Don’t Skip a Beat:
A Refresher on Anticoagulation for Atrial Fibrillation in 2018

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Presenter Disclosure

• Faculty / Speaker’s name: Mahwash Saeed

• Relationships with commercial interests:
  – Grants/Research Support: None
  – Speakers Bureau/Honoraria: Bayer
  – Consulting Fees: None
  – Other: None
Mitigating Potential Bias

• All recommendations involving clinical medicine are based on evidence from well-designed clinical trials published in peer-reviewed journals and current Canadian guidelines

• All novel oral anticoagulants available in Canada will be discussed
Learning Objectives

1) Briefly review the mechanisms of warfarin, rivaroxaban, apixaban and dabigatran

2) Review potential anticoagulation options in common ambulatory cardiac patients with non valvular atrial fibrillation
The “CCS Algorithm” for OAC Therapy in AF

- **Age ≥ 65**
  - **YES** → **OAC** (consider and modify if possible)
  - **NO**
    - **Prior stroke or TIA or Hypertension or Heart failure or Diabetes mellitus (CHADS₂ risk factors)**
      - **YES** → **OAC** (consider and modify if possible)
      - **NO**
        - **CAD or Arterial vascular disease (coronary, aortic, peripheral)**
          - **YES** → **ASA**
          - **NO**
      - **NO**
        - **No Antithrombotic**

Anticoagulation for Atrial Fibrillation

Atrial Fibrillation/Flutter

Any of:
- Age ≤ 65 years
- Previous Stroke/TIA/peripheral embolism
- Hypertension
- Congestive Heart Failure
- Diabetes Mellitus

Coronary artery disease or arterial vascular disease (aortic or peripheral)

Anticoagulation Recommended

Any of:
- CKD with CrCl ≤ 30 ml/min
- Mechanical prosthetic valve
- Moderate to severe rheumatic mitral stenosis

Warfarin

Acetylsalicylic acid (ASA) 81 mg daily

No antithrombotic therapy

NOAC Recommended

Includes patients with:
- Bioprosthetic valves (except first 3 months post-operatively)
- Mitral valve repair (except first 3 to 6 months post-operatively)
- Valve disease, except moderate to severe rheumatic mitral stenosis
- Hypertrophic Cardiomyopathy
- Trans Aortic Valve Implantation (TAVI)

CKD = Chronic Kidney Disease
NAOC = Non vitamin K antagonist oral anticoagulants
Case 1

- 89 year old gentleman, NSTEMI
  - Receives DES x 3 to mid to distal RCA
  - New diagnosis atrial fibrillation, LVEF 30%
**Meds at home:**
- Clopidogrel 75 mg OD
- Atorvastain 80 mg OD
- Candesartan 16 mg OD
- HCTZ 25 mg OD
- Naproxen 500 mg BID
- Metformin 500 mg BID
- Pregabalin 150 mg BID
- Lorazepam 1 mg TID

**Meds DC’d:**
- Candesartan HCTZ

**New Meds added:**
- ASA 81 mg OD
- Dabigatran 110 mg OD
- Ramipril 2.5 mg BID
- Metoprolol 25 mg TID
Case 1

- Patient presents to GP’s office 3 weeks after discharge with bruising over forearms
- Very concerned about addition of anticoagulant to his medications – he has a friend who recently fell and suffered a subdural hematoma
Polling Question

• What is your greatest concern when it comes to managing elderly patients on an oral anticoagulant?
  A. Fear of bleeding  
  B. Fear of falling  
  C. Concerns with renal function  
  D. Adherence  
  E. Other
# Patient and Physician Values

<table>
<thead>
<tr>
<th>Patients</th>
<th>Physicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interactions with food/drug</td>
<td>Risk of major bleeding</td>
</tr>
<tr>
<td>Rapid reversal in emergency situations</td>
<td>Interactions with food/drug</td>
</tr>
<tr>
<td>Clinical experience</td>
<td>Requirement for regular blood testing</td>
</tr>
<tr>
<td>Requirement for regular blood testing</td>
<td>Rapid reversal in emergency situations</td>
</tr>
<tr>
<td>Risk of major bleeding</td>
<td>Dosing frequency</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>Clinical experience</td>
</tr>
<tr>
<td>Efficacy (stroke-free survival)</td>
<td>Efficacy (stroke-free survival)</td>
</tr>
</tbody>
</table>

**Highest rated attribute**: Requirement for regular blood testing

**Lowest rated attribute**: Risk of major bleeding
In 48% of patients, physician choice was the reason an OAC was not given to patients with a CHADS$_2$ score $\geq 2^3$

The risk of stroke in AF increases dramatically with age$^1$

However, the use of anticoagulation decreases$^2$
Bleeding Risk Management

• Address reversible risk factors:
  • Falling → provide mobility aid
  • Hypertension → treat blood pressure to target
  • Alcohol → encourage abstinence
  • Labile INR → use NOACs
  • Drugs → replace NSAIDs with other analgesics, avoid ASA unless clearly indicated for secondary prevention
  • GI bleeding → use proton pump inhibitors (PPI)
Follow-up Considerations for Elderly Patients

• **Follow-up plan**
  • Patient should be seen every 3-6 months
  • Encourage adherence
  • Check concomitant/over the counter medications
  • Check for other side effects, thromboembolic or bleeding events

Follow-up Considerations for Elderly Patients

- Renal function should be monitored yearly, or more frequently if CKD or acute illness
- Monitor hemoglobin and liver function yearly
- Review use of NSAIDs
- Mobility aids (e.g., cane, walker and grab bars in the bathroom) can be used to help prevent falls

Case 2

• 75 year old lady presents with new onset palpitations and AF
  • PmHx: DM2, HTN, CKD (CrCl 35 ml/min)
  • Was in ED last week – told to talk to GP about blood thinners
  • Very nervous – sister died of brain hemorrhage

Medications:

ASA 81 mg OD
Metoprolol 25 mg BID
Lasix 80 mg BID
Amlodipine 10 mg OD
Insulin varying doses
Zopiclone 3.75 mg at HS
CKD is a Risk Factor for Thrombotic and Bleeding Events

No renal disease (n=127,884)  Non end-stage CKD (n=3587)

CCS Guidelines Recommend NOACs for Eligible AF Patients with eGFR $\geq 30$ mL/min

- **Warfarin**
  - Patients with AF and eGFR $<30$ mL/min
- **Rivaroxaban, Apixaban, Dabigatran**
  - Patients with AF and eGFR $\geq 30$ mL/min
- **Warfarin if NOAC contraindicated**

Verma et al. Can J Cardiol. 2014:30;1114-30
Rivaroxaban

Apixaban

Dabigatran

Edoxaban

Creatinine Clearance (mL/min)

Apixaban¹

Dabigatran²

Edoxaban³

Rivaroxaban⁴

1. Apixaban (Eliquis) Product Monograph. Bristol-Meyers Squibb Canada
2. Dabigatran (Pradaxa) Product Monograph. Boehringer Ingelheim Canada Ltd
3. Edoxaban (Lixiana) Product Monograph. Progress Therapeutics
4. Rivaroxaban (Xarelto) Product Monograph. Bayer Inc
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Vitamin K Antagonist</td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>Inhibits synthesis of Factors II, VII, IX, X</td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Direct Thrombin Inhibitor</td>
<td>Renal</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct Factor Xa Inhibitor</td>
<td>Renal and Hepatic</td>
</tr>
<tr>
<td>Apixiban</td>
<td>Direct Factor Xa Inhibitor</td>
<td>Renal and Hepatic</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Direct Factor Xa Inhibitor</td>
<td>Renal and Biliary</td>
</tr>
</tbody>
</table>
NOACs remain safe and effective in patients with moderate renal impairment

Increased Rates of SSE and Major Bleeding in Warfarin Arm with Declining Renal Function

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Pooled NOAC (events)</th>
<th>Pooled warfarin (events)</th>
<th>RR (95% CI)</th>
<th>p interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>249/5539</td>
<td>311/5503</td>
<td>0.79(0.65-0.96)</td>
<td></td>
</tr>
<tr>
<td>50-80</td>
<td>405/13055</td>
<td>546/13155</td>
<td>0.75(0.66-0.85)</td>
<td>0.12</td>
</tr>
<tr>
<td>&gt;80</td>
<td>256/10626</td>
<td>255/10533</td>
<td>0.98(0.79-1.22)</td>
<td></td>
</tr>
</tbody>
</table>

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<tr>
<th>Creatinine clearance (mL/min)</th>
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<th>Pooled warfarin (events)</th>
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<th>p interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>514/4376</td>
<td>620/4346</td>
<td>0.74(0.52-1.05)</td>
<td></td>
</tr>
<tr>
<td>50-80</td>
<td>1104/10139</td>
<td>1174/10228</td>
<td>0.91(0.76-1.08)</td>
<td>0.57</td>
</tr>
<tr>
<td>&gt;80</td>
<td>625/8681</td>
<td>672/8595</td>
<td>0.85(0.66-1.10)</td>
<td></td>
</tr>
</tbody>
</table>

Favours NOAC  Favours Warfarin

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>5 mg BID</td>
<td>150 mg BID</td>
<td>60 mg daily</td>
<td>20 mg daily</td>
<td>Dose adjusted for INR 2.0-3.0</td>
</tr>
<tr>
<td>30-49</td>
<td>5 mg BID (consider 2.5 BID)</td>
<td>150 mg BID</td>
<td>30 mg daily</td>
<td>15 mg daily</td>
<td></td>
</tr>
<tr>
<td>15-29</td>
<td>Limited data</td>
<td>No RCT data</td>
<td>Limited data</td>
<td>No RCT data</td>
<td>No RCT data</td>
</tr>
<tr>
<td>&lt;15 or dialysis</td>
<td>No RCT data</td>
<td>No RCT data</td>
<td>No RCT data</td>
<td>No RCT data</td>
<td>No RCT data</td>
</tr>
</tbody>
</table>

Summary – Renal Dysfunction

• Renal impairment is associated with an increased risk of stroke and bleeding
• NOACs are safe and effective in patients with moderate renal impairment and worsening renal function
• Dosing recommendations for patients with renal impairment differ among NOACs
• Warfarin is preferred over NOACs for patients with severe renal impairment (eGFR 15-30 mL/min/1.73 m²)
Case 3

67 year old gentleman, AF on NOAC
• Scheduled for hernia surgery
• Normal renal function

• When should we hold his NOAC?
  A. 1 day before surgery?
  B. 2 days before surgery?
  C. 3 days before surgery?
  D. 5 days before surgery?
  E. I would not stop his NOAC.
Perioperative Considerations for NOACs

- Reliable laboratory tests to assess anticoagulant effect of NOACs are not widely available
- Half-lives vary and increase with worsening renal function
- NOACs have a rapid onset of action, with peak anticoagulant effect occurring 1-2 hours after oral intake
<table>
<thead>
<tr>
<th>Low Risk of Bleeding</th>
<th>Intermediate to High Risk of Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Day Before</strong></td>
<td><strong>3 Days Before</strong></td>
</tr>
<tr>
<td>Apixiban</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>CrCl &gt;30 ml/min</td>
<td>CrCl 30 to 50ml/min</td>
</tr>
<tr>
<td>Skip 2 doses</td>
<td>Skip 6 doses</td>
</tr>
<tr>
<td></td>
<td><strong>2 Days Before</strong></td>
</tr>
<tr>
<td>Apixiban</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>CrCl &gt;30 ml/min</td>
<td>CrCl 30 to 50ml/min</td>
</tr>
<tr>
<td>Skip 4 doses</td>
<td>Skip 10 doses</td>
</tr>
<tr>
<td></td>
<td><strong>5 Days Before</strong></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>CrCl &gt;50 ml/min</td>
<td>CrCl &gt;50 ml/min</td>
</tr>
<tr>
<td>Skip 2 doses</td>
<td>Skip 4 doses</td>
</tr>
<tr>
<td></td>
<td><strong>2 Days Before</strong></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td>CrCl &gt;30 ml/min</td>
<td>CrCl &gt;30 ml/min</td>
</tr>
<tr>
<td>Skip 1 dose</td>
<td>Skip 2 doses</td>
</tr>
<tr>
<td></td>
<td><strong>5 Days Before</strong></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>CrCl &gt;30 ml/min</td>
<td>CrCl &gt;30 ml/min</td>
</tr>
<tr>
<td>Skip 1 dose</td>
<td>Skip 2 doses</td>
</tr>
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</table>

Bridging?

• Bridging (LMWH or UFH) is not required for non valvular a fib patients on a NOAC undergoing elective surgery or invasive procedures requiring interruption of anticoagulation

• Bridging in warfarin patients is required in:
  • Patients with mechanical mitral valves or older aortic valves
  • Patients with INR below therapeutic level in patients at high risk of thromboembolic events (CHADS$_2$ ≥4)

• NOACs and warfarin should be restarted once adequate hemostasis has been established

Summary – Perioperative Management

• Prolonged discontinuation of a NOAC perioperatively is unnecessary

• Perioperative management of NOACs must take into consideration:
  • Renal function
  • Half-life
  • Bleeding risk of the procedure
Summary – Perioperative Management

• Determine timing of temporary discontinuation as per recommendations
• Bridging therapy is generally not required unless procedure will be delayed longer than 72 hours
• Ensure anticoagulant is restarted following procedure
Take home messages

• Elderly patients are at high risk of stroke and should be considered for anticoagulation in the right clinical setting
  – Care must be taken to reduce risk of serious bleeding
Take home messages

• NOACs are safe and effective in patients with moderate renal impairment and worsening renal function
  – Care must be taken to dose adjust NOACs in the setting of renal dysfunction
  – Warfarin is preferred at an eGFR of less than 30 ml/min
Take home messages

• Perioperative management of NOACs must take into consideration renal function, half life and bleeding risk of the procedure
• Always ensure anticoagulant is restarted post procedure!
Anticoagulation for Atrial Fibrillation

**Atrial Fibrillation/Flutter**

- **Any of:**
  - Age ≤ 65 years
  - Previous Stroke/TIA/peripheral embolism
  - Hypertension
  - Congestive Heart Failure
  - Diabetes Mellitus

- **NO:**
  - Coronary artery disease or arterial vascular disease (aortic or peripheral)
  - Acetylsalicylic acid (ASA) 81 mg daily
  - No antithrombotic therapy

- **Anticoagulation Recommended**

- **Any of:**
  - CKD with GFR ≤ 30 mL/min
  - Mechanical prosthesis valve
  - Moderate to severe rheumatic mitral stenosis

- **NO:**

  - **NOAC Recommended**
    - Includes patients with:
      - Bioprosthetic valves (except first 3 months post operatively)
      - Mitral valve repair (except first 3 to 6 months post operatively)
      - Valve disease, except moderate to severe rheumatic mitral stenosis
      - Hypertrophic Cardiomyopathy
      - Trans Aortic Valve Implantation (TAVI)

- **Warfarin**

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**Consider Referral to Cardiology in Patients with:**

- Cardiomyopathy
- Moderate to severe valvular disease
- Symptoms (dyspnea, presyncpe)
- Difficult to control ventricular rates
- Especially those over age > 75 on 2 or more rate controlling agents (for possible AV node ablation/pacemaker insertion)
- Age less than < 60
- Recurrent atrial flutter (for possible ablation)
- Recent myocardial infarction and stent insertion
- High risk for bleeding
- Professional driver’s/pilot’s licenses

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**CKD** = Chronic Kidney Disease

**NAOC** = Non vitamin K antagonist oral anticoagulants
Thank you

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