World Thrombosis Day
Monday, October 13th

**What is World Thrombosis Day?**
WTD is an annual day that will energize a collective drive to increase awareness and action through educational activities for the public and health professionals throughout the year, year to year.

**Who is involved with Thrombosis Day Activities**
Led by the ISTH in collaboration with numerous national and international professional organizations and health advocates.

**Why October 13th?**
Birthday of Rudolf Virchow, the pioneer in the pathophysiology of thrombosis.
World Thrombosis Day
Thrombosis Canada Activities

✓ Virtual Webinar

✓ Launch of patient and family web resource

WWW.VTEPROBLEMSOLVED.CA

✓ Media Initiatives
  Patient and Family Video on VTE – Dr. Menaka Pai
  Patient and Family Video on VTE and Woman’s Health – Dr. Shannon Bates
  Web Radio Interview – Dr. Ben Bell
  News interview – Dr. Mark Crowther

Support from Bayer Canada was provided to assist with Thrombosis Canada WTD Activities
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
Thrombosis Canada members are involved in:

- Clinical Research
- International Guideline Development
- Education
How Can I Find This Information on the Thrombosis Canada Website?

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!
Acetyl Salicylic Acid
Anticoagulant and Antithrombotic Drugs
To provide information on the use of acetyl salicylic acid in the treatment and prevention of vascular events.
New Oral Anticoagulants in Everyday Practice: Addressing Common Clinical Scenarios and Questions… not covered by the big trials

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• Dr Marc Jolicoeur
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Disclosure of Commercial Support

- This program has been created solely by Thrombosis Canada without the input of any commercial or non-commercial organization.
- Today's webinar is supported by Bayer Canada.

Potential for conflict(s) of interest:
- Dr. Douketis has received (last 10 years) honouraria/consulting fees from: Actelion, Astra-Zeneca, Biotie, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Leo Pharma, Medicines Co., Pfizer, Sanofi, some of whose product(s) are being discussed in this program.

- These funds have been deposited in university-based/research accounts.
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
After attending this session, participants will:

• Have an approach to the management of NOAC-treated patients who need an elective or urgent surgery/procedure and the use and interpretation of coagulation tests in the perioperative setting;

• Have an approach to the management of NOAC-treated patients with minor or more serious bleeding;

• Be able to address common “what if’s” relating to NOAC use
New Oral Anticoagulants and Antiplatelet Drugs

- P2Y₁₂ platelet receptor blockers:
  - Ticagrelor – reversible
  - Prasugrel – irreversible

- Direct thrombin inhibitors:
  - Dabigatran

- Direct Xa inhibitors:
  - Rivaroxaban
  - Apixaban
Novel Oral Anticoagulants:
Which drugs, what doses, what indications?

- **Dabigatran**
  - DVT prophylaxis….150 mg or 220 mg OD
  - VTE treatment……150 mg BID *(LMWH for first 5 days)*
  - AF………………….. 110 mg or 150 mg BID

- **Rivaroxaban**
  - DVT prophylaxis…..10 mg OD
  - VTE treatment…….15 mg BID x 3 weeks, 20 mg OD x 9 weeks
  - AF………………… 20 mg OD *(15 mg OD if CrCl 30-50 mL/min)*

- **Apixaban**
  - DVT prophylaxis…..2.5 mg BID
  - AF….5 mg BID *(2.5 mg BID if 2/3 of: age>80, wt <60, creat >133)*
Which NOAC to Use?

- High risk for stroke (prior stroke, CHA$_2$DS$_2$VASc >5)?
  - dabigatran 150 mg BID (greatest RRR for stroke vs warfarin)

- Prior GI bleed or at increased bleed risk (HASBLED >3)?
  - apixaban, 5 mg BID or dabigatran 110 mg BID (less bleeds vs warfarin)

- Renal insufficiency (CrCl <50 mL/min)?
  - rivaroxaban 15 mg OD or apixaban 2.5 mg BID (25-33% renal)

- Compliance issues?
  - rivaroxaban 20 mg OD
Pros and Cons of NOACs

Pros:
- Rapid onset
- Predictable effect
- Specific target
- Few food / drug interactions
- Short half-life
- 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
- Short half-life
- No antidote
Case Vignette No. 1: Minor Procedure

- A 68 year old female on apixaban for SPAF (normal renal function) needs 2 dental extractions that will include local anesthetic injections...

- How do you manage peri-procedure?

- **Suppl. Question:** She also takes ASA to prevent a first heart attack and stroke. Is this appropriate?
Patients Requiring Minor Procedures

- **ACCP 2012 Recommendation**: In patients who require minor dental surgery and are receiving VKA therapy, we suggest either continuing VKA with co-administration of an oral prohemostatic agent or stopping VKAs 2-3 days before the procedure instead of alternative strategies *(Grade 2C)*

- **Recommendations for NOACs?**
  - No evidence-based guidelines
  - Probably reasonable to continue apixaban and give pro-hemostatic mouthwash
  - Equally reasonable to stop 24 hours before procedure
Combining NOACs and Antiplatelet Drugs

- No additional stroke prevention benefit

- Increased risk for major bleeding: dabigatran + AP drugs
  - Concomitant use of a single antiplatelet drug increased risk of major bleeding: HR = 1.60 (1.42-1.82)

- Increased risk for major bleeding: apixaban or rivaroxaban + ASA
  - Apixaban + ASA: HR = 1.42 (1.21-1.67)
  - Rivaroxaban + ASA: 100-pt events, 13.3 to 16.7

3. Rivaroxaban FDA briefing doc. (pg. 218)
Clinical Guide Sources

• NOACs and Perioperative Management

• Related Guides:
  ▪ Dabigatran
  ▪ Rivaroxaban
  ▪ Apixaban
Case Vignette No. 2: 

Elective Surgery

78-year old female with atrial fibrillation receiving dabigatran, 150 mg BID

CHADS score = 4 (prior TIA, age >75 yrs, hypertension)

scheduled for elective hip replacement on Monday and is to receive spinal/epidural anesthesia

weight = 65 kg
serum creatinine = 120 μmol/L
CrCl = 35 mL/min (moderate renal insufficiency)
Interruption of Dabigatran

High-bleed risk surgery/procedure (CrCl >50 mL/min)
Low-bleed risk surgery/procedure (CrCl >50 mL/min)

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# Interruption of Dabigatran

High-bleed risk surgery/procedure (CrCl: 30-50 mL/min)
Low-bleed risk surgery/procedure (CrCl: 30-50 mL/min)

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## Interruption of Apixaban

### High-bleed risk surgery/procedure

### Low-bleed risk surgery/procedure

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## Interruption of Rivaroxaban

**High-bleed risk surgery/procedure**

**Low-bleed risk surgery/procedure**

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### Post-operative Management of NOACs

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<th>NOAC</th>
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<tr>
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<tr>
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<tr>
<td>apixaban</td>
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Anticoagulant Interruption in RE-LY: Patients

- 4,591 (25% of all) patients studied with first treatment interruption for a surgery/procedure (8% urgent)
- Surgery/procedure types:
  - 22% diagnostic (e.g., colonoscopy)
  - 10% pacemaker/ICD insertion
  - 10% dental
  - 9% cataract
  - 6% joint replacement
  - 43% other surgery (minor/major)

Anticoagulant Interruption in RE-LY: Major Bleeding

- Any surgery/procedure: No significant difference in bleeding
  - dabigatran, 110 mg…… 3.8%
  - dabigatran, 150 mg…… 5.1%
  - warfarin.........................4.6%

- Urgent surgery/procedure: No significant difference in bleeding
  - dabigatran, 110 mg…… 17.8%
  - dabigatran, 150 mg…… 17.7%
  - warfarin.........................21.6%

- Incidence of stroke or TE low (<0.5%) and not significantly different between treatment arms

Clinical Guide Sources

• NOACs and Perioperative Management
• NOACs and Laboratory Monitoring

• Related Guides:
  - Dabigatran
  - Rivaroxaban
  - Apixaban
Case Vignette No. 3:
Urgent Surgery

60-year old woman with bioprosthetic mitral valve and atrial fibrillation on rivaroxaban 20 mg OD, falls and fractures her hip.

Presents to ER on Friday at 1PM and requires urgent (ideally within 24 hrs) hip repair…her last rivaroxaban dose was 4 hrs ago.

INR = 1.8
weight = 65 kg, creatinine = 100 umol/L, CrCL = 52 mL/min

What do you do to get her ready for surgery?
Suppl. Question: Is it OK to use NOACs with bioprosthetic valve?
Correlation between PT and Plasma Rivaroxaban Levels

Healthy human subjects

![Graph showing correlation between prothrombin time and plasma concentration of rivaroxaban. The graph includes a linear model with an r value of 0.958.]

Periprocedure Laboratory Monitoring of Rivaroxaban and Apixaban

- **Step 1: prothrombin time (PT)**
  - if elevated PT, likely some rivaroxaban effect
  - if normal PT, no significant rivaroxaban effect
  - PT not good to reflect apixaban anticoagulant effect!

- **Step 2: anti-factor Xa assay**
  - more precise measurement, but…
  - not widely-available

What about Dabigatran’s Effect on Coagulation Tests?

**Hemoclot test**

- Linear fit: $y = 31.44 + 0.1437x$
- 95% Prediction interval

**PT (INR)**

- Multiple dose:
  - $y = 1.047 + 0.00246x$
  - $r^2 = 0.8459$

**Thrombin time**

- Multiple dose:
  - $y = 2.4040 + 0.05851x$
  - $r^2 = 0.8568$

**aPTT**

- Multiple dose:
  - $y = 0.86 + 0.06873x^{1/2}$
  - $r^2 = 0.8514$
Peri-procedure Laboratory Monitoring of Dabigatran

- **Step 1:** partial thromboplastin time (aPTT)
  - if elevated aPTT, likely some dabigatran effect
  - if normal aPTT, no significant dabigatran effect

- **Step 2:** thrombin time (TT) or Hemoclot test (dilute TT)
  - if normal TT (<30 sec) no dabigatran effect but TT is too sensitive and detects clinically unimportant levels…avoid TT!
  - Hemoclot test is more precise but, not widely available

Case Vignette No. 4: Minor Bleeding

- 82-yr female, fully independent, with AF was switched from warfarin to apixaban, 2.5 mg BID, due to recurrent bruising
- ‘petit’ body habitus, frail skin, weight = 55 kg

- Presents with ‘red eye’ – what do you do with apixaban?

- Suppl. Question: Patient ask you about a family member with a mechanical aortic valve who want to take a NOAC instead of warfarin?

- N.B. reduced apixaban dose since 2 of:
  1. wt <60 kg;
  2. >80 yrs;
  3. creatinine >133 μmol/L
Minor Bleeding with Anticoagulants
DOACs for Mechanical Heart Valves?

- RE-ALIGN trial: *dabigatran* (150 mg or 300 mg BID) vs *warfarin* (INR: 2.5-3.5) after mechanical aortic/mitral valve replacement (within 7 d or ≥3 m)

- Trial stopped prematurely after 252 patients enrolled:
  - stroke/valve thrombosis/MI: 18 patients (11%) vs 2 (2%) patients in dabigatran and warfarin groups
  - major bleeds (all pericardial): 7 patients (4%) vs 2 patients (2%) in dabigatran and warfarin groups

Mechanism for DOAC-associated Valve Thrombosis?

Intrinsic Pathway: *surface contact*
- XII → XIIa → XI → X → Xa → IX → IXa → VIII

Extrinsic Pathway: *tissue injury*
- tissue factor → VII → VIIa → X → Xa → Prothrombin (II) → Thrombin (IIa) → Thrombin-Fibrin Clot

- dabigatran (competitive factor II inhibition)
Case Vignette No. 5: Serious Bleeding

- 74-year-old male with AF and hypertension, type 2 diabetes, obesity presents with upper GI bleed on Friday, 5PM
  - BP = 100/60 mmHg, HR = 110/min
  - Hgb = 72 g/L
  - aPTT = 59, INR = 1.3, TT >150 sec
  - CrCl = 55 mL/min

- Receiving dabigatran, 150 mg BID (last dose at 11AM)

- How to manage the bleeding?
- Suppl. Question: after bleeding resolves, would you change from dabigatran to another NOAC or to warfarin?
Endoscopy Reveals Bleeding Duodenal Ulcer
...Treated Endoscopically
Summary of (Non-clinical) Studies Assessing PCCs/rFVIIa to Reverse NOAC Effect

- Relationship between anticoagulation and prediction of cessation of bleeding not well understood with NOACs

- PCCs and rFVIIa may be effective at least with dabigatran and rivaroxaban-induced bleeding…but no clinical data!

- Many study limitations:
  - animal data may not be reflective of clinical practice
  - healthy volunteer studies do not induce bleeding
  - lack of clinical data in urgent clinical situations
Clinical Guide Sources

- NOACs and Bleeding

- Related Guides:
  - Dabigatran
  - Rivaroxaban
  - Apixaban
Is a major bleed worse in dabigatran- or warfarin-treated patients?

**Pooled analysis of 5 RCTs**

Reduced risk for death with dabigatran* vs. warfarin during 30 days after major bleeding (P = 0.052)

*Data combined from dabigatran 150 mg and 110 mg BID groups. Only first major bleed included. Analysis not adjusted for covariates.

FDA Analysis of Safety and Efficacy of Dabigatran in Real World Clinical Practice

In USA, licensed doses for dabigatran etexilate are 150 mg BID and 75 mg BID for SPAF patients with nonvalvular AF.

Numbers on bars denote hazard ratios vs warfarin; MI = myocardial infarction
Bleeding-related Mortality with Rivaroxaban and Apixaban

- Risk for death from bleed with rivaroxaban vs warfarin:
  - HR = 0.69 (95% CI: 0.46-1.04), 24.4% vs. 26.1%

- Risk for death from bleed with apixaban vs. warfarin:
  - HR = 0.50 (95% CI: 0.33-0.74)

## Antidotes for NOACs

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<tr>
<th>Structure</th>
<th>Idarucizamab</th>
<th>Andexanet alpha</th>
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<tbody>
<tr>
<td>Humanized Fab fragment</td>
<td>Human rXa variant</td>
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<table>
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<tr>
<th>Target</th>
<th>dabigatran</th>
<th>factor Xa inhibitors</th>
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<td>• binds to dabigatran (350 x greater affinity than thrombin)</td>
<td>• competitive binding of Xa inhibitor decreases unbound drug concentration</td>
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<td>• prevents dabigatran from binding to thrombin; neutralizes anticoagulant effect</td>
<td>• allows native factor Xa to participate in hemostasis</td>
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| Clinical Studies | rapid complete reversal | rapid complete reversal |

Take-home Messages

Approach to perioperative management based on:
- drug half-lives (9-17 hrs) and rapid peak effect (1-3 hrs)
- effect of renal function
- surgery/procedure type and risk for bleeding

Use and interpretation of coagulation tests:
- rivaroxaban: PT (screen), anti-factor Xa (quantitative)
- apixaban: anti-factor Xa
- dabigatran: aPTT (screen), dilute TT/Hemoclot (quantitative)
Approach to bleeding based on:
- treat as any anticoagulant-related bleed (if minor or major)
- PCC may be helpful if life-threatening bleeding
Other ‘what ifs’: 

- **OK** to use NOACs for: 
  - most valvular HD (except mod-to-severe mitral stenosis?) 
  - bioprosthetic HV (assuming another indication for NOAC) 

- **not OK** to use NOACs for: 
  - any mechanical HV (RCT-proven harm) 
  - splanchnic/UE vein thrombosis (other treatments) 
  - superficial thrombosis (other proven treatments) 
  - cancer-associated VTE (unless exceptional circumstances)
Questions