Some Practical Insights into the Selection and Use of the New Oral Anticoagulants (NOAC) in Stroke Prevention in Atrial Fibrillation

Jafna L. Cox, MD, FRCPC, FACC
Heart and Stroke Foundation of Nova Scotia Endowed Chair in Cardiovascular Outcomes Research
Director of Research, Division of Cardiology
Professor of Medicine and of Community Health and Epidemiology, CDHA/Dalhousie University
Past ACC Governor, Atlantic Provinces
Disclosure

- Dr Cox
  - Has served on advisory boards for AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Pfizer, and Sanofi-Aventis
  - Has participated in research funded by Bayer, Merck, Pfizer and Sanofi-Aventis
  - Has served as/is a consultant to the Nova Scotia Department of Health, the New Brunswick Department of Health, the Public Health Agency of Canada, and the Canadian Agency for Drugs and Technologies in Health
  - Is a member of the Canadian Cardiovascular Society’s Atrial Fibrillation Guidelines Panel and Chair of its Atrial Fibrillation Quality Indicator Subcommittee
Presentation Objectives

• To review the advantages and limitations of prior stroke preventing treatments in atrial fibrillation

• To review briefly the recent major randomized controlled trials comparing the new oral anticoagulants to warfarin

• To provide some practical tips around the choice and use of the new oral anticoagulants in SPAF

To do all of the above in the context of a patient case in order to highlight the practical issues and challenges
The Case of Patient Kyunghee Ryu

- A 74 year old female with a one month history of intermittent palpitations
  - Past medical history:
    - Stable CAD, prior GI bleed, hyperlipidemia
  - Physical examination:
    - 5’ 1” (1.55 m) tall, 120 lbs (54.4 kg)
    - HR 112 bpm, irreg irreg; BP 130/70 mmHg
    - Chest and CVS examinations otherwise normal
  - Medication:
    - ASA, bisoprolol, atorvastatin, Tylenol extra strength prn
  - Investigations:
    - CBC, liver function tests, TSH all normal; CrCl = 48 ml/min
    - ECG: AF at 115 bpm, otherwise unremarkable
    - Echo: Mild LA enlargement; normal RV and LV size and function
The Case of Ms. KR

- She cardioverts spontaneously in the office and her bisoprolol dose is increased from 2.5 mg to 5 mg daily

*What do you recommend for stroke prophylaxis?*

1. Nothing
2. ASA
3. ASA + Clopidogrel
4. Warfarin (to a target INR 2-3)
5. Dabigatran 150 mg BID
6. Dabigatran 110 mg BID
7. Rivaroxaban 15 mg OD
8. Rivaroxaban 20 mg OD
9. Apixaban 2.5 mg BID
10. Apixaban 5 mg BID
**Stroke Risk in Patients with Nonvalvular AF: CHA\textsubscript{2}DS\textsubscript{2}-VASc Risk Score**

<table>
<thead>
<tr>
<th>CHA\textsubscript{2}DS\textsubscript{2}-VASc Score Findings:</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure / Left Ventricular Dysfunction (EF&lt;40%)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 Years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Prior Stroke or TIA or Systemic Embolism</td>
<td>2</td>
</tr>
<tr>
<td><strong>Vascular Disease</strong> (prior MI, PAD, aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 65 but &lt; 75</td>
<td>1</td>
</tr>
<tr>
<td>Sex category – Female</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHA\textsubscript{2}DS\textsubscript{2}-VASc Score</th>
<th>Stroke Rate per Year (%/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td><strong>3.2</strong></td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>6.7</td>
</tr>
<tr>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>7</td>
<td>9.6</td>
</tr>
<tr>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td>9</td>
<td>15.2</td>
</tr>
</tbody>
</table>

*KR’s Risk is Intermediate (2-5% / year)*

Gage et al JAMA 2001; 285: 2864-70
**Major Bleeding Risk in Patients with AF: HAS-BLED Score**

<table>
<thead>
<tr>
<th>Letter</th>
<th>Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension (Systolic BP&gt;160 mm Hg)</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal (dialysis, transplant, &gt;200umol/L) &amp; liver function (cirrhosis or bili&gt; 2 x ULN with AST/ALT/Alk Phos &gt; 3 x ULN)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs (Labile INRs, TTR &lt; 60%)</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (i.e., &gt; 65 years)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs (concomitant antiplatelet, NSAID) or alcohol “excess” (&gt;8 U/wk)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Original derivation of HAS-BLED did not use creatinine clearance; but, KR has “abnormal kidney function” (CrCl ~40-50 ml/min)

Pisters et al Chest 2010; 138: 1093-1100
Major Bleeding Risk in Patients with AF: HAS-BLED Score

BEWARE: Do not fall into the habit of using the HAS-BLED score as an excuse not to anticoagulate a patient with AF; this is not its intent and is inappropriate

Pisters et al Chest 2010; 138: 1093-1100
European Society of Cardiology 2012: AF guidelines focused update
Major Bleeding Risk in Patients with AF: HAS-BLED Score

HAS-BLED Score

Annual Approximate Major Bleeding Risk On Warfarin (%)

- 0: 1.13%
- 1: 1.02%
- 2: 1.88%
- 3: 3.74%
- 4: 8.7%
- $\geq 5$: 12.5%

But it can be markedly reduced – e.g., just by stopping her ASA

KR’s Risk is High

Pisters et al Chest 2010; 138: 1093-1100
The benefits of oral anticoagulant therapy for stroke prevention in most cases outweigh the risk of bleeding – elevated bleeding risk (unless extreme) is not a reason to withhold anticoagulation.
Warfarin for Stroke Prevention in AF

- Warfarin is highly effective for stroke prevention in AF – reduces risk by 64% – but its use is problematic
  - Associated with significant increase in intracranial and other haemorrhage, especially in the elderly
  - Only about 1 in 4 patients are optimally treated
    - Registries show that only 50-60% of eligible patients receive warfarin
    - In clinical trials, time in therapeutic range (TTR) is 60-68%; in general practice, TTR is typically <50%

Underuse of Oral Anticoagulation in AF: Results from Recent Studies

Warfarin Use (%)

- ATRIA
- Samsa
- Gage
- NABOR
- Euro Heart Survey
- Hylek
- Birman-Deych
- Friberg
- Monte
- Boulanger
- Glazer
- Walker
- Zimetbaum

1999-2000:
- ATRIA: 60%
- Samsa: 35%
- Gage: 34%
- NABOR: 55%
- Euro Heart Survey: 64%
- Hylek: 51%
- Birman-Deych: 49%
- Friberg: 54%
- Monte: 34%
- Boulanger: 67%
- Glazer: 59%
- Walker: 45%
- Zimetbaum: 43%

2005-06:
- ATRIA
- Samsa
- Gage
- NABOR
- Euro Heart Survey
- Hylek
- Birman-Deych
- Friberg
- Monte
- Boulanger
- Glazer
- Walker
- Zimetbaum

2007-10:
- ATRIA
- Samsa
- Gage
- NABOR
- Euro Heart Survey
- Hylek
- Birman-Deych
- Friberg
- Monte
- Boulanger
- Glazer
- Walker
- Zimetbaum

References:

- Go Ann Intern Med 1999;131:927
- Samsa Arch Intern Med 2000;160:967
- Gage Stroke 2000;31:822
- 2010;123:446
- Waldo J Am Coll Cardiol 2005;46:1729
- Nieuwlaat Eur Heart J 2006;27:3018
- Hylek Stroke 2006;37:1075
- Birman-Deych Stroke 2006;37:1075
- Friberg Eur Heart J 2006;27:1954
- Monte Eur Heart J 2006;27:2217
- Boulanger Int J Clin Pract 2006;60:258
- Glazer Arch Intern Med 2007:167
- Walker Heart Rhythm 2008;5:1365
- Birman-Deych Stroke 2006;37:1070
Use of Oral Anticoagulation in AF:
Results from a Global Registry

Based on 15,174 patients presenting to an Emergency Department with AF/AFL between Jan. 2008 and Apr. 2011

OAC Use in CHADS$_2$ ≥2

Time in Therapeutic Range*

*based on 3 most recent INR values

Appropriate use of OAC continues to remain low. When OAC is used, INR control is suboptimal.
Adding Insult to Injury: Patient Persistence With Warfarin for Atrial Fibrillation

Ontario patients > 66 years of age, 1997-2008 (N= 125,195)

43% stop in 2 years, 61% stop in 5 years (median 2.9 years)

Key Factors in Underutilization Of VKAs in AF

- **Lifestyle issues**
  - Need for regular monitoring, lifestyle restrictions, compliance and other patient factors

- **Resource challenges**
  - Lack of availability of a coordinated anticoagulant outpatient monitoring process or clinic

- **Perceived bleeding risk**
  - Concern about risk of hemorrhage, not always appropriately balanced against risk of stroke
An 87 year old female, severely kyphotic but ambulatory with a cane, gives a one month history of intermittent palpitations

- Past medical history:
  - Stable CAD, prior GI bleed, frequent falls, hyperlipidemia

- Physical examination:
  - 5’ 1” (1.55 m) tall, 120 lbs (54.4 kg)
  - HR 112 bpm, irreg irreg; BP 130/70 mmHg
  - Chest and CVS examinations otherwise normal

- Medication:
  - ASA, bisoprolol, atorvastatin, Tylenol extra strength prn

- Investigations:
  - CBC, liver function tests, TSH all normal; CrCl = 48 ml/min
  - ECG: AF at 115 bpm, otherwise unremarkable
  - Echo: Mild LA enlargement; normal RV and LV size and function
An Age-Related Treatment Paradox With Warfarin Use in SPAF

- Risk of stroke in AF patients increases with age
  - 1.5% per year in 50-59 year olds
  - 23.5% in 80-89 year olds
Anticoagulation and Risk of Falls in the Elderly – Putting Matters in Perspective

Choosing Antithrombotic Therapy for Elderly Patients With Atrial Fibrillation Who Are at Risk for Falls

Malcolm Man-Son-Hing, MD, MSc, FRCP, Graham Nichol, MD, MPH, FRCP; Anita Lau; Andreas Laupacis, MD, MSc, FRCP

Objectives: To determine whether the risk of falling (with a possible increased chance of subdural hematoma) should influence the choice of antithrombotic therapy in elderly patients with atrial fibrillation.

Design: A Markov decision analytic model was used to determine the preferred treatment strategy (no antithrombotic therapy, long-term aspirin use, or long-term warfarin use) for patients with atrial fibrillation who are 65 years of age and older, are at risk for falling, and have no other contraindications to antithrombotic therapy. Input data were obtained by systematic review of MEDLINE. Outcomes were expressed as quality-adjusted life-years.

Results: For patients with average risks of stroke and falling, warfarin therapy was associated with 12.90 quality-adjusted life-years per patient; aspirin therapy, 11.17 quality-adjusted life-years; and no antithrombotic therapy, 10.15 quality-adjusted life-years. Sensitivity analysis demonstrated that, regardless of the patients’ age or baseline risk of stroke, the risk of falling was not an important factor in determining their optimal antithrombotic therapy.

Conclusions: For elderly patients with atrial fibrillation, the choice of optimal therapy to prevent stroke depends on many clinical factors, especially their baseline risk of stroke. However, patients’ propensity to fall is not an important factor in this decision.

Arch Intern Med 1999; 159:677-685

• A patient with a 5% annual stroke risk from AF would need to fall **295 times** in a year for the calculated risk of subdural hematoma from falling to outweigh the stroke reduction benefit of warfarin
Stroke Prevention in the Elderly With AF Remains A Challenge – Fear of Bleeding

Major Hemorrhage on Warfarin in First Year of Therapy Among Elderly Patients with AF

New Oral Anticoagulants for SPAF

• **Direct Thrombin Inhibitors**
  - Dabigatran

• **Factor Xa Inhibitors**
  - Rivaroxaban
    - Phase III data published Aug. 2011
  - Apixaban
    - Phase III data published Aug. 2011
  - Edoxaban
    - Phase III data expected Aug. 2013

http://www.clinicaltrials.gov/ct2/search
Adapted from Turpie *Eur Heart J* 2008; 29:155
# Key Features of New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Dabigatran&lt;sup&gt;1,2,3,7&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;3,4,7&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;3,5,7,8&lt;/sup&gt;</th>
<th>Edoxaban&lt;sup&gt;3,6,7,*&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct thrombin inhibitor</td>
<td>Direct Xa inhibitor</td>
<td>Direct Xa inhibitor</td>
<td>Direct Xa inhibitor</td>
<td>Direct Xa inhibitor</td>
</tr>
</tbody>
</table>

## Current Indications

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SPAF</td>
<td>• SPAF</td>
<td>• SPAF</td>
<td>None</td>
</tr>
<tr>
<td>• VTE prophylaxis post orthopedic OR</td>
<td>• VTE prophylaxis post orthopedic OR</td>
<td>• VTE prophylaxis post orthopedic OR</td>
<td>None</td>
</tr>
<tr>
<td>• VTE treatment</td>
<td>• VTE treatment</td>
<td>• VTE treatment</td>
<td>None</td>
</tr>
<tr>
<td>• PE treatment</td>
<td>• PE treatment</td>
<td>• PE treatment</td>
<td>None</td>
</tr>
</tbody>
</table>

## Prodrug

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

## Bioavailability

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>6%</td>
<td>&gt; 80%</td>
<td>66%</td>
<td>45%</td>
</tr>
</tbody>
</table>

## Tmax

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hrs</td>
<td>2-4 hrs</td>
<td>3 hrs</td>
<td>1.5 hrs</td>
</tr>
</tbody>
</table>

## Half-life

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-17 hours</td>
<td>5-9 hours (young, healthy)</td>
<td>8-15 hours</td>
<td>9-11 hours</td>
</tr>
<tr>
<td>11-13 hours (elderly)</td>
<td></td>
<td>11-13 hours (elderly)</td>
<td></td>
</tr>
</tbody>
</table>

## Dosing Frequency

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD (orthopedic)</td>
<td>OD</td>
<td>BID (orthopedic &amp; AF)</td>
<td>OD (AF)</td>
</tr>
<tr>
<td>BID (AF)</td>
<td>OD</td>
<td>BID (orthopedic &amp; AF)</td>
<td></td>
</tr>
</tbody>
</table>

## Renal Excretion

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>33%</td>
<td>25%</td>
<td>35%</td>
</tr>
</tbody>
</table>

## Food Interactions

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

## Drug Interactions

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-glycoprotein</td>
<td>CYP3A4 and P-glycoprotein</td>
<td>CYP3A4 and P-glycoprotein</td>
<td>Potentially P-glycoprotein</td>
</tr>
</tbody>
</table>

---

<sup>1</sup> Pradaxa SPC 2012; <sup>2</sup> Stangier Clin Pharmacokinet 2008; <sup>3</sup> Eriksson Clin Pharmacokinet 2009; <sup>4</sup> Xarelto SPC 2012; <sup>5</sup> Raghaven Drug Metab Dispos 2009; <sup>6</sup> Ruff Am Heart J 2010; <sup>7</sup> Nutescu J Thromb Thrombolysis 2011; <sup>8</sup> Eliquis SPC 2011; * Not yet available on market anywhere
<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban*</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Via</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>P-gp competition and CYP3A4 inhibition</td>
<td>+18%&lt;sup&gt;29&lt;/sup&gt;</td>
<td>No data yet</td>
<td>No effect&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
<tr>
<td>Digoxin</td>
<td>P-gp competition</td>
<td>No effect&lt;sup&gt;32&lt;/sup&gt;</td>
<td>No data yet</td>
<td>No effect&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
<tr>
<td>Verapamil</td>
<td>P-gp competition (and weak CYP3A4 inhibition)</td>
<td>+12–180%&lt;sup&gt;24&lt;/sup&gt; (reduce dose and take simultaneously)</td>
<td>No data yet</td>
<td>+53% (SR)&lt;sup&gt;30&lt;/sup&gt; (reduce dose by 50%)&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>P-gp competition and weak CYP3A4 inhibition</td>
<td>No effect&lt;sup&gt;34&lt;/sup&gt;</td>
<td>+40%&lt;sup&gt;smPC&lt;/sup&gt;</td>
<td>No data yet</td>
</tr>
<tr>
<td>Quinidine</td>
<td>P-gp competition</td>
<td>+50%</td>
<td>No data yet</td>
<td>+80%&lt;sup&gt;30&lt;/sup&gt; (reduce dose by 50%)&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>P-gp competition</td>
<td>+12–60%&lt;sup&gt;24&lt;/sup&gt;</td>
<td>No data yet</td>
<td>No effect&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>P-gp and CYP3A4 inhibitor</td>
<td>-70–100%&lt;sup&gt;24&lt;/sup&gt; (US: 2 × 75 mg)</td>
<td>No data yet</td>
<td>-85% (reduce dose by 50%)&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ketoconazole; itraconazole; voriconazole; posaconazole</td>
<td>P-gp and BCRP competition; CYP3A4 inhibition</td>
<td>+140–150%&lt;sup&gt;24&lt;/sup&gt; (US: 2 × 75 mg)</td>
<td>+100%&lt;sup&gt;smPC&lt;/sup&gt;</td>
<td>No data yet</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Moderate CYP3A4 inhibition</td>
<td>No data yet</td>
<td>No data yet</td>
<td>No data yet</td>
</tr>
<tr>
<td>Cyclosporin; tacrolimus</td>
<td>P-gp competition</td>
<td>No data yet</td>
<td>No data yet</td>
<td>No data yet</td>
</tr>
<tr>
<td>Clarithromycin; erythromycin</td>
<td>P-gp competition and CYP3A4 inhibition</td>
<td>+15–20%</td>
<td>No data yet</td>
<td>No data yet</td>
</tr>
<tr>
<td>HIV protease inhibitors (e.g. ritonavir)</td>
<td>P-gp and BCRP competition or inducer; CYP3A4 inhibition</td>
<td>No data yet</td>
<td>Strong increasing&lt;sup&gt;indPC&lt;/sup&gt;</td>
<td>No data yet</td>
</tr>
<tr>
<td>Rifampicin; St John’s wort; carbamazepine; phenytoin; phenobarbital</td>
<td>P-gp/ BCRP and CYP3A4/CYP2J2 inducers</td>
<td>-66%&lt;sup&gt;4&lt;/sup&gt;</td>
<td>-54%&lt;sup&gt;smPC&lt;/sup&gt;</td>
<td>-35%</td>
</tr>
<tr>
<td>Antacids (H2B, PPI; AI-Mg-hydroxide)</td>
<td>GI absorption</td>
<td>-12–30%&lt;sup&gt;22–24&lt;/sup&gt;</td>
<td>No data yet</td>
<td>No effect</td>
</tr>
</tbody>
</table>

**Other factors**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 80 years</td>
<td>Increased plasma level</td>
<td></td>
<td>No data yet</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>Increased plasma level</td>
<td></td>
<td>No data yet</td>
<td></td>
</tr>
<tr>
<td>Weight &lt; 60 kg</td>
<td>Increased plasma level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal function</td>
<td>Increased plasma level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other increased bleeding risk</td>
<td>Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants; history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED &gt; 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Red: contraindicated/not recommended.
Orange: reduce dose (from 150 mg bid to 110 mg bid for dabigatran; from 20 mg to 15 mg qd for rivaroxaban; from 5 mg bid to 2.5 mg bid for apixaban).
Yellow: consider dose reduction if another 'yellow' factor is present.
Hatching: no data available; recommendation based on pharmacokinetic considerations.
*No EMA approval yet. Needs update after finalization of SmPC.
*Prespecified dose reduction has been tested in Phase 3 clinical trial (to be published).
BCRP: breast cancer resistance protein; NSAID: non-steroidal anti-inflammatory drugs; H2B, H2-blockers; PPI: proton pump inhibitors; P-gp, P-glycoprotein; GI, gastro-intestinal.
Summary of Completed Phase III Trials of New Oral Anticoagulants in AF vs Warfarin

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Dose</th>
<th>Comparator</th>
<th>N</th>
<th>Trial Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>Dabigatran</td>
<td>110 &amp; 150 mg BID</td>
<td>Warfarin</td>
<td>18,113</td>
<td>Open-label</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban</td>
<td>20 / 15 mg QD</td>
<td>Warfarin</td>
<td>14,264</td>
<td>Double-blind</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Apixaban</td>
<td>5 / 2.5 mg BID</td>
<td>Warfarin</td>
<td>18,201</td>
<td>Double-blind</td>
</tr>
</tbody>
</table>

All were designed from the outset as non-inferiority trials

http://www.clinicaltrials.gov/ct2/search
RE-LY: Dabigatran and Stroke or Systemic Embolism

ROCKET AF: Rivaroxaban and Stroke or Systemic Embolism

**ITT Analysis**
RR 0.88 (95% CI 0.75–1.03)

*p* < 0.001 (non-inferiority)
*p* = 0.12 (superiority)

**OT Analysis**
RR 0.79 (95% CI 0.66–0.96)

*p* < 0.001 (non-inferiority)
*p* = 0.02 (superiority)

---

**Events in Per-Protocol Population**

- Warfarin
- Rivaroxaban

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6958</td>
<td>7004</td>
</tr>
<tr>
<td>120</td>
<td>6211</td>
<td>6327</td>
</tr>
<tr>
<td>240</td>
<td>5786</td>
<td>5911</td>
</tr>
<tr>
<td>360</td>
<td>5468</td>
<td>5542</td>
</tr>
<tr>
<td>480</td>
<td>4406</td>
<td>4461</td>
</tr>
<tr>
<td>600</td>
<td>3407</td>
<td>3478</td>
</tr>
<tr>
<td>720</td>
<td>2472</td>
<td>2539</td>
</tr>
<tr>
<td>840</td>
<td>1496</td>
<td>1538</td>
</tr>
</tbody>
</table>

ARISTOTLE: Apixaban and Stroke or Systemic Embolism

No. at risk:
- Apixaban: 9120, 8726, 8440, 6051, 3464, 1754
- Warfarin: 9081, 8620, 8301, 5972, 3405, 1768

HR 0.79 (95% CI: 0.66-0.95)

p<0.001 (Non-inferiority)
p=0.01 (Superiority)

Stroke or Systemic Embolism on a NOAC: Keeping the Phase III Trial Results in Proper Perspective

<table>
<thead>
<tr>
<th>Drug</th>
<th>Event rate</th>
<th>RRR</th>
<th>ARR</th>
<th>Time (years)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Warf</td>
<td>NOAC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran 150</td>
<td>3.3%</td>
<td>2.2%</td>
<td>33%</td>
<td>1.1%</td>
<td>91 (83-202)</td>
</tr>
<tr>
<td>Dabigatran 110</td>
<td>3.3%</td>
<td>3.0%</td>
<td>8.4%</td>
<td>0.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>3.4%</td>
<td>2.6%</td>
<td>22%</td>
<td>0.7%</td>
<td>135 (77-550)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2.9%</td>
<td>2.3%</td>
<td>20%</td>
<td>0.6%</td>
<td>168 (95-773)</td>
</tr>
</tbody>
</table>

### Prevention of Stroke

#### Stroke or Systemic Embolism

- **Dabigatran 110 mg BID**
- **Dabigatran 150 mg BID**
- **Rivaroxaban 20 mg QD**
- **Apixaban 5 mg BID**

#### Ischemic Stroke

- **Dabigatran 110 mg BID**
- **Dabigatran 150 mg BID**
- **Rivaroxaban 20 mg QD**
- **Apixaban 5 mg BID**

**Superiority p-value**

- **Dabigatran 110 mg BID**: 0.29
- **Dabigatran 150 mg BID**: <0.001
- **Rivaroxaban 20 mg QD**: 0.12
- **Apixaban 5 mg BID**: 0.01

**Comparators**

- Comparator better
- Warfarin better

---

Reducing the Bleeding Risk

**Intracranial Haemorrhage**

- **Dabigatran 110 mg BID**
- **Dabigatran 150 mg BID**
- **Rivaroxaban 20 mg QD**
- **Apixaban 5 mg BID**

**ISTH Major Bleeding**

- **Dabigatran 110 mg BID**
- **Dabigatran 150 mg BID**
- **Rivaroxaban 20 mg QD**
- **Apixaban 5 mg BID** *

* > 2g/L bleed within 24 hours in ARISTOTLE vs. no time limit in RE-LY or ROCKET-AF

**Superiority p-value**

- **Dabigatran 110 mg BID**
- **Dabigatran 150 mg BID**
- **Rivaroxaban 20 mg QD**
- **Apixaban 5 mg BID**

Sensitivity Analysis – Major Bleeding

Apixaban 5 mg BID versus Adjusted Dose Warfarin
Dabigatran 110 mg BID versus Adjusted Dose Warfarin
Dabigatran 150 mg BID versus Adjusted Dose Warfarin
Rivaroxaban 20 mg OD versus Adjusted Dose Warfarin
No treatment/Placebo versus Adjusted Dose Warfarin
Low Dose Aspirin (≤ 100 mg OD) versus Adjusted Dose Warfarin
Medium Dose Aspirin (> 100 mg and ≤ 300 mg OD) versus Adjusted Dose Warfarin
Clopidogrel 75 mg OD & Low dose Aspirin (≤ 100 mg OD) versus Adjusted Dose Warfarin

Odds Ratio (95% Crl)
Mortality

**All-Cause Mortality**

- Dabigatran 110 mg BID
- Dabigatran 150 mg BID
- Rivaroxaban 20 mg QD
- Apixaban 5 mg BID

**Cardiovascular Mortality**

- Dabigatran 110 mg BID
- Dabigatran 150 mg BID
- Rivaroxaban 20 mg QD
- Apixaban 5 mg BID

**Comparative Analysis**

- **Comparator better**
- **Warfarin better**

**Superiority p-value**

- Dabigatran 110 mg BID: 0.13
- Dabigatran 150 mg BID: 0.051
- Rivaroxaban 20 mg QD: 0.073
- Apixaban 5 mg BID: 0.047

**References**


NR: Not Reported
<table>
<thead>
<tr>
<th>Risk of stroke</th>
<th>Canadian Guidelines CCS</th>
<th>American Guidelines ACCP</th>
<th>European Guidelines ECS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (CHADS$_2$ = 0)</td>
<td>Higher risk* = OAC Dabigatran, rivaroxaban, apixaban recommended over warfarin.† Lower risk* = ASA Lowest risk* = No therapy</td>
<td>No therapy</td>
<td>Higher risk* = OAC Lowest risk* = No therapy</td>
</tr>
<tr>
<td>Intermediate (CHADS$_2$ = 1)</td>
<td>OAC Dabigatran, rivaroxaban, apixaban recommended over warfarin.†</td>
<td>OAC Dabigatran recommended over warfarin.‡</td>
<td>OAC Dabigatran, rivaroxaban, apixaban recommended over warfarin.</td>
</tr>
<tr>
<td>High (CHADS$_2$ ≥2)</td>
<td>OAC Dabigatran, rivaroxaban, apixaban recommended over warfarin.†</td>
<td>OAC Dabigatran recommended over warfarin.‡</td>
<td>OAC Dabigatran, rivaroxaban, apixaban recommended over warfarin.</td>
</tr>
</tbody>
</table>

ASA = acetylsalicylic acid; OAC = oral anticoagulants; VKA = vitamin K antagonist.

* Based on the consideration of other risk factors (age 65-74 years, female sex and presence of vascular disease).
† Preference for newer agents less clear in patients under warfarin with stable INR and no bleeding complications.
‡ At the time the American Guidelines were published (2012), only dabigatran received regulatory approval for use in AF and therefore, the Guidelines do not make recommendations for apixaban and rivaroxaban.
The Case of Ms. KR

What do you recommend for stroke prophylaxis?

1. Nothing
2. ASA
3. ASA + Clopidogrel
4. Warfarin (to a target INR 2-3)
5. Dabigatran 150 mg BID
6. Dabigatran 110 mg BID
7. Rivaroxaban 15 mg OD
8. Rivaroxaban 20 mg OD
9. Apixaban 2.5 mg BID
10. Apixaban 5 mg BID
Dosing Recommendations for SPAF: Dabigatran

Figure adapted from Huisman et al. *Thromb Haemost* 2012: 107: 838-847; *Pradax Product Monograph (Canada)*, 13 June 2011 (revised)
**Age, Major Bleeding and Dabigatran**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dabigatran 110 vs Warfarin</th>
<th>Dabigatran 150 vs Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>D110</td>
<td>Rate (% per year)</td>
<td>p (interaction)</td>
</tr>
<tr>
<td>D150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>War</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>0.76</td>
<td>0.79</td>
</tr>
<tr>
<td>Age 65–74</td>
<td>2.12</td>
<td>2.45</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>4.21</td>
<td>4.81</td>
</tr>
</tbody>
</table>

Dabigatran 150 mg dose:
- Avoid absolutely in patients ≥80 years old
- Consider avoiding in patients ≥75 years old

“For both rivaroxaban and apixaban, efficacy against stroke/SE and safety for the avoidance of major hemorrhage is not significantly different between patients ≥75 years vs those <75 years”

Skanes. *Can J Cardiol* 2012;28:125

†Interaction with age was seen for major extracranial bleeding but not for intracranial bleeding
Dosing Recommendations for SPAF: Rivaroxaban

Figure adapted from Huisman et al. *Thromb Haemost* 2012: 107: 838-847; *Xarelto Product Monograph* (Canada), 11 January 2012 (revised)
**ROCKET AF:**
Patients With Moderate Renal Impairment Substudy

**Efficacy Endpoints on Treatment**

<table>
<thead>
<tr>
<th>Clinical endpoint (% per year)</th>
<th>Rivaroxaban (n=7111)</th>
<th>Warfarin (n=7116)</th>
<th>CrCl ≥50 ml/min†</th>
<th>CrCl 30–49 ml/min</th>
<th>HR (95% CI) Rivaroxaban vs warfarin</th>
<th>p (interaction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy endpoint*</td>
<td>1.57</td>
<td>2.00</td>
<td></td>
<td></td>
<td>0.78 (0.63–0.98)</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>2.32</td>
<td>2.77</td>
<td></td>
<td></td>
<td>0.84 (0.57–1.23)</td>
<td></td>
</tr>
<tr>
<td>PE + vascular death</td>
<td>2.76</td>
<td>3.32</td>
<td></td>
<td></td>
<td>0.83 (0.70–0.98)</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>4.64</td>
<td>4.83</td>
<td></td>
<td></td>
<td>0.96 (0.73–1.27)</td>
<td></td>
</tr>
<tr>
<td>PE + MI, vascular death</td>
<td>3.55</td>
<td>4.16</td>
<td></td>
<td></td>
<td>0.85 (0.73–0.99)</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>5.58</td>
<td>6.54</td>
<td></td>
<td></td>
<td>0.85 (0.67–1.09)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>1.20</td>
<td>1.34</td>
<td></td>
<td></td>
<td>0.90 (0.69–1.16)</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>1.98</td>
<td>1.78</td>
<td></td>
<td></td>
<td>1.11 (0.71–1.73)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.26</td>
<td>0.42</td>
<td></td>
<td></td>
<td>0.62 (0.37–1.03)</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>0.29</td>
<td>0.52</td>
<td></td>
<td></td>
<td>0.56 (0.21–1.51)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>0.07</td>
<td>0.10</td>
<td></td>
<td></td>
<td>0.68 (0.24–1.90)</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>0.09</td>
<td></td>
<td></td>
<td>0.51 (0.05–5.67)</td>
<td></td>
</tr>
</tbody>
</table>

Based on per-protocol population on treatment; *Stroke and systemic embolism; †Rivaroxaban 20 mg od; ‡Rivaroxaban 15 mg od.

The Case of Ms. KR

*What do you recommend for stroke prophylaxis?*

1. Nothing
2. ASA
3. ASA + Clopidogrel
4. Warfarin (to a target INR 2-3)
5. Dabigatran 150 mg BID
6. Dabigatran 110 mg BID
7. Rivaroxaban 15 mg OD
8. Rivaroxaban 20 mg OD
9. Apixaban 2.5 mg BID
10. Apixaban 5 mg BID
Efficacy and Safety Endpoints Across Trials


<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Treatment 3</th>
<th>Treatment 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause Stroke/SE</td>
<td>Apixaban 5 mg bid</td>
<td>Dabigatran 110 mg bid</td>
<td>Dabigatran 150 mg bid</td>
<td>Rivaroxaban 20 mg od</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>Apixaban 5 mg bid</td>
<td>Dabigatran 110 mg bid</td>
<td>Dabigatran 150 mg bid</td>
<td>Rivaroxaban 20 mg od</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>Apixaban 5 mg bid</td>
<td>Dabigatran 110 mg bid</td>
<td>Dabigatran 150 mg bid</td>
<td>Rivaroxaban 20 mg od</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>Apixaban 5 mg bid</td>
<td>Dabigatran 110 mg bid</td>
<td>Dabigatran 150 mg bid</td>
<td>Rivaroxaban 20 mg od</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>Apixaban 5 mg bid</td>
<td>Dabigatran 110 mg bid</td>
<td>Dabigatran 150 mg bid</td>
<td>Rivaroxaban 20 mg od</td>
</tr>
</tbody>
</table>
Antithrombotic Management of AF/AFL in CAD

Stable CAD

Choose antithrombotic based on stroke risk

- CHADS₂ = 0
  - Aspirin

- CHADS₂ ≥ 1
  - OAC *

Recent ACS

Choose antithrombotic based on balance of risks and benefits

- CHADS₂ ≤ 1
  - aspirin + clopidogrel

- CHADS₂ ≥ 2
  - aspirin + clopidogrel + OAC †

PCI

Choose antithrombotic based on balance of risks and benefits

- CHADS₂ ≤ 1
  - aspirin + clopidogrel

- CHADS₂ ≥ 2
  - aspirin + clopidogrel + OAC †

* +/- ASA if a NOAC (especially dabigatran) †Warfarin preferred?


www.ccsguidelineprograms.ca

Atrial Fibrillation Guidelines
The Case of Ms. RK

What do you recommend for stroke prophylaxis?

1. Nothing
2. ASA
3. ASA + Clopidogrel
4. Warfarin (to a target INR 2-3)
5. Dabigatran 150 mg BID
6. Dabigatran 110 mg BID
7. Rivaroxaban 15 mg OD
8. Rivaroxaban 20 mg OD
9. Apixaban 2.5 mg BID
10. Apixaban 5 mg BID
Is Once-Daily Dosing Associated With Higher Adherence Rates Than Twice-Daily Dosing?

- AF patients with full insurance drug coverage, newly initiated on diabetes or antihypertensive medication
  - Those (n=8,256) on once daily regimens had a 26% higher adherence than those (n=2,441) on twice daily regimens

Patient RK Revisited

- RK was started on rivaroxaban 15 mg OD, remained on it for over a year, and she is now 88-years-old
  - She presents for assessment because of burning on urination and occasional incontinence
  - Physical exam reveals a mild temperature and tenderness on palpation of the lower abdomen
  - Her CrCl now measures 32 ml/min

What should you be concerned with now? Why?
Practical Considerations:
Patient Follow-up

- Patients require regular, ongoing monitoring:
  - Assess and reinforce adherence to their anticoagulant
  - Monitor renal function
    - No dabigatran if CrCl < 30 ml/min (role of 75 mg BID dose?)
    - No rivaroxaban if CrCl < 30* ml/min (15 mg OD for CrCl 30-50)
    - No apixaban if CrCl < 25 ml/min (when to use 2.5 mg BID dose?)

*The US (and EU) product monographs suggest a role for rivaroxaban 15 mg OD at CrCl 15-29

“Patients with CrCl 15 to 30 ml/min were not studied, but administration of XARELTO 15 mg once daily is also expected to result in serum concentrations of rivaroxaban similar to those in patients with normal renal function”

whereas the Canadian one expressly counsels against using it below a CrCl of 30 ml/min

Based on best available information; expert recommendations; Pradax Product Monograph (Canada), 13 June 2011 (revised); Xarelto Product Monograph (Canada), 11 January 2012 (revised); Xarelto Product Monograph (United States), December 2011 (revised)
### Therapeutic Choices in Patients with AF and Chronic Kidney Disease


<table>
<thead>
<tr>
<th>GFR</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR ≥ 60 mL/min</td>
<td>Dose adjusted for INR 2.0-3.0 (^1)</td>
<td>150 mg bid or 110 mg bid (^18)</td>
<td>20 mg daily (^19)</td>
<td>5 mg bid (^20)</td>
</tr>
<tr>
<td>GFR 50-59 mL/min</td>
<td>Dose adjusted for INR 2.0-3.0 (^1)</td>
<td>150 mg bid or 110 mg bid (^18)</td>
<td>20 mg daily (^19)</td>
<td>5 mg bid (^20)</td>
</tr>
<tr>
<td>GFR 30-49 mL/min</td>
<td>Dose adjusted for INR 2.0-3.0 (^1)</td>
<td>150 mg bid or 110 mg bid (^18)</td>
<td>15 mg daily (^19)</td>
<td>5 mg bid (for GFR &gt; 25 mL/min only) (^20) Consider 2.5 mg bid (^1)</td>
</tr>
<tr>
<td>GFR 15-29 mL/min (not on dialysis)</td>
<td>No RCT data (^\dagger)</td>
<td>No RCT data (^\S)</td>
<td>No RCT data (^\F)</td>
<td>No RCT data (^\S)</td>
</tr>
<tr>
<td>GFR &lt; 15 mL/min (on dialysis)</td>
<td>No RCT data (^\dagger)</td>
<td>No RCT data (^\F)</td>
<td>No RCT data (^\S)</td>
<td>No RCT data</td>
</tr>
</tbody>
</table>

bid, twice daily; CHADS\(_2\), Congestive Heart Failure, Hypertension, Age > 75, Diabetes Mellitus, and Prior Stroke or Transient Ischemic Attack score; GFR, glomerular filtration rate; INR, international normalized ratio; RCT, randomized clinical trial.

*Not yet approved by Health Canada.

\(^\dagger\) Consider Apixaban 2.5 mg po bid if GFR ≤ 25 mL/min, especially if age > 80 or body weight < 60 kg. \(^20\)

\(^\dagger\) Dose adjusted warfarin has been used, but observational data regarding safety and efficacy is conflicting (see text).

\(^\S\) Modelling studies suggest that dabigatran 75 mg bid might be safe for patients with GFR 15-29 mL/min, but this has not been validated in a prospective cohort. \(^18\)

\(^\F\) No published studies support a dose for this level of renal function; product monographs suggest the drug is contraindicated for this level of renal function.
Patient RK Revisited

- RK is prescribed rivaroxaban 15 mg daily (CrCl < 50 ml/min)
  - She does well but returns complaining of recurrent cholecystitis that ultimately requires surgery

*What do you do?*
Practical Considerations:
Perioperative Management of Anticoagulant Therapy

- Alteration of oral anticoagulant regimen may not be necessary for most patients undergoing low risk procedures:
  - Dental procedures (including extractions of up to 4 teeth), joint and soft tissue injections, arthrocentesis, cataract surgery, upper endoscopy or colonoscopy with/without biopsy

- For other invasive and surgical procedures, oral anticoagulation needs to be withheld:
  - Decision on whether to pursue an aggressive strategy of perioperative administration of IV heparin or SQ low molecular-weight heparin should be individualized based on an estimation of the patient’s risks of thromboembolism and bleeding and the patient’s preference

Dunn AS and Turpie AGG. Arch Intern Med 2003;163:901-908
Practical Considerations:
Perioperative Management of Anticoagulant Therapy

- Determine renal function (CrCl or eGFR)
- Determine drug half-life
- Evaluate stroke and bleeding risks
  - Decide timing of temporary discontinuation
  - Consider any need for bridging therapy
  - Plan timing of resumption of therapy
- Re-evaluate after surgical or diagnostic procedure

**Practical Considerations:**
Perioperative management – Summary of CCS Guidelines

**Patient with AF Undergoing Surgical or Diagnostic Procedure With Major Bleeding Risk**

**Very Low to Moderate Stroke Risk***
- **Low Bleeding Risk**
  - Continue Antithrombotic (INR <3 if warfarin)

**High Stroke Risk***
- **High Bleeding Risk**
  - Stop Antithrombotic Preprocedure
  - Re institute when risk of bleeding reduced

**High Stroke Risk***
- **Low Bleeding Risk**
  - Continue OAC or stop OAC and bridge with UFH or LMWH perioperatively

**High Stroke Risk***
- **High Bleeding Risk**
  - Stop OAC and bridge with UFH or LMWH perioperatively¶

---

* CHADS$_2$ ≤ 2  
** Mechanical valve, recent stroke or TIA, rheumatic valve disease, CHADS$_2$ ≥ 3  
¶ Stop 12 to 24 hours preprocedure, restart when hemostasis secure and bridge to therapeutic OAC

Practical Considerations:
If a Novel Anticoagulant Must be Stopped Before a Procedure

• For dabigatran:
  – If CrCl ≥ 30 ml/min and patient is at low risk of bleeding, withhold dabigatran for ≥ 24 hours; restart the evening after the procedure
  – If CrCl < 30 ml/min and if the procedure is complicated, withhold dabigatran for 2-5 days; consider switching the patient to warfarin after the procedure

• For rivaroxaban and apixaban:
  – If CrCl ≥ 30 ml/min and patient is at low risk of bleeding, withhold for ≥ 24 hours; restart the evening after the procedure
  – If CrCl < 30 ml/min and if the procedure is complicated, withhold for ≥ 36 hours; consider switching the patient to a lower dose (15 mg for rivaroxaban, 2.5 mg for apixaban) or to warfarin after the procedure

1. Pradax Product Monograph 2010, Boehringer Ingelheim Canada Ltd
2. Xarelto Product Monograph 2012, Bayer Inc (Canada)
New OACs: Total Drug Exposure (AUC) with Declining Renal Function

Apixaban
(27% cleared renally†³)

Dabigatran
(85% cleared renally)²

Rivaroxaban
(33% cleared renally*)¹

AUC ratio vs. Normal Renal Function

* active drug
† Factoring in the absolute bioavailability of apixaban, ~ 50% of the systemically available dose is eliminated in urine⁴

Renal Function:
Timing of Dabigatran Discontinuation Prior to Procedure

<table>
<thead>
<tr>
<th>Renal function (CrCl ml/min)</th>
<th>Half-life, hours (range)</th>
<th>Timing of discontinuation of dabigatran before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Moderate bleeding risk</td>
</tr>
<tr>
<td>&gt; 50 to ≤ 80</td>
<td>15 (12–34)</td>
<td>1–2 days</td>
</tr>
<tr>
<td>31–50</td>
<td>18 (13–23)</td>
<td>3–4 days</td>
</tr>
<tr>
<td>≤ 30*</td>
<td>27 (22–35)</td>
<td>4–5 days</td>
</tr>
</tbody>
</table>

*Dabigatran is contraindicated for use in patients with severe renal impairment (CrCl < 30ml/min)

Adapted from:
2. Pradax Monograph 2010, Boehringer Ingelheim Canada Ltd
Patient RK Revisited

- RK successfully undergoes her surgical procedure without complication
  - Several months later she develops a GI bleed

What should happen now?
Measures to Take for Bleeding on NOAC

**Direct thrombin inhibitors (dabigatran)**
- Ask about last intake + dosing regimen
- Estimate normalization of hemostasis
  - Normal renal function: 12-24 hours
  - CrCl 50-80 ml/min: 24-36 hours
  - CrCl 30-50 ml/min: 36-48 hours
  - CrCl <30 ml/min: ≥48 hours

**FXa inhibitors (apixaban, rivaroxaban)**
- Ask about last intake + dosing regimen
- Normalization of hemostasis: 12-24 hours

Assess whether a NOAC is in circulation:
- Check PTT for dabigatran
- Check PT for rivaroxaban
- No clear method for apixaban
Patient RK Revisited

- Patient RK receives 2 units of blood and undergoes endoscopy with successful cauterization of a gastric ulcer

Do you restart an oral anticoagulant?
Which one? When?
442 patients with warfarin-associated GI bleed → 260 patients (59%) resumed warfarin

– Resumption within 90 days after the GI bleed was associated with a lower risk for thrombosis and death without significantly increasing the risk for recurrent GI bleeding

For many patients with warfarin-associated GI bleeding, the benefits of resuming OAC therapy will outweigh risks
Patient RK Revisited

• Imagine that, instead of a GI bleed, RK slipped on a flight of stairs and fell, striking her head
  – CT head reveals a right subdural hematoma without midline brain shift

_Do you wish she had been on warfarin so you could have “reversed” her anticoagulation?_
Anticoagulants and Antidotes

• There is no antidote for any of the new oral anticoagulants

  However, there is also no antidote for warfarin!

  – Vitamin K takes time to work (12 or more hours), far too long if
    the patient is presenting with an intracranial haemorrhage
    • By 12-24 hours of stopping a NOAC, hemostasis will have
      normalized

  – PCC therapy rapidly corrects INR in most patients on warfarin,
    yet with debatable prognostic impact

  – Antidotes for the Factor Xa inhibitors are in development
    (benefit shown in mice with apixaban, betrixaban, rivaroxaban)

Warfarin-Associated ICH: Poor Prognosis Despite Anticoagulation Reversal

Canadian PCC (prothrombin complex concentrate) Registry:
- N=141 anticoagulation associated intracerebral hemorrhages
- 72% with INR < 1.5 within < 1h; yet 42% mortality (50% of cases)

Baseline CT
INR 3.6
Total hematoma volume 15.3 mL

Follow-up CT (19 hours)
INR 1.2
Total hematoma volume 67.6 mL

Dowlatshahi. Stroke 2012; 43: 1812
Bleeding Risk Reduction Strategies For Patients on Oral Anticoagulants

• Address the potentially “reversible” components of the HAS-BLED score
  – Adequate hypertension control
  – Optimal INR control if on warfarin or use a NOAC that doesn’t require INR monitoring and reduces intracranial bleeding risk
  – Avoidance of unnecessary ASA or NSAID; alcohol reduction

• Monitor renal function at least yearly
  – More often if renal function is abnormal
    • Every 6 months if CrCl = 30-60 ml/min
    • Every 3 months if CrCl = 15-30 ml/min

• Balance and mobility aids for those with a history of falls

• Consideration of PPI use in patients at risk of GI bleeding
A Cardiologist’s Perspective:
On Stroke Risk of AF and its Management

• The high risk and markedly severe outcomes of AF-related stroke need to be appreciated
• Risk is greatest in the elderly, those who are most likely to be under-treated
• Bleeding risk is present with antithrombotic therapy, but should neither be overestimated or overemphasized
A Cardiologist’s Perspective: On The Shifting Role of Warfarin

- Warfarin is an effective agent that has long served as our foundation for anticoagulation in AF
- Warfarin has important limitations that contribute to underutilization and poor INR control
  - 3 of 4 patients with AF are unprotected or poorly protected against stroke
- New agents offer important safety and efficacy advantages over warfarin
- Warfarin will continue to play an important role:
  - For other indications (e.g., prosthetic valves)
  - In patients with renal impairment (i.e., CrCl < 15 ml/min)
Compared with warfarin, each of the 3 new agents:

- Are at least as effective in preventing stroke/systemic embolism
- Reduce intracranial bleeding

Differences among agents will play a role in selecting treatment strategies for individual patients, based on:

- Patient characteristics (e.g., renal impairment, bleeding risk)
- Patient values (e.g., preventing ischemic stroke vs. OD dosing)

Many patients will benefit from the advantages offered by these drugs that ideally should be started by primary care/emergency department physicians rather than cardiologists.
# Choice of Anticoagulant Based on Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Drug Choice</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical or valvular AF</td>
<td>Warfarin</td>
<td>New agents not studied</td>
</tr>
<tr>
<td>Liver dysfunction with elevated INR</td>
<td>Warfarin</td>
<td>New agents require hepatic metabolism</td>
</tr>
<tr>
<td>Poor compliance</td>
<td>Warfarin or nothing</td>
<td>Missed doses of greater consequence with shorter acting agents</td>
</tr>
<tr>
<td>Stable on warfarin</td>
<td>Warfarin</td>
<td>Consider switching at patient request</td>
</tr>
<tr>
<td>CrCl &lt; 30 mL/min</td>
<td>Warfarin</td>
<td>Such patients were excluded from trials with new agents</td>
</tr>
<tr>
<td>CrCl of 30-50 mL/min</td>
<td>Rivaroxaban or Apixaban</td>
<td>Oral Xa inhibitors are less affected by impaired renal function than dabigatran</td>
</tr>
<tr>
<td>Dyspepsia or upper GI complaints</td>
<td>Rivaroxaban or Apixaban</td>
<td>Dyspepsia in up to 10% given dabigatran</td>
</tr>
<tr>
<td>Recent GI bleed</td>
<td>Apixaban</td>
<td>More GI bleeding with dabigatran (150 mg BID) or rivaroxaban than with warfarin</td>
</tr>
<tr>
<td>Recent ischemic stroke on Warfarin</td>
<td>Dabigatran</td>
<td>Dabigatran (150 mg BID) associated with lowest risk of ischemic stroke vs warfarin</td>
</tr>
<tr>
<td>Recent acute coronary syndrome</td>
<td>Rivaroxaban or Apixaban</td>
<td>Small MI signal with dabigatran</td>
</tr>
<tr>
<td>Poor compliance with BID regimen or desire for once daily</td>
<td>Rivaroxaban</td>
<td>Only oral agent that is currently once a day</td>
</tr>
</tbody>
</table>

*Adapted/modified from Weitz & Gross, Hematology 2012:536-40*
Oral Anticoagulant Prescribing Trends in the United States

• Latest figures from the IMS National Prescription Audit Weekly:
  – Rivaroxaban (only first approved by the FDA in 2011) is now being prescribed by cardiologists more often (40%) than warfarin (35%)
  – Many patients and physicians are appearing to tolerate the high cost (about $8 per pill in the US vs. pennies a day for warfarin) for a drug that, by comparison to warfarin, “does not need to be monitored”, has “few drug-drug interactions” and “practically no drug-food interactions”

Some Final Insane Musings

• Imagine if the novel anticoagulants had been established therapy for some 6 decades and a new drug appeared that:
  – Was unpredictable in terms of patient therapeutic response
  – Had slow therapeutic onset and offset
  – Had a narrow therapeutic window
  – Required close monitoring via frequent blood tests
  – Required frequent dose adjustment
  – Was plagued by drug-drug and drug-food interactions
  – Was associated with more intracranial haemorrhage
  – Resulted in a 10% increase in mortality

Would anyone in their right mind think it had a chance of getting to market and, if it did, would anyone prescribe it?
Quick Quiz!

• Where does the name Xarelto come from?
  
  – Xa reliably taken orally

  Or

  – Xa reliably taken once daily

  Or

  - Xa real inhibitor
Thank You
Practical Considerations:
Starting Patients on One of the New Oral Anticoagulants

• Start patients not currently on any OAC immediately

• Switching from warfarin to a new OAC:
  – Stop warfarin
  – Initiate once INR <2.0 for dabigatran or apixaban,
    <3.0 for rivaroxaban

• Switching from a new OAC to a parenteral one
  – Wait 12 hours after the last dose of dabigatran or apixaban
  – Wait 24 hours after the last dose of rivaroxaban

• Switching from a parenteral to a new anticoagulant
  – Start 0-2 hours prior to the time that the next dose of the
    alternate therapy would be due

Based on best available information; expert recommendations; Pradax Product Monograph (Canada), 13 June 2011 (revised);
Xarelto Product Monograph (Canada), 11 January 2012 (revised); Xarelto Product Monograph (United States), December 2011 (revised)
Lesson Learned From ROCKET AF: Difficulty Transitioning to Open-Label VKA

First dose of study drug

Rivaroxaban

Last dose of study drug

Stop rivaroxaban

Suboptimal anticoagulation

13 days

Cross-over

Start warfarin

Suboptimal anticoagulation

2 days

Continue with warfarin

Double-blind treatment period

Post-treatment observation period

Follow-up

Study duration

VKA = Vitamin K antagonist
R = randomization

Lesson Learned From ROCKET AF: On-Treatment Efficacy Dilution by Off-Treatment Events

Warfarin

Rivaroxaban

306/269 12% RRR

243/189 22.2% RRR

63

243

80

On-treatment events: comparison of active treatment blinded warfarin vs blinded rivaroxaban

Off-treatment events: comparison of aspirin, VKA, or nothing in the warfarin cohort vs aspirin, VKA, or nothing in the rivaroxaban cohort

VKA = vitamin K antagonist

HR 0.88
CI 0.74-1.03

HR 0.79
CI 0.65-0.95

Overall OAC Market in Canada:
Total and Relative Shares by Individual Compound
NOAC Market in Canada: New to Brand Prescriptions

New to Brand Prescriptions (NBRx) = New Therapy Starts + Switches
Rivaroxaban Market in Canada

How is Xarelto 15 & 20mg TRx share tracking?

Dec Exit Share 6.2%

TRx Share of AC Market

Xarelto 15+20MG

Xarelto 15+20MG Trend

Budget Share Target
Xarelto Market Share: By Type of Prescribing Physician

What is Xarelto's share uptake with Cardiologists?
16% of Xarelto TRx

What is Xarelto's share uptake with Internists?
9% of Xarelto TRx

What is Xarelto 15+20mg share uptake with Haemtologists?
2% of Xarelto TRx

What is Xarelto's share uptake with GP/FMs?
12.5% of Xarelto TRx
Rivaroxaban Market in Canada: New Starts vs Switches

Xarelto 15&20mg Weekly New Therapy Starts vs Switches

YTD New Starts: 7,156
YTD Switches: 6,731

New Starts
Switches
Rivaroxaban Market in Canada:
Where Switches to Rivaroxaban Are Coming From

Where are switches to Xarelto 15+20mg coming from?

- dabigatran
- warfarin
Changing Warfarin Market in Canada: Where Switches are Going To

Where are warfarin switches going to?

Net Switch

-800
-700
-600
-500
-400
-300
-200
-100
0

Apr13/12
Apr27/12
May11/12
May25/12
Jun8/12
Jun22/12
Jul6/12
Jul20/12
Aug3/12
Aug17/12
Aug31/12
Sep14/12
Sep28/12
Oct12/12
Oct26/12
Nov9/12
Nov23/12
Dec7/12
Dec21/12
Jan4/13
Jan18/13
Feb1/13
Feb15/13
Mar1/13
Mar15/13
Mar29/13
Apr12/13

Dabigatran
Xarelto15 & 20mg
Changing Dabigatran Market in Canada: Relative To Warfarin
Changing Dabigatran Market in Canada: Relative To Rivaroxaban

Dabi Wins/Losses - From/To Xarelto

Switches From Xarelto  Switches To Xarelto