Update with the New Oral Anticoagulants: Today’s Issues for the Front Line Pharmacist

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Winnipeg Regional Health Authority
Clinical Assistant Professor
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Objectives

At the end of this session, you should be able to:

- Discuss where the new agents are at in Canada
- Describe some actual patients which warrant proactive pharmacy involvement
- Know how to access some local resources on the new oral agents
Disclosures

- In the past 2 yrs I have either been sponsored to speak at education event, introduced speakers or attended advisory meeting provided advice to the following pharmaceutical companies:
  - AstraZeneca Canada
  - Boehringer Ingelheim Canada
  - Paladin Labs Inc.
  - Pfizer Canada
  - Sanofi Aventis Canada
New Oral Agents

- Are all small molecules targeted at specific sites in the coagulation system

- Primary target is either
  - Thrombin; i.e. activated factor II (F IIa)
  - Activated factor X (F Xa)
New Oral Anticoagulants

- Direct Thrombin Inhibitors:
  - Dabigatran (Pradax®, Pradaxa® in other countries)

- Direct F Xa Inhibitors:
  - Rivaroxaban (Xarelto®)
  - Apixaban (Eliquis®)
Coagulation Cascade

Intrinsic Pathway (surface contact)
- XIIa
- Xla
- IX
- IXa
- X
- Xa
- Thrombin (IIa)

Extrinsic Pathway (tissue factor)
- VIIa
- TF Pathway Inhibitor
- Heparin / LMWH (AT-III dependent)
- Ximelagatran
- Dabigatran (direct antithrombin)

Warfarin:
- F II, VII, IX, X

Apixaban
- Rivaroxaban

Fondaparinux
- (AT-III dependent Pure Anti-Xa)

Thrombin-Fibrin Clot
New Oral Anticoagulants

- Benefits of new oral agents include:
  - Predictable pharmacokinetics with low interpatient variability: LMW Heparin like
  - Much lower rate of drug interactions than warfarin
  - Much faster onset of action than warfarin - few hrs versus days
  - Generally, much shorter duration of action than warfarin
New Oral Anticoagulants

- Benefits of new oral agents also include a flatter dose response curve than warfarin. Should translate into a lower risk of major bleeding with overshooting the “therapeutic range”

- With warfarin increased bleeding incidence becomes exponential once INR > 4.5
New Orals: Indications

- Approved for use in Canada
  - Hip and knee orthopedic surgery prophylaxis (dabigatran and rivaroxaban). WRHA lists rivaroxaban for this
  - Atrial fibrillation (dabigatran alone at this time)
- Other Indications likely to see in use:
  - Venous thromboembolism treatment (all three. Apixaban may be the first one approved for this)
- Possibly see in the future:
  - Acute coronary syndromes (some negative phase III data)
  - Venous thromboembolism prophylaxis
  - Anything else that warfarin is used for (except kill rodents)
<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>~ 50 %</td>
<td>Low</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Hrs to Cmax</strong></td>
<td>~ 2</td>
<td>~ 2</td>
<td>2 - 4</td>
</tr>
<tr>
<td><strong>Liver (CYP) Metabolism</strong></td>
<td>Yes, multiple pathways</td>
<td>None</td>
<td>CYP 3A4</td>
</tr>
<tr>
<td><strong>Renal Elimination</strong></td>
<td>27 - 40 %</td>
<td>80%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------</td>
<td>------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>CYP 3A4 &amp; P-gp</td>
<td>Strong P-gp</td>
<td>CYP 3A4 &amp; P-gp</td>
</tr>
<tr>
<td><strong>Renal Elimination</strong></td>
<td>Mild (27%)</td>
<td>Extensive</td>
<td>Mild (~ 1/3)</td>
</tr>
<tr>
<td><strong>Use in Liver Failure</strong></td>
<td>Ok Child B</td>
<td>Data for ok Child B; label less clear</td>
<td>Contraindicated Child B or C with bleeding risk</td>
</tr>
<tr>
<td><strong>Wt Extremes (Δ exposure)</strong></td>
<td>&lt; 50 kg ~ 30%</td>
<td>~ 48 kg: 25%</td>
<td>&lt; 50 kg 24%</td>
</tr>
<tr>
<td></td>
<td>&gt; 120 kg ~ 30 %</td>
<td>~ 120 kg 20 %</td>
<td>&gt; 120 kg &lt; 24%</td>
</tr>
</tbody>
</table>

Product Monographs
Dabigatran Drug Interactions

Canada
- Contraindicated: ketoconazole
- Generally be avoided: rifampin
- Reduce dose to 150 mg daily: verapamil
- Give at least 2 hrs before dabigatran: quinidine
- No dose adjustment generally recommended: amiodarone, clarithromycin, number of others

US

7 DRUG INTERACTIONS
The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided [see Clinical Pharmacology (12.3)].

P-gp inhibitors ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin do not require dose adjustments. These results should not be extrapolated to other P-gp inhibitors [see Clinical Pharmacology (12.3)].
Nov 2011 US labeling changes

In patients with moderate renal impairment (CrCl 30-50 mL/min), consider reducing the dose of PRADAXA to 75 mg twice daily when administered concomitantly with the P-gp inhibitor dronedarone or systemic ketoconazole.

The use of P-gp inhibitors (verapamil, amiodarone, quinidine, and clarithromycin) does not require a dose adjustment of PRADAXA. These results should not be extrapolated to other P-gp inhibitors.

The concomitant use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) should be avoided.
Dabigatran Drug Interactions: P Glycoprotein

Peter’s Thoughts:

- P gp inhibition or induction only affects absorption of dabigatran etexilate. ↑ or ↓ in bioavailability of dabigatran etexilate not active drug (dabigatran)
- Dabigatran molecule itself is not subject to P gp inhibition or induction
- Increased plasma concentrations of dabigatran is a result of increased bioavailability of dabigatran etexilate, not decreased clearance of dabigatran
Dabigatran Drug Interactions: P Glycoprotein

Peter’s Thoughts:

- Hence, suspect half life of dabigatran DOES NOT change in presence of other drugs. Clearance of drug in circulation is dependent on renal function – not drug interactions.
- So if wait 4 half lives before surgery, > 90 % of the drug be gone
- This doesn’t hold true for all drugs subject to P gp effects as P pg is present in tissues other than the GI tract (e.g. kidneys) and P-gp often goes hand in hand with CYP 3A4
Drug Interactions

Although drug interactions are a relatively minor issue with dabigatran, powerful inhibitors of the p-glycoprotein pump increase plasma levels of dabigatran. It is recommended not to use dabigatran with ketoconazole, and to take the dabigatran dose at least 2 hours before either quinidine or verapamil.
## Atrial Fibrillation Trials

<table>
<thead>
<tr>
<th></th>
<th>Re-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=18,113)</td>
<td>(n = 14,266)</td>
<td>(n = 18,206)</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>150, 110 mg BID</td>
<td>20 mg OD</td>
<td>5 mg BID</td>
</tr>
<tr>
<td><strong>Entry Criteria</strong></td>
<td>CHADS ≥ 1 (avg CHADS ~ 2)</td>
<td>CHADS ≥ 2 (avg CHADS &gt; 3)</td>
<td>CHADS ≥ 1 (avg CHADS ~ 2)</td>
</tr>
<tr>
<td><strong>Follow Up</strong></td>
<td>qs &gt; 2 yrs</td>
<td>qs &gt; 2 yrs</td>
<td>qs &gt; 2 yrs</td>
</tr>
<tr>
<td><strong>Comment</strong></td>
<td>Exclude Clcr &lt; 30</td>
<td>15 mg OD Clcr 30–49</td>
<td>2.5 mg bid if ≥ 80yr, Wt ≤ 60 kg, Scr &gt; 133. Exclude Scr &gt; 221</td>
</tr>
</tbody>
</table>

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.
Therapies for the Prevention of Stroke in Atrial Fibrillation

John Cairns, Chair
Stuart Connolly
Sean McMurtry
Michael Stephenson
Mario Talajic
Grant Stotts (Stroke liaison)
3. We recommend that patients at low risk of stroke (\textit{CHADS}_2 = 1) should receive \textbf{OAC} therapy (either warfarin [INR 2 – 3] or dabigatran). (Strong recommendation, High Quality Evidence). We suggest, based on individual risk/benefit considerations, that \textit{aspirin} is a reasonable alternative for some. (Conditional recommendation, Moderate Quality Evidence).

4. We recommend that patients at moderate risk of stroke (\textit{CHADS}_2 \geq 2) should receive \textbf{OAC} therapy (either warfarin [INR 2 – 3] or dabigatran). (Strong recommendation, High Quality Evidence)
5. We suggest, that when OAC therapy is indicated, most patients should receive dabigatran in preference to warfarin. In general, the dose of dabigatran 150 mg po bid is preferable to a dose of 110 mg po (exceptions discussed in text). (Conditional recommendation. High Quality Evidence).
Clinical Hematology

Recommendations on Use of Dabigatran

Dabigatran is a new direct thrombin inhibitor that has been approved for use in Canada for the prevention of stroke and systemic embolism in patients with atrial fibrillation, as an alternative to warfarin. At present, dabigatran is not on the Manitoba Pharmacare benefit list, and patients prescribed it will need to pay the full cost of approximately $3.20 per day plus pharmacy markup unless they have private insurance that will cover it.

Dabigatran has advantages over warfarin for some patients including: moderately greater efficacy for preventing stroke, fixed dosing without requirement for monitoring, and few drug and diet interactions. It also has some disadvantages including: need for twice daily administration, accumulation in renal insufficiency, more frequent GI side effects, lack of antidote in the event that bleeding occurs, and cost.

Dabigatran has not been approved for use in a number of situations in which warfarin is used, including: mechanical heart valves, deep vein thrombosis, pulmonary embolism, acute coronary syndromes, antiphospholipid syndrome, or cardiac mural thrombus. It is contraindicated in pregnancy and in renal failure (eGFR < 30mI/min). Like any anticoagulant, it should not be administered to any patient with active bleeding or very high risk of bleeding.

A series of recommendations on the appropriate use of this new agent have been developed by the Section of Hematology/Oncology and Section of Cardiology, University of Manitoba. They address the following:

- When dabigatran is an appropriate treatment
- When dabigatran should be avoided
- Issues of monitoring
Recommendations on Use of Dabigatran

Developed by the Sections of Hematology/Oncology and Cardiology, University of Manitoba
5 April 2011

[NOTE: As of this writing, dabigatran is licensed for use in Canada but is NOT currently on the Manitoba Pharmacare benefit list. At present, patients prescribed this drug will pay its full cost (approximately $3.20 per day plus pharmacy markup) unless they have private insurance that will cover it. This must be discussed with a patient before the prescription is written.]

Introduction

Dabigatran is the vanguard of a new era of anticoagulant therapy. New oral agents are anticipated to revolutionize the prevention and management of thromboembolic disorders. All health care professionals caring for patients on anticoagulation will need to be aware of these agents, as routine anticoagulation management and monitoring will be very different.

These recommendations have been developed to aid health professionals in making appropriate use of this new agent, and to highlight potential problems. The intent is to maximize positive outcomes and ensure patient safety as this new drug enters practice.
Recommendation:

Until federal and provincial drug plans formally review dabigatran, we recommend dabigatran be considered as a good alternative to warfarin for patients with atrial fibrillation who are comfortable to pay the cost, and in particular in cases:

- where INR has been difficult to stabilize for reasons OTHER than poor adherence to medication (see below), on the basis that dabigatran’s advantage in terms of efficacy accrues to populations with poorer INR control
- who have higher stroke risk as defined by higher CHADS2 or CHADS-Vasc scores (on basis of greater absolute stroke risk, and therefore greater absolute benefit)

- where INR monitoring is problematic (e.g. poor venous access, or patient travels frequently or lives in remote location). Note that use of finger-poke point-of-care INR test devices (e.g. CoaguChek XS) is an alternative solution to this problem
- who have had embolic events despite warfarin (on basis of superior efficacy overall with the 150mg b.i.d. dose)
- for elective cardioversion
Adverse Effects
### Atrial Fib Trials: Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Re-LY (n=18,113) % Events</th>
<th>ROCKET (n = 14,236) % Events</th>
<th>ARISTOTLE (n = 18,160) % Events/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabi 110/150</td>
<td>2.7</td>
<td>5.6</td>
<td>2.1</td>
</tr>
<tr>
<td>Warf</td>
<td>3.4</td>
<td>5.4</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>Life-threatening</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>1.2</td>
<td>0.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Warf</td>
<td>1.8</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>1.1</td>
<td>3.2</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>2.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Preferred term/Investigator term</td>
<td>DE 110 BID N (%)</td>
<td>DE 150 BID N (%)</td>
<td>Warfarin N (%)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>5983 (100.0)</td>
<td>6059 (100.0)</td>
<td>5998 (100.0)</td>
</tr>
<tr>
<td>Total with dyspepsia/gastritis</td>
<td>983 (16.4)</td>
<td>940 (15.5)</td>
<td>470 (7.8)</td>
</tr>
<tr>
<td>Dyspepsia-like symptoms(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>368 (6.2)</td>
<td>345 (5.7)</td>
<td>83 (1.4)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>177 (3.0)</td>
<td>170 (2.8)</td>
<td>80 (1.3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>130 (2.2)</td>
<td>137 (2.3)</td>
<td>141 (2.4)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>119 (2.0)</td>
<td>112 (1.8)</td>
<td>64 (1.1)</td>
</tr>
<tr>
<td>Epigastric discomfort</td>
<td>40 (0.7)</td>
<td>40 (0.7)</td>
<td>9 (0.2)</td>
</tr>
<tr>
<td>Gastritis-like symptoms(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastritis</td>
<td>147 (2.5)</td>
<td>127 (2.1)</td>
<td>87 (1.5)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>117 (2.0)</td>
<td>99 (1.6)</td>
<td>46 (0.8)</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>32 (0.5)</td>
<td>27 (0.4)</td>
<td>8 (0.1)</td>
</tr>
<tr>
<td>Gastritis erosive</td>
<td>21 (0.4)</td>
<td>19 (0.3)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Gastric hemorrhage</td>
<td>0 (0.0)</td>
<td>4 (0.1)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Gastritis hemorrhagic</td>
<td>5 (0.1)</td>
<td>4 (0.1)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Hemorrhagic erosive gastritis</td>
<td>2 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

\(^1\) Represents a composite of sponsor-identified AEs (preferred terms) that were similar and likely reported in the same subject.
## RELY: GI Events

<table>
<thead>
<tr>
<th></th>
<th>Dabi 110 (n=5983)</th>
<th>Dabi 150 (n=6059)</th>
<th>Warfarin (n=5998)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major GIB (all)</td>
<td>119</td>
<td>161</td>
<td>111</td>
</tr>
<tr>
<td>Upper GI Bleeds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluated</td>
<td>87</td>
<td>107</td>
<td>72</td>
</tr>
<tr>
<td>Upper GI Bleed</td>
<td>46 (53 %)</td>
<td>57 (53 %)</td>
<td>54 (75%)</td>
</tr>
<tr>
<td>Lower GI Bleed</td>
<td>41 (47 %)</td>
<td>50 (47 %)</td>
<td>18 (25%)</td>
</tr>
</tbody>
</table>

Eikelboom JW Circulation 2001; 123 on line Data suppl

## RELY: GI Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Dabi 110 (n=5983)</th>
<th>Dabi 150 (n=6059)</th>
<th>Warfarin (n=5998)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major GI Bleed (all)</td>
<td>119</td>
<td>161</td>
<td>111</td>
</tr>
<tr>
<td>Major GI Bleed With Dyspepsia/Gastritis</td>
<td>31</td>
<td>43</td>
<td>23</td>
</tr>
<tr>
<td>Assumed Major GI Bleed with No Dyspepsia/Gastritis</td>
<td>88</td>
<td>118</td>
<td>88</td>
</tr>
</tbody>
</table>

RELY: GI Events

- Incidence of upper GI bleeds appear similar between both doses of dabigatran and warfarin
- Appears more lower GI bleeds with dabigatran (both 110 and 150 mg) than with warfarin
- ~ 3/4 of cases of GI major bleeds did not have dyspepsia/gastritis like symptoms
Case 3

- 73 yr old male with diabetes, BPH, hypertension and previous stroke
- You receive a prescription for 150 bid dabigatran
But what does the community pharmacist see?
Case

- But what does the community pharmacist see?
  - Diamicron 30 mg MR once daily
  - Ramipril 5 mg daily
  - Metoprolol 50 mg bid
  - Atorvastatin 40 mg daily
  - Amlodipine 5 mg daily
  - Warfarin 3 mg daily
  - Furosemide 80 mg bid
  - Finasteride 5 mg once daily
  - Tamsulosin 0.4 mg daily
What additional information do the decentralized hospital pharmacists see?
Case 3

- 73 yr old male with DM2, AFib (since 2006), CHF (EF 25% on MUGA 2006), HT, CVA (ICH 1980), BPH, CKD (baseline Scr 220),
- Cardiology started patient on 150 bid dabigatran
- 1 month later patient has come into hospital with a CHF exacerbation. On admission: Scr 241, aPTT 96.2
Multiple dose

\[ y = 0.86 + 0.06873x^{1/2} \]

\[ r^2 = 0.8514 \]
### Drug Half Life with Renal Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>7</td>
<td>12</td>
<td>13.8</td>
<td>8.3</td>
</tr>
<tr>
<td><strong>Mild</strong></td>
<td>10</td>
<td>AUC ↑ 16%</td>
<td>16.6</td>
<td>8.7</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>11</td>
<td>AUC ↑ 29%</td>
<td>18.7</td>
<td>9.0</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>16</td>
<td>AUC ↑ 44%</td>
<td>27.5</td>
<td>9.5</td>
</tr>
<tr>
<td><strong>ESRD</strong></td>
<td></td>
<td></td>
<td></td>
<td>AUC ↑ 1.5X</td>
</tr>
</tbody>
</table>

Mean Clcr Dabi normal 110, mild 57, mod 36, severe 21, ESRC NC

Case

But what does the community pharmacist see?

- Diamicron 30 mg MR once daily
- Ramipril 5 mg daily
- Metoprolol 50 mg bid
- Atorvastatin 40 mg daily
- Amlodipine 5 mg daily
- Warfarin 3 mg daily
- Furosemide 80 mg bid
- Finasteride 5 mg once daily
- Tamsulosin 0.4 mg daily
Nov 2011 US labeling changes

In patients with moderate renal impairment (CrCl 30-50 mL/min), consider reducing the dose of PRADAXA to 75 mg twice daily when administered concomitantly with the P-gp inhibitor dronedarone or systemic ketoconazole.

The use of P-gp inhibitors (verapamil, amiodarone, quinidine, and clarithromycin) does not require a dose adjustment of PRADAXA. These results should not be extrapolated to other P-gp inhibitors.

The concomitant use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) should be avoided.
Noted Exclusions

- New agents (i.e. dabigatran at this time) should not be used in:
  - Advanced renal dysfunction (Clcr < 30)
  - Valvular heart disease, Mechanical valves
  - Concomittant ketoconazole (Pgp interaction)
  - Pregnancy
  - Pediatrics
  - Others: recent MI, high risk coronary events
did those receiving warfarin. Although there was a trend to a reduction of the composite clinical outcome in the dabigatran groups, there was a trend to more frequent myocardial infarction with dabigatran, which was significant at the 150-mg dose. There was no hint of greater hepatic toxicity with dabigatran than with warfarin, but the total clinical experience extends to only a mean of 2 years, and careful long-term follow-up data are needed. Dabigatran tablets are much more costly than warfarin, but rigorous cost-effectiveness analyses will be needed to assess total costs.

We recommend that when an OAC is indicated for stroke prevention, most patients should receive dabigatran in preference to warfarin. Possible exceptions would include patients with a propensity to dyspepsia, gastrointestinal bleeding, or both and those at substantial risk of coronary events (see more detailed discussion under the heading Coronary Artery Disease). The dose of 150 mg twice a day is preferable to 110 mg twice a day, except in patients of low body weight, decreased renal function, or at increased risk of major bleeding.

Idraparinux is a specific inhibitor of activated factor X,
ratio 1.38; 95% CI, 1.00-1.91; \( P = .048 \)). There has not yet been a trial of dabigatran to evaluate the agent for the primary or secondary prevention of coronary events. Given the known benefits of warfarin for the reduction of coronary events, which can be substantial in those patients at higher risk, when OAC is indicated to prevent stroke in those who have AF and are also at high risk of a coronary event (eg, those without evidence of coronary artery disease whose Framingham risk is \( \geq 2\% \) per year, those with stable coronary artery disease with high risk features, and those with or ACS in recent months), it seems prudent to recommend warfarin in preference to dabigatran.

**RECOMMENDATION**

We suggest that patients with AF or AFL who have stable coronary artery disease should receive antithrombotic therapy selected on the basis of their risk of stroke (aspirin for \( \text{CHADS}_2 = 0 \) and OAC for \( \text{CHADS}_2 \geq 1 \)). Warfarin is preferred over dabigatran for those at high risk of coronary events (Conditional Recommendation, Moderate-Quality Evidence).

We suggest that patients with AF or AFL who have experienced ACS or who have undergone PCI should receive
Dabigatran Contraindications

Canada

- Severe renal impairment (CrCl < 30mL/min)
- Haemorrhagic manifestations, bleeding diathesis, or patients with spontaneous or pharmacological impairment of haemostasis
- Lesions at risk of clinically significant bleeding, e.g. extensive cerebral infarction (hemorrhagic or ischemic) within the last 6 months, active peptic ulcer disease with recent bleeding
- Concomitant treatment with strong P-glycoprotein (P-gp) inhibitors, i.e. oral ketoconazole (see DRUG INTERACTIONS)
- Known hypersensitivity to dabigatran or dabigatran etexilate or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

US

4 CONTRAINDICATIONS
PRADAXA is contraindicated in patients with:

- Active pathological bleeding [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].
- History of a serious hypersensitivity reaction to PRADAXA (e.g., anaphylactic reaction or anaphylactic shock).
Nov 2011 US labeling changes

The concomitant use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) should be avoided.
**Recommendation:**

Until more data are available, we recommend dabigatran NOT be preferred to warfarin in patients who have:

- renal insufficiency (estimated creatinine clearance 30-50 ml/min) or unstable renal function (on basis that drug accumulates in renal insufficiency)
- recent MI or unstable angina (on basis of possible higher risk of MI). Phase III trials in ACS are ongoing
- a history of untreated GI bleeding or symptomatic upper GI tract disorders
- weight less than 50kg
- a record of stable anticoagulation control on warfarin maintaining more than 70% of INR results within therapeutic range (on basis of analysis showing no advantage accrues to populations with high quality INR control on warfarin)
- difficulty to swallow whole capsules

Additionally, we recommend patients > 80 yrs have special attention paid to their renal function. The Canadian product monograph recommends that they receive a lower dosage of 110 mg twice daily. This lower dose should also be considered in patients especially above 75 yrs with at least one other risk factor from bleeding.
Question

- Shouldn’t we be monitoring the anticoagulant response to these agents, just like we do for warfarin?
<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Enoxaparin Dalteparin</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti Xa</td>
<td>aPTT ↑, others maybe better (e.g. PT), anti Xa</td>
<td>aPTT better though INR prolonged</td>
<td>PT better though aPTT prolonged</td>
</tr>
</tbody>
</table>
Monitoring

Dabigatran acts as a direct thrombin inhibitor. No monitoring has been validated for this agent and monitoring in general is not recommended. Dabigatran was given without monitoring or dose adjustment in the pivotal clinical trials.

The INR increases somewhat but is NOT very sensitive to the effect of dabigatran and cannot be used to assess or adjust dosing. In healthy volunteers on standard doses of dabigatran the INR is typically mildly elevated (about 1.2 - 1.8). DABIGATRAN DOSE SHOULD NOT BE ADJUSTED TO ACHIEVE AN INR OF 2 TO 3 AS IS THE PRACTICE FOR WARFARIN. Because of the influence on INR values, warfarin cannot be monitored if co-administered with dabigatran.

The aPTT is sensitive to dabigatran. A normal aPTT indicates that the patient has a minimal drug level; a normal aPTT may therefore be used to exclude therapeutic or supertherapeutic dabigatran levels in a bleeding patient for whom no history is available, or to determine that the drug effect has worn off in a patient previously taking it. However, beyond this, the aPTT does not reliably determine whether dabigatran levels are too high or too low.
Questions

- If someone starts to bleed, what should we tell them to do?
- Is there an antidote?
Patient with bleeding on dabigatran therapy

Mild bleeding
- Delay next dose or discontinue treatment as appropriate

Moderate-Severe bleeding

Life-threatening bleeding
- Consideration of rFVIIa or PCC*
- Charcoal filtration*

Fluid replacement and hemodynamic support
- Blood product transfusion
- Oral charcoal application* (if dabigatran etexilate ingestion <2 hours before)
- Hemodialysis

*Recommendation based only on limited non-clinical data, there is no experience in volunteers or patients

Thrombosis and Haemostasis 103.6/2010
<table>
<thead>
<tr>
<th>Antidote ?</th>
<th>Dalteparin</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Protamine</td>
<td>None, PCC, VIIa listed options</td>
<td>None, PCC, VIIa listed options</td>
<td>None, PCC, VIIa listed options</td>
</tr>
<tr>
<td></td>
<td>(partial)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For all serious bleeds call Hematology

(St. B or HSC on call person)

They want to help on the bleeds
How long do you have to wait before you can do procedures safely?
<table>
<thead>
<tr>
<th>Renal function ((\text{CL}_{\text{CR}}, \text{ml/min}))</th>
<th>Half-life (hours)(^{a})</th>
<th>Timing of discontinuation after last dose of dabigatran before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>13 (11–22)</td>
<td>24 hours</td>
</tr>
<tr>
<td>&gt; 50 to ≤ 80</td>
<td>15 (12–34)</td>
<td>24 hours</td>
</tr>
<tr>
<td>&gt; 30 to ≤ 50</td>
<td>18 (13–23)</td>
<td>at least 2 days (48 hours)</td>
</tr>
<tr>
<td>≤ 30(^{c})</td>
<td>27 (22–35)</td>
<td>2–5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High risk of bleeding(^{b})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2–4 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 days 2–5 days</td>
</tr>
</tbody>
</table>

\(^{a}\)Data from renal impairment study in healthy volunteers (11), geometric mean (range). \(^{b}\)Types of surgery associated with a high risk of bleeding (or in major surgery where complete hemostasis may be required) include but is not limited to cardiac surgery, neurosurgery, abdominal surgery or those involving a major organ. Other procedures such as spinal anesthesia may also require complete hemostatic function. Other important determinants of bleeding risk include advancing age, co-morbidities (e.g. major cardiac, respiratory or liver disease) and concomitant use of antiplatelet therapy. \(^{c}\)Dabigatran etexilate is contraindicated for use in these patients. \(\text{CL}_{\text{CR}}\) = creatinine clearance.

Thrombosis and Haemostasis 103.6/2010
Dabigatran Capsule

- Should be kept in original foil until use
- Capsules should not be opened, sprinkled or put down feeding tubes. Possible increased absorption by up to 75 %
- Bottles of capsules available in US
Nov 2011 US labeling changes

_Bottles_
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Once opened, the product must be used within 4 months. Keep the bottle tightly closed. Store the original package to protect from moisture.

_Blisters_
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Store in the original package to protect from moisture.
Case 2

- Young, knowledgeable surgeon changes the standard post op “anticoagulation with dalteparin only” order to:
  - Rivaroxaban 10 mg po od until INR 2 – 3
  - Wafarin 5 mg evening of OR and daily X 3 then 4 mg po daily
FDA NEWS RELEASE

For Immediate Release: Nov. 4, 2011
Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves Xarelto to prevent stroke in people with common type of abnormal heart rhythm

The U.S. Food and Drug Administration today approved the anti-clotting drug Xarelto (rivaroxaban) to reduce the risk of stroke in people who have abnormal heart rhythm (non-valvular atrial fibrillation).

Atrial fibrillation occurs in more than 2 million Americans and is one of the most common types of abnormal heart rhythm. In atrial fibrillation, the beating of the heart's two upper heart chambers (atria) is irregular and poorly coordinated. This leads to blood pooling in these chambers, resulting in blood clots. Non-valvular atrial fibrillation refers to atrial fibrillation in patients who do not have significant problems in their heart valves.

“Atrial fibrillation can lead to the formation of blood clots, which can travel to the brain, blocking blood flow and causing a disabling stroke,” said Norman Stockbridge, M.D., Ph.D., director of the Division of Cardiovascular and Renal Products in the FDA’s Center for Drug Evaluation and Research. “This approval gives doctors and patients another treatment option for a condition that must be managed carefully.”
Case 4

- Decentralized pharmacist is rounding with the D4 house staff on B3 after couple days off. One of the new patients had stated dabigatran based on recommendations on the cardiology consult.

- Wife had prescription filled at their community pharmacy and brought the drug in yesterday.
Current WRHA Formulary Status

- **Apixaban:**
  - Not currently approved for use in Canada

- **Dabigatran:**
  - Been under review/discussion since early spring for use in Atrial Fibrillation. Will continue dabi if come in on it

- **Rivaroxaban:**
  - Approved for use in orthopedic hip and knee arthroplasty
The following amendments will take effect on November 24, 2011.

The amended Manitoba Specified Drug Regulation and Drug Interchangeability Formulary Regulation will be available on the Manitoba Health website http://www.gov.mb.ca/healthmdbif on the effective date of November 24, 2011.

<table>
<thead>
<tr>
<th>02316986</th>
<th>Xarelto</th>
<th>rivaroxaban</th>
<th>10 mg</th>
<th>Tablet</th>
<th>BAY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

For the prophylaxis of venous thromboembolism following total knee replacement for up to two (2) weeks, and following total hip replacement surgery for up to five (5) weeks, as an alternative to low molecular weight heparins.
Case 5

- Peter gets asked by one of the other pharmacists about a new order for dabigatran
- Physician has prescribed dabigatran 75 mg bid
Dabigatran A Fib Dosing

**Canada**

- 150 mg twice daily
- Aged ≥ 80 yrs 110 mg bid
- Geriatric esp. ≥ 75 yrs with at least 1 other risk factor for bleeding 110mg bid may be considered

**US**

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**DOSAGE AND ADMINISTRATION**

- For patients with CrCl >30 mL/min: 150 mg orally, twice daily (2.1)
- For patients with CrCl 15-30 mL/min: 75 mg orally, twice daily (2.1)
- Instruct patients not to chew, break, or open capsules (2.1)
- Review recommendations for converting to or from other oral or parenteral anticoagulants (2.2, 2.3)
- Temporarily discontinue PRADAXA before invasive or surgical procedures when possible, then restart promptly (2.4)
Dabigatran Dose: Orthopedic Hip and Knee Replacement

- **Standard Dose**
  - 110 mg 1-4 hr post op then 220 mg daily X 10 days (knees) X 28-35 d (hips)

- **Special Population Dose**
  - Age > 75 yrs 150 mg daily
  - Clcr 30 – 50 ml/min 75 mg 1-3 hr post op then 150 mg daily
November 3, 2011

Dear Health Care Professional:

Subject: Risk of potential patient harm associated with brand name confusion involving Pradax® (dabigatran etexilate) and Plavix® (clopidogrel bisulfate).

Boehringer Ingelheim (Canada) Ltd., and sanofi-aventis Canada Inc. (on behalf of Bristol-Myers Squibb Sanofi Canada partnership) in consultation with Health Canada, would like to alert you to the risk of medication errors associated with name confusion between the anticoagulant Pradax® (dabigatran etexilate) from Boehringer Ingelheim (Canada) Ltd. and the antiplatelet drug Plavix® (clopidogrel bisulfate) from sanofi-aventis Canada Inc.

Since January 2011, a total of 5 Canadian cases, associated with drug name confusion between Pradax® and Plavix®, have been received by Boehringer Ingelheim (Canada) Ltd. and Health Canada, including 1 case resulting in patient harm (non-serious bleeding after a medical procedure). An additional 2 reports of concern were received from health care professionals about the potential for confusion between the names of these two drugs.
• The Pradax® and Plavix® names, verbally and by script have been mistaken for one another. These mix-ups have been associated with similarities in orthographics, phonetics, strength, and use in patients with cardiovascular disorders.

• Receiving Pradax® instead of Plavix® or vice versa, may result in patient harm, including increased risk of bleeding, stroke, systemic embolism, venous thromboembolic events (VTE), atherothrombotic events or other unknown medical outcomes.

• The patient is also at risk of receiving incorrect concomitant medications or medical procedures when Pradax® or Plavix® is noted in patient history in error as a result of name confusion.

• To reduce the potential for name confusion errors, healthcare professionals are encouraged to include the generic name dabigatran when referring to Pradax®, or the name clopidogrel when referring to Plavix®. Spelling the name of the medication for verbal prescriptions or medication reconciliation (e.g. emergency room triage), is also suggested.
Anticoagulants deliver a high degree of benefit but have the potential for high risk of harm.

Landscape has already changed in how we prevent strokes.

Pharmacists, both in the hospital and community setting, have a huge role to play in ensuring the new oral anticoagulants are being used safely and effectively.