<table>
<thead>
<tr>
<th>Program Name:</th>
<th>New Oral Anticoagulants: Addressing Pharmacist Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning Committee:</td>
<td></td>
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<tr>
<td></td>
<td>William Semchuk, BSP, MSc, PharmD</td>
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<td></td>
<td>Carlene Oleksyn, B.S.P. Pharm.</td>
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<td>Peter Thomson, BSc(Pharm), PharmD</td>
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<td>Moe Abdallah, BSc, BscPhm, R.Ph</td>
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<tr>
<td>Accreditation Information:</td>
<td>This version of the program is unaccredited and intended for informational purposes only. An accredited version is available online at <a href="http://www.rxBriefCase.com">www.rxBriefCase.com</a> until February 28, 2015.</td>
</tr>
<tr>
<td>Sponsor:</td>
<td>This case study is supported by an educational grant from Bayer</td>
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Learning Objectives
At the end of the program participants will be able to:

1. Make appropriate recommendations for the safe and effective use of new oral anticoagulant drugs (NOACs) to reduce stroke risk in the presence of non-valvular atrial fibrillation (AF).
2. Make appropriate recommendations for the safe and effective use of new oral anticoagulant drugs (NOACs) to manage venous thromboembolism (VTE).
3. Make appropriate recommendations to minimize bleeding risk for patients being initiated on NOACs.

Pre-course Survey

2. How comfortable are you in your understanding of bleeding risk factors for patients requiring preventive anticoagulant therapy? [Low 1 – High 5]
3. How comfortable are you in recommending adjustments to oral anticoagulant therapy in accordance with individual patient risk factors (such as renal impairment)? [Low 1 – High 5]
4. How commonly do act on opportunities for improved VTE prophylaxis or management at your pharmacy? [Low 1 – High 5]
5. How confident are you in your knowledge of contraindications, and drug interactions for the new oral anticoagulants? [Low 1 – High 5]
Introduction
For decades, the only class of oral anticoagulants available were the vitamin K antagonists (VKAs). With the arrival of new oral anticoagulants, apixaban, dabigatran, rivaroxaban, there is now a broader range of choice. The objective of this program is to consider some of the practical questions and challenges that pharmacists may encounter regarding NOACs, involving dose adjustments, drug-drug interactions, and contraindications as well as communicating about these issues with patients and prescribers.

The program will specifically consider case studies in the use of NOACs in the management of stroke risk for patients with non-valvular atrial fibrillation (AF), and in the management of venous thromboembolism (VTE).

Case Study #1
Meet Melvin
Melvin is a 69-year-old male with newly diagnosed non-valvular atrial fibrillation. He has had type 2 diabetes mellitus for over 8 years. Melvin is a widower and retired warehouse worker who has facet joint syndrome with some associated minor osteoarthritis in his lumbar vertebrae (L3, L4, L5) after many years of heavy lifting. His current medications include antihyperglycemics metformin 1000 mg BID, insulin glargine 10 units once daily, and for cardiovascular protection, atorvastatin 10 mg once daily, and ramipril 10 mg once daily. He manages his back pain with ibuprofen, 400-1200 mg daily. Melvin has 14 alcoholic drinks per week (2 low carbohydrate beers per day). For physical activity, he walks his dog for a half hour to 45 minutes per day but is otherwise sedentary.

Age = 69
BMI = 34.9 kg/m²
A1C = 8.1%
BP = 138/88 mmHg
TC:HDL cholesterol: 5.2, LDL-C 3.2 mmol/L

Case challenge
After conducting a medication assessment for Melvin, should you contact his physician to recommend an antithrombotic therapy for stroke prevention for Melvin (in accordance with Canadian Cardiovascular Society guidelines)?

a. Yes
b. No
Atrial Fibrillation (AF)

- is the most common arrhythmia, and its prevalence increases with age (prevalence of 10-15% in patients who are ≥ 80 years) \(^1\)
- is an independent risk factor for stroke and other systemic embolism (SE); AF increases stroke risk by ~ 3-6-fold \(^2\)
- stroke risk in AF is further increased in the presence of diabetes, congestive heart failure, structural heart disease (especially mitral valve disease), hypertension, and prior arterial thromboembolic events. \(^1\)
- can be persistent or paroxysmal; both increase stroke risk similarly \(^1,3-5\)

Cumulative incidence of stroke, heart failure, and death by atrial fibrillation pattern \(^6\)

A recent study characterized AF patterns between 1980 and 2005 among Framingham Heart Study participants. Figure shows cumulative incidence of stroke, heart failure, and death by atrial fibrillation pattern. The cumulative incidence of (A) stroke, (B) heart failure, and (C) death is displayed stratified by atrial fibrillation pattern over the 10 years of follow-up after atrial fibrillation pattern classification. Compared with individuals without 2-year AF recurrences, the 10-year prognosis was worse for individuals with either sustained or recurrent AF, both of which were associated with similar stroke and mortality.

Predicting Stroke Risk

Risk of stroke, and the need for preventive antithrombotic treatment, in patients with AF can be assessed using the CHADS\textsubscript{2} score. This schema has been well validated, and is easy to remember and to use. A higher CHADS\textsubscript{2} score indicates a greater stroke risk. When the CHADS\textsubscript{2} score is 0, additional risk factors should be considered. Anticoagulant therapy is recommended in AF patients who have a CHADS\textsubscript{2} score of 1 or greater, or a CHADS\textsubscript{2} score of 0 but with additional risk factors.\textsuperscript{5,7,8}

### CHADS\textsubscript{2} Score\textsuperscript{5,7}

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)</td>
<td>1</td>
</tr>
<tr>
<td>A Age $\geq$75 years</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S\textsubscript{2} Prior Stroke or TIA or Thromboembolism</td>
<td>2</td>
</tr>
</tbody>
</table>
Predicting Bleed Risk

To predict and systematically consider the risk of hemorrhage with antithrombotic therapy to reduce stroke risk in patients with AF, the Canadian Cardiovascular Society guidelines recommend use of the HAS-BLED schema.\(^5\)

**HAS-BLED Score\(^5,9\)**

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H</strong> Hypertension (uncontrolled, &gt; 160 mm Hg systolic)</td>
<td>1</td>
</tr>
<tr>
<td><strong>A</strong> Abnormal renal and liver function (1 point each) (one point for presence of renal or liver impairment, maximum two points)</td>
<td>1 or 2</td>
</tr>
<tr>
<td><strong>S</strong> Stroke (previous history, particularly lacunar)</td>
<td>1</td>
</tr>
<tr>
<td><strong>B</strong> Bleeding history or predisposition (anemia)</td>
<td>1</td>
</tr>
<tr>
<td><strong>L</strong> Labile INRs (i.e., therapeutic time in range &lt; 60%)</td>
<td>1</td>
</tr>
<tr>
<td><strong>E</strong> Elderly (&gt; 65 years)</td>
<td>1</td>
</tr>
<tr>
<td><strong>D</strong> Drugs or alcohol (1 point each) concomitantly (antiplatelet agents, nonsteroidal anti-inflammatory drugs; one point for drugs plus one point for alcohol excess (&gt; 8 units/week), for maximum two points)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

**Ask The Expert Video Question**

*How can pharmacists work with patients and prescribers to help minimize bleed risk in patients taking anticoagulants?*
Case Revisited

Melvin Revisited

Melvin is a 69-year-old male with newly diagnosed non-valvular atrial fibrillation. He has had type 2 diabetes mellitus for over 8 years. Melvin is a widower and retired warehouse worker who has facet joint syndrome with some associated minor osteoarthritis in his lumbar vertebrae (L3, L4, L5) after many years of heavy lifting. His current medications include antihyperglycemics metformin 1000 mg BID, insulin glargine 10 units once daily, and for cardiovascular protection, atorvastatin 10 mg once daily, and ramipril 10 mg once daily. He manages his back pain with ibuprofen, 400-1200 mg daily. Melvin has 14 alcoholic drinks per week (2 low carbohydrate beers per day). For physical activity, he walks his dog for a half hour to 45 minutes per day but is otherwise sedentary.

Age = 69
BMI = 34.9 kg/m²
A1C = 8.1%
BP = 138/88 mmHg
TC:HDL cholesterol: 5.2, LDL-C 3.2 mmol/L

Case Challenge

Which statement is correct?

a. Melvin has a CHADS² score of 1 and a HAS-BLED score of 2.
b. Melvin has a CHADS² score of 2 and a HAS-BLED score of 1.
c. Melvin has a CHADS² score of 2 and a HAS-BLED score of 2.
d. Melvin has a CHADS² score of 1 and a HAS-BLED score of 3.
Interpreting Risk

Interpreting the Relative Risk of Strokes versus Bleeds

Important points about interpreting the HAS-BLED score:5

• The score can aid in comparing the relative risks of stroke vs major bleeding with antithrombotic therapy.
• Stroke risk is usually higher than risk of major bleeding.
• Strokes with AF are more likely to be fatal or disabling than major bleeds.
• Increased risk of major bleeding does not contraindicate antithrombotic therapy.
• Increased risk of major bleeding warrants extra caution and closer monitoring of antithrombotic therapy.
• Only a very high risk/benefit ratio favours no antithrombotic therapy (e.g., a young patient with AF and few or no stroke risk factors, but a high risk of major hemorrhage because of malignancy, prior major hemorrhage, or participation in contact sports)

Anticoagulant Underuse

Registry data shows that appropriate use of OAC remains low. When warfarin is used, INR control is suboptimal.10

Use of Oral Anticoagulation in AF: Results from a Global Registry
Key Factors in Underutilization of Anticoagulation in AF

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

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

Perceived bleeding risk
  o Concern about risk of hemorrhage, not always appropriately balanced against risk of stroke

Case Revisited

Melvin Revisited
Which type of agent would you recommend for Melvin, for stroke prevention, in accordance with Canadian Cardiovascular Society guidelines?

a. warfarin
b. heparin
c. NOAC
d. ASA
e. none; his bleed risk is too high
Stroke Prevention

Canadian Cardiovascular Society Treatment Recommendations, Based on Stroke Risk

- assess stroke risk using CHADS
- assess bleed risk (e.g., HAS-BLED)
- most patients should receive either an OAC or ASA
- when OAC therapy is indicated, most patients should receive apixaban, dabigatran, or rivaroxaban

Practice Tip!
Help patients understand how certain health factors affect the recommended guidelines for alcohol intake. View or download the Canada Low Risk Drinking Guidelines

(Source: Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control)

[caption] Summary of Canadian Cardiovascular Society recommendations for antithrombotic agent use for patients with AF, based on congestive heart failure, hypertension, age > 75, diabetes mellitus, and prior stroke or transient ischemic attack (CHADS2) score. Additional risk factors of age > 65, vascular disease, and female sex are integrated to increase granularity at low CHADS2 score (CHADS2 = 0).

ASA = acetylsalicylic acid
(N)OAC = (new) oral anticoagulant
Ask the Expert Video Question
How should pharmacists advise prescribers when they notice off label use of an anticoagulant while filling a prescription?

Case Challenge
If Melvin had NOT had diabetes, but DID have vascular disease, which type of agent would be recommended for Melvin for stroke prevention?

a. warfarin  
b. heparin  
c. NOAC  
d. ASA  
e. none

NOACs
Until recently, therapeutic options for lowering the risk of stroke in patients with AF were warfarin and antiplatelet agents (RR reduction ~ 60% and 20% respectively). However, the new oral anticoagulants introduce effective and well tolerated options for treatment.

The benefit of NOACs compared with warfarin in reducing stroke or systemic embolic events

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Factor Xa</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>VKORC1</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>60%</td>
<td>6%</td>
<td>80-100%*</td>
<td>100%</td>
</tr>
<tr>
<td>Dosing</td>
<td>Twice daily</td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>Time to peak effect</td>
<td>1-2 h</td>
<td>1-3 h</td>
<td>2-4 h</td>
<td>4-5 d</td>
</tr>
<tr>
<td>Half-life</td>
<td>12 h</td>
<td>11 h</td>
<td>5-13 h</td>
<td>40 h</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>25%</td>
<td>80%</td>
<td>33%</td>
<td>None</td>
</tr>
<tr>
<td>INR monitoring</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Interactions</td>
<td>3A4/P-gp</td>
<td>P-gp</td>
<td>3A4/P-gp</td>
<td>Multiple</td>
</tr>
</tbody>
</table>

*When the 15 mg and 20 mg dose is taken with food.

†Because of renal clearance of unchanged drug, there is a potential for drug accumulation in patients with severe renal impairment. This potential is greater for dabigatran than it is for the oral factor Xa inhibitors.
Weighing Risks

Risk Ratios with NOACs versus Warfarin

A recent meta-analysis of pivotal phase 3 clinical trials for stroke prevention or systemic embolic events in patients with atrial fibrillation found that the NOACs had a favourable risk–benefit profile, with significant reductions in stroke, intracranial hemorrhage, and mortality. Major bleeding was similar to warfarin, but increased gastrointestinal bleeding. Figure shows stroke or systemic embolic events subgroups (A) and major bleeding subgroups (B). The relative efficacy and safety of new oral anticoagulants was consistent across a wide range of patients.

Ruff et al. Lancet 2013; pii: S0140-6736(13)62343-0.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>NOAC</th>
<th>Warfarin</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;70</td>
<td>70-79</td>
<td>&gt;80</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>yes</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>yes</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAS-BLED score</td>
<td>&gt;5</td>
<td>≤5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOAC status</td>
<td>DAPA</td>
<td>VKA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in therapeutic range (TTR)</td>
<td>&lt;40%</td>
<td>≥40%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOACs had a favourable risk–benefit profile, with significant reductions in stroke, intracranial hemorrhage, and mortality.

NOAC = new oral anticoagulant
RR = risk ratio
TIA = transient ischaemic attack
VKA = vitamin K antagonist
TTR = time in therapeutic range

\[ \text{NOACs had a favourable risk–benefit profile, with significant reductions in stroke, intracranial hemorrhage, and mortality} \]

\[ \text{NOAC} = \text{new oral anticoagulant} \]
\[ \text{RR} = \text{risk ratio} \]
\[ \text{TIA} = \text{transient ischaemic attack} \]
\[ \text{VKA} = \text{vitamin K antagonist} \]
\[ \text{TTR} = \text{time in therapeutic range} \]
NOAC Indications

The New Oral Anticoagulants: Indications

<table>
<thead>
<tr>
<th>Agent</th>
<th>prevention of VTE for THR/TKR</th>
<th>prevention of stroke + SE in AF</th>
<th>treatment of VTE and prevention of VTE recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>apixaban</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>dabigatran</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>rivaroxaban</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>

THR = total hip replacement
TKR = total knee replacement

Apixaban, dabigatran, and rivaroxaban are indicated:

- for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective knee or hip replacement surgery
- prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate

Rivaroxaban is further indicated:

- for treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE.

**Practice Tip!**

Patients with AF who are taking blood thinners can benefit from a Medical Alert ID bracelet: [http://www.medicalert.ca/Who-needs-it/Medications/Blood-thinners](http://www.medicalert.ca/Who-needs-it/Medications/Blood-thinners)

In a medical emergency, the Medic Alert informs paramedics, nurses, and doctors that the patient has atrial fibrillation and is taking an anticoagulant.
NOAC Contraindications\textsuperscript{12-14}

- **Bleeding or significant increased bleeding risk** (Clinically significant active bleeding or bleeding conditions, lesions, or increased risk of bleeding; hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy, and having clinically relevant bleeding risk)
- **Concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-glycoprotein** (P-gp), such as azole-antimycotics ketoconazole, itraconazole, posaconazole, or, voriconazole, or HIV protease inhibitors, e.g., ritonavir
- **Concomitant treatment with any other anticoagulant** (unfractionated heparin (UFH)), except at doses used to maintain a patent central venous or arterial catheter, low molecular weight heparins (LMWH), such as enoxaparin and dalteparin, heparin derivatives, such as fondaparinux, and oral anticoagulants, such as warfarin, dabigatran, rivaroxaban, except under circumstances of switching anticoagulant therapy)
- **Prosthetic heart valves**
- **Hypersensitivity** to the product or any of its ingredients
- **Not recommended, or contraindicated in severe renal impairment** (see dose adjustments, next)
- **Not recommended in pregnancy or breast feeding**
Other NOAC Interactions

Drug-Food Interactions

Apixaban, dabigatran, and rivaroxaban 10mg can be taken with or without food. Rivaroxaban 15 mg and 20 mg should be taken with food.

Grapefruit juice is only a moderate CYP 3A4 inhibitor, therefore grapefruit juice consumption is not expected to be clinically relevant.

Drug-Herb Interactions

The concomitant use of NOACs with strong inducers of both CYP 3A4 and P-gp inducers (e.g. St. John’s Wort) may lead to reduced drug plasma concentrations. Combined use with strong inducers of both CYP 3A4 and P-gp should generally be avoided, since efficacy may be compromised.

Drug-Laboratory Interactions

- Apixaban:
  Clotting tests, e.g., PT (including INR), and aPTT, are affected as may be expected by the mechanism of action of apixaban. Changes observed in these clotting tests at the expected therapeutic dose are relatively small, subject to noteworthy variability, and are not useful for assessing the anticoagulant effect of apixaban.

- Dabigatran:
  At recommended doses, dabigatran prolongs coagulation time as measured by the activated partial thromboplastin time (aPTT), thrombin time (TT) and ecarin clotting time (ECT). In patients who are bleeding due to excess activity of dabigatran, these coagulation tests would be expected to be elevated and may be helpful in assessing anticoagulant activity of dabigatran, if necessary. If TT or ECT are not available, the aPTT test provides an approximation of dabigatran anticoagulant activity.

  A Calibrated Hemoclot® Thrombin Inhibitor assay (a diluted TT assay) with dabigatran standards should be used to calculate the dabigatran concentration, if deemed medically appropriate, rather than using a standard TT measurement.

  Note that a PT (INR) test is not useful to assess the anticoagulant activity of PRADAXA, and should not be used for this purpose.

- Rivaroxaban:
  Although various clotting parameter tests (PT, aPTT, Heptest®) are affected by the mode of action of rivaroxaban, none of these clotting tests have been demonstrated to reliably assess the anticoagulant activity of rivaroxaban following rivaroxaban administration under usual conditions.

  The prothrombin time (PT), measured in seconds, is influenced by rivaroxaban in a dose-dependent way with a close correlation to plasma concentrations if the Neoplastin® reagent is used. In patients who are bleeding, measuring the PT (Neoplastin® reagent) in seconds, but not INR, may be useful to assist in determining an excess of anticoagulant activity.
Ask the Expert Video Question
What key pieces of information should pharmacists look for when a patient is initiated on a new oral anticoagulant?

Apixaban Dosing
Canadian Dosing Recommendations for Stroke Prevention in AF – Apixaban\textsuperscript{12,18}

\textbf{Apixaban}

- Patient has risk factor for stroke
  - Estimate CrCl
  - <15 mL/min
    - Not recommended
  - \geq 15 - 24 mL/min
    - No dosing recommendation can be made*
  - \geq 25 mL/min
    - Check Age
      - \geq 80 years
      - \leq 60 kg
      - \geq 133 micromol/L
    - Check Weight
    - Check Serum Creatinine
      - If \geq 2 features listed above
        - 2.5 mg BID
      - If \leq 1 features listed above
        - 5 mg BID

Dabigatran Dosing

Canadian Dosing Recommendations for Stroke Prevention in AF – Dabigatran\textsuperscript{13,18}

\textbf{Dabigatran}

Patient has risk factor for stroke

Estimate CrCl

- <30 mL/min: Contraindicated
- 30-49 mL/min: Age ≥65 years and/or risk factors for bleeding
- >50 mL/min:
  - Age <75 years
  - Age 75-80 years
  - Age >80 years

110mg BID
150mg BID
150mg BID
110mg BID
150mg BID
110mg BID

Rivaroxaban Dosing

Canadian Dosing Recommendations for Stroke Prevention in AF – Rivaroxaban

Antidotes

Antidotes for anticoagulants

- There is no antidote for any of the new oral anticoagulants
- However, the “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
- Prothrombin complex concentrate (PCC) therapy (a combination of clotting factors) rapidly corrects INR in most patients on warfarin, yet with uncertain prognostic impact
- Antidotes for the Factor Xa inhibitors are in development (phase 2 studies with andexanet alfa in healthy volunteers showing reversal of factor Xa inhibitors were completed, and phase 3 will start in 2014)

Warfarin-Associated ICH: Poor Prognosis Despite Anticoagulation Reversal

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

Melvin Revisited

Melvin’s doctor initiated him on rivaroxaban 20mg daily. When Melvin comes in to fill his prescription, you see that his lab values indicate renal impairment, with a GFR of 48 mL/min.

Discussion Forum

1. What would you do: Would you fill the prescription or contact the physician with a recommendation?
2. What recommendation would you make?
3. Have you done this in the past? What was the outcome?
Case Study 2

Meet Ron

Ron is a 55-year-old male who has come to the pharmacy to ask for an over-the-counter cream for a leg rash. You recognize Ron as a regular at the pharmacy, where he fills prescriptions for his young son who has asthma. You ask Ron more about his rash. He describes a red, warm discolouration on his left calf. You know that Ron has just returned from a long trip during which he flew to South Africa and then took an ocean cruise. You are concerned that Ron might have DVT.

Case Challenge

What is the chance of pulmonary embolism if Ron has DVT and it is left untreated?

   a. About 1 in 3
   b. About 1 in 10
   c. About 1 in 50
   d. About 1 in 100

Deep Vein Thrombosis

Deep vein thrombosis (DVT)²²

- DVT affects ~45,000 patients in Canada per year (incidence ~ 1-2 cases per 1,000 persons annually)
- About one third of untreated DVT result in potentially fatal pulmonary embolism (PE)
- About one third will suffer from post-thrombotic syndrome (chronic lower leg edema, pain, pigment changes and skin breakdown)
- About one third will have a DVT recurrence within 10 years

Fast diagnosis and treatment is necessary to optimize outcomes.

Ask the Expert Video Question

Because patients do not ‘feel’ an effect of their anticoagulant medication working, adherence can be challenging for patients needing anticoagulant therapy. How can pharmacists help ensure patient adherence?
DVT Risk Factors

Risk Factors for DVT

Although most cases of DVT are unprovoked (idiopathic), certain conditions and provoking factors play a role in approximately half of DVT cases:

- active malignancy
- surgery
- immobilization > 8 hours
- estrogen use/pregnancy

Practice Tip!

Help patients with medication adherence. Several smartphone apps are available to provide reminders to help patients take their medication as prescribed. The following three were rated highest in a recent review, because of their basic medication reminder features and enhanced functionality.

- MyMedSchedule: www.mymedschedule.com (website only; mobile apps not available in Canada)
- MyMeds: Android iTunes
- RxmindMe: iTunes

Case revisited

Which of the following lists agents that EACH should be avoided in combination with rivaroxaban?

a. grapefruit juice, ketoconazole, ritonavir
b. atorvastatin, rifampicin, ketoconazole
c. midazolam, naproxen, ritonavir
d. St. John’s Wort, ritonavir, rifampicin

Discussion Forum

Do you routinely ask patients who are taking anticoagulants about their alternative medications, and potential drug-herb interactions?
Role of NOACs

Role of NOACs in Treatment of DVT

At the time of this publication, only one NOAC is indicated in Canada for treatment of DVT; rivaroxaban.

Rivaroxaban:

- is an oral anticoagulant that works through inhibition of factor Xa
- is approved for the treatment of venous thromboembolic events (deep vein thrombosis (DVT), pulmonary embolism (PE)* and prevention of recurrent DVT and PE

For an alternative to injections, rivaroxaban allows several treatment advantages, including:

- no need to refer to emergency rooms, resulting in more rapid treatment initiation
- greater convenience for the patient and physician
- potentially reduced health care costs
- no need for patient to self-inject

* For the treatment of VTE, rivaroxaban is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolus who are haemodynamically unstable, or who may receive thrombolysis or pulmonary embolectomy, since the safety and efficacy of rivaroxaban have not been established in these clinical situations.

Dosing

Rivaroxaban Dosing in DVT

Recommended dosing is 15 mg twice daily for the first 21 days, followed by 20 mg once daily for the duration of treatment. (Rivaroxaban should not be used in women who are pregnant or breast-feeding.)
Key Points

- AF is the most common form of arrhythmia and its prevalence increases with age
- AF increases stroke risk by approximately 3 to 6 fold
- Stroke risk for patients with AF can be estimated using the CHADS² score
- Bleed risk for patients needing anticoagulant therapy to reduce stroke in AF can be estimated using the HAS-BLED score
- Certain items in the HAS-BLED score can be modified to reduce bleed risk factors (e.g., drugs, alcohol, or uncontrolled hypertension)
- Anticoagulants are underutilized for patients at risk. Perceived bleeding risk remains an obstacle to appropriate anticoagulant use.
- Until recently, therapeutic options for lowering the risk of stroke in patients with AF were warfarin and antiplatelet agents. However, the new oral anticoagulants introduce effective and well tolerated options for treatment.
- Canadian guidelines recommend that most patients with AF should receive either a NOAC or ASA. ASA is only recommended first-line in patients with a CHADS² score of 0, who are either female or have vascular disease.
- DVT is associated with serious consequences, including potentially fatal pulmonary embolism, post-thrombotic syndrome, and DVT recurrence. Fast diagnosis and treatment are required to optimize outcomes.
- The NOAC rivaroxaban is currently the only NOAC indicated in Canada for treatment of DVT (and prevention of recurrent DVT).
- Pharmacists play a key role in ensuring patient adherence to anticoagulant therapy.

Resources

Thrombosis Canada http://thrombosiscanada.ca


References


Post-Test

1. The prevalence of AF increases with age. In people over 80 years of age, the prevalence is:
   a. 3-5%
   b. 5-10%
   c. 10-15%
   d. 15-20%

2. True or false? Stroke risk in patients with atrial fibrillation is usually lower than bleed risk.
   a. True
   b. False

3. Risk factors for DVT include all but:
   a. active malignancy
   b. surgery
   c. immobilization > 8 hours
   d. corticosteroid use
   e. estrogen use
   f. pregnancy

4. True or false? Major bleeds are more likely to be fatal or disabling than strokes with atrial fibrillation.
   a. True
   b. False

5. Indications:
   i. for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective knee or hip replacement surgery
   ii. prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate
   iii. for treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE.

Which below option accurately captures the indications for the new oral anticoagulants, as stated in the three statements above?

   a. Apixaban, dabigatran, and rivaroxaban are indicated for i, ii, and iii.
   b. Apixaban and dabigatran are indicated for i, ii, and iii and rivaroxaban is indicated for i and ii.
   c. Apixaban is indicated for i, ii, and iii, and dabigatran and rivaroxaban are indicated for i and ii.
   d. Apixaban and dabigatran are indicated for i and ii, and rivaroxaban is indicated for i, ii, and iii.
6. True or false? Anticoagulant therapy is contraindicated when there is risk of major bleeding.
   a. True
   b. False

7. The new oral anticoagulants are contraindicated when used concomitantly with:
   a.azole-antimycotics
   b. HIV protease inhibitors
   c. ACE inhibitors
   d. statins
   e. all of the above
   f. A and B but not C and D
   g. C and D but not A and B

8. Roughly what proportion of patients with deep vein thrombosis will suffer from post-thrombotic syndrome?
   a. one half
   b. one third
   c. one quarter
   d. one tenth

9. Canadian clinical guidelines recommend which option as antithrombotic therapy in AF patients who are at low stroke risk (CHADS2 score of 0 and female sex or vascular disease)?
   a. warfarin
   b. heparin
   c. NOAC
   d. ASA
   e. None

10. Canadian clinical guidelines recommend which option as antithrombotic therapy in AF patients who are at stroke risk with CHADS2 score >1?
    a. warfarin
    b. heparin
    c. NOAC
    d. ASA
    e. none