at increased risk of early mortality
- They should be considered for systemic thrombolysis
  - May reduce mortality
  - May increase risk of major bleeding – including 2% risk of intracranial hemorrhage
Do I need to consider thrombolytic therapy?

Consider first-line systemic thrombolysis and evaluation of bleeding risk factors if THIS was the case...

- A 25 year old woman with a past history of mild asthma presents to the emergency room with sharp chest pain, worsened on deep inspiration. She is tachycardic, mildly hypotensive, and peripheral oxygen saturations were 95% on room air. Her D-dimer is markedly elevated (>3000). She reports starting a combined oral contraceptive pill 30 days ago.

- CT-PA shows extensive pulmonary emboli, including a saddle embolus. There is evidence of right heart strain, including dilatation of the inferior vena cava, tricuspid incompetence and right ventricular dilatation.
Do I need to consider thrombolytic therapy?

- Various thrombolytic regimens have been used.

- Most popular:
  - rt-PA 100 mg IV, with 10 mg given over 10 minutes and remaining 90 mg given over 2 hours.
  - Followed by IV heparin infusion with no initial bolus.

What about thrombolysis of extensive lower limb DVT?

- When you compare lysis to anticoagulation...
  - Significant decrease in post-thrombotic syndrome
    (47.5% vs 65%, RR 0.66, 95% CI 0.47-0.94)
  - Significant increase in bleeding
    (10% vs 7.9%, RR 1.73, 95% CI 1.04-2.88)
  - No difference in mortality or PE events
- Catheter-directed thrombolysis may reduce postthrombotic syndrome more than systemic thrombolysis
- Consider thrombolysis for: massive proximal (iliofemoral) DVT associated with severe symptomatic swelling or limb-threatening ischemia (ie, phlegmasia cerulea dolens)

Do I need to use an IVC filter?

- No randomized trial or prospective cohort study has evaluated inferior vena caval (IVC) filters as sole therapy in patients with DVT.

- IVC filters may be useful in patients with acute DVT who cannot be anticoagulated.

- Words of warning about IVC filters:
  - Decrease rate of PE, but increase rate of DVT.
  - Have no impact on established PE.
    - “the horse is out of the barn” phenomenon.
  - Have local adverse effects.
  - Are not always easily retrievable.
# Main Complications of IVC Filters

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to retrieve a “retrievable” filter</td>
<td>0-22</td>
</tr>
<tr>
<td>Complications from insertion</td>
<td>4-11</td>
</tr>
<tr>
<td>Insertion site thrombosis</td>
<td>2-28</td>
</tr>
<tr>
<td>IVC thrombosis</td>
<td>6-30</td>
</tr>
<tr>
<td>Filter migration</td>
<td>3-69</td>
</tr>
<tr>
<td>IVC perforation</td>
<td>9-24</td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td>5-70</td>
</tr>
</tbody>
</table>

Reported IVC filter related events in a national FDA-sponsored voluntary database over an 11-year period.

VTE and NOACs: “What if…”

“… my patient has superficial thrombophlebitis?”
- No evidence for NOACs in this setting
- Evidence for LMWH, vitamin K antagonists, fondaparinux, oral or topical NSAIDs, supportive measures
- Thrombosis physicians tend to base “strength” of therapy on extent and clinical severity of phlebitis

“… my patient has splanchnic vein thrombosis?”
- No evidence for NOACs in this setting
- Evidence for LMWH and vitamin K antagonists, if patients have acute thrombosis
VTE and NOACs: “What if...”

• “... my patient has cancer-associated VTE?”
  ▪ These patients are at high risk of recurrence!
  ▪ Evidence for longterm LMWH over vitamin K antagonists
  ▪ Further studies with NOACs are needed
    • <5% of patients in pivotal clinical trials had cancer-associated VTE
    • Pooled analysis of EINSTEIN DVT and PE studies looked at the key subgroup of cancer patients - efficacy and safety of rivaroxaban were similar compared with standard-therapy.

VTE and NOACs: “What if...”

“... my patient is pregnant?”

- UFH and LMWH are safe during pregnancy and lactation
- Warfarin is safe during lactation
- Fondaparinux should be used with caution during lactation
- Fondaparinux should only be used during pregnancy in women with severe allergic reactions to heparin, including heparin-induced thrombocytopenia, who cannot receive danaparoid
- The NOACs are not recommended during pregnancy or lactation
VTE and NOACs: “What if...”

“... my patient has upper extremity DVT?”

- No evidence for NOACs in this setting
- Treat spontaneous upper extremity DVT like its lower extremity counterpart, using traditional anticoagulants
- Venous outflow obstruction, if suspected, should be confirmed with imaging
- Treat catheter-induced DVT with traditional anticoagulants for 3 months, and leave the catheter in place during this period if it works and is needed!
VTE and NOACs: “What if...”

• “... my patient is frail?”
  ▪ Frailty should not deter use of NOACs
    • Pooled analysis of EINSTEIN DVT and PE studies looked at subgroup of fragile patients - efficacy and safety of rivaroxaban similar to standard therapy
  ▪ Try to optimize your patient’s overall health
    • Nutrition
    • Mobility aids
    • Management of comorbid conditions
  ▪ Ensure you are calculating creatinine clearance accurately and frequently (at least every 6 months)

Take-home Messages

• NOACs have major benefits over traditional anticoagulants in treating VTE
  ▪ Consider patient's values and preferences
  ▪ Consider patient's bleeding risk factors

• Duration of therapy is influenced by risk factors, comorbidities, history of VTE, and patient’s values and preferences
Take-home Messages

- Thrombolysis and IVC filters may be useful in selected patients

- NOACs remain off-label in many challenging clinical settings:
  - superficial thrombophlebitis
  - cancer-associated VTE
  - pregnancy-associated VTE
  - splanchnic thrombosis
  - upper extremity DVT
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 members represent medical and non-medical generalists and specialists
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 Website and APP

www.thrombosiscanada.ca

CLINICAL GUIDES

Thrombosis Canada has developed practical and actionable guides related to the treatment and management of thrombosis.

View Guides!

Click to view or download!
We treat DVT in order to:

A. Minimize symptoms
B. Prevent embolization
C. Prevent extension
D. Prevent recurrence
E. All of the above
A 39 year old male with unresected glioblastoma multiforme and small, asymptomatic PEs should be offered systemic thrombolysis.

A. True
B. False
Which of the following novel oral anticoagulants can be used initially in Canada for a 65 year old patient with a new DVT and a creatinine clearance of 52? (On-label!)

A. Dabigatran 150 mg bid  
B. Dabigatran 110 mg bid  
C. Rivaroxaban 20 mg od  
D. Rivaroxaban 15 mg bid  
E. Apixaban 5 mg bid
Rivaroxaban 15 mg PO bid is an evidence-based choice for patients with newly diagnosed cancer-associated thrombosis.

A. True
B. False
Patients with a second unprovoked VTE should receive anticoagulation...

A. For a minimum of 6 months, and potentially long-term
B. For a minimum of 3 months, then potentially long-term
C. For a minimum of 1 month, then potentially long-term
D. Long-term
E. All of the above
Please indicate how well this program met the stated learning objectives.

After attending this session, participants will be better able to:

- Use the most appropriate therapy to treat deep vein thrombosis (DVT) and pulmonary embolism (PE)
  - Uncomplicated” DVT in the setting of a transient risk factor
  - Unprovoked DVT
  - Provoked PE – stable and unstable patients
  - Challenging clinical situations, including superficial thrombophlebitis, cancer-associated venous thromboembolism (VTE), pregnancy-associated VTE, splanchnic thrombosis, upper extremity DVT

- Evaluate the risks and benefits of novel and traditional anticoagulants in patients with DVT and PE

A. Exceeded
B. Met
C. Poorly Met
D. Did Not Meet
Please rate Dr James Douketis on his presentation.

A. Excellent
B. Good
C. Fair
D. Poor

0% 0% 0% 0%
Was this program free of industry bias?

A. Yes
B. No
Do you feel this program complied with Rx&D/Mainpro Code of Ethics?

A. Yes
B. No