Antithrombotics in Stroke management

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• Relationships with commercial interests:
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  • Consulting Fees: Astra Zeneca, Bayer, Boehringer Ingelheim, Glaxo Smith Klein, Pfizer
  • Other: N/A

• I perceive no conflicting interest but am open to negotiation
Antithrombotics in Stroke management

• Evidence and its relation to practice.
• Risk and benefit: finding the right balance.
How do clinicians feel about Evidence and Guidelines?

• Education events: Polling of physicians indicates that reviewing evidence is not desirable and does not contribute to changes in practice.

• Answer questions, make recommendations that actually make sense and are applicable to a person's practice.

• Trust me I’m an expert or

• Don’t trust me because I am an expert and I don’t take care of real patients in the real world
Experts: help with choice of drug and timing…
Things I know that you know

• Antithrombotics are effective in reducing stroke risk
• Antithrombotics are effective in treating stroke
• Antithrombotics can be dangerous
Blood clots are bad: Stroke, MI, PE, DVT, limb ischemia, organ infarction

Antithrombotics are bad but less bad.

Timing is everything

Things I think you want to know

• What patients get thrombolytics, antiplatelet agents, anticoagulants?
• When should drugs be started and stopped?
• What agents are better? Medication choices
• What agents are riskier and when?
Things I think I know

• Difficult treatment decisions can’t be made without knowing phenotype
• Size matters: Big stroke little stroke
• Timing is everything.
• Prevention is better than treating stroke
• NOACS/DOACS: no evidence of superiority of any agent, all significantly reduce risk of mortality, stroke, ICH vs VKA, no direct comparisons between agents…makes bleeding risks harder to evaluate. Patient Characteristics in ROCKET AF, RE-LY and ARISTOTLE...
Anticoagulation and VTE prophylaxis in Stroke

- Phenotype: essential for treating individuals not populations
- There is no reliable “recipe” because of phenotype
- Ethnicity: Asians (Slide 20)
- Chads2 Chads2 Vasc score, (risk) Has bled (bleed risk)
- ACS; Stent, AF, EF, vascular plaque
- Hs troponins are continuing to create opportunity and potential harm;
- BP control
- Renal status (eGFR, CrCl)
- Size of stroke: 3-6-9; 5-10-15
- ICH: trauma, no trauma, anticoagulation before; ICH expansion, hemorrhagic transformation
Things you should know

• What patients receive antiplatelet agents and when?
• What patients receive anticoagulants and when?
• What anticoagulants for what patient? VTE prophylaxis, stroke risk reduction, ACS, DVT/PE?
• Imaging results When decisions need to be made
• NOACS/DOACS: Are preferred in patients who have CrCl >50; probably preferred for CrCl 30-49.
• There is growing concern with underdosing of the NOACS/DOACS
Stroke Prevention in Patients with Atrial Fibrillation
Atrial Fibrillation (AF)

- Currently, it is estimated that ~350,000 Canadians have atrial fibrillation (AF)\(^1\)

- AF affects approximately:
  - 3% of Canadians over the age of 45\(^1\)
  - 6% over the age of 65\(^1\)
  - 10% over the age of 80\(^2,3\)

- The lifetime risk of AF is 1 in 4 after the age of 40\(^4,5\)

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Effect of first ischemic stroke in AF patients

![Graph showing effect of first ischemic stroke in patients with AF (n=597)]
Stroke severity and AF

Among patients who had a stroke, those with AF experienced a:

- 20% increase in the length of hospital stay
- 40% decrease in the relative chance of discharge to own home
- 70% increase in in-hospital mortality

...compared to those without AF

The Copenhagen stroke study, a prospective community-based study. n=1,197

**In hospital mortality: 72 deaths, n=217 with AF vs. 171 deaths n=968 without AF
†Discharge to own home: n=104 with AF vs. 662 deaths n=968 without AF
‡Length of hospital stay: 50.4 days with AF vs. 39.8 days without AF
AF consequences

- Independent risk factor for stroke
- Fivefold increased risk
- One in six strokes occur in patients with AF
- AF-related strokes are typically more severe than strokes due to other etiologies
- Stroke risk persists even in patients with asymptomatic or intermittent AF
AF consequences

- Independent risk factor for mortality
- Twofold increased risk
- Independent risk factor for heart failure
- Heart failure further aggravates AF, worsening overall prognosis
The “CCS Algorithm” for OAC Therapy in AF

Guideline says:

- **Age ≥ 65**
  - **YES**
  - OAC*
  - **NO**
    - Prior stroke or TIA or Hypertension or Heart failure or Diabetes mellitus (CHADS₂ risk factors)
      - **NO**
      - **YES**
        - OAC*
          - Consider and modify (if possible) all factors influencing risk of bleeding during OAC treatment (hypertension, antiplatelet drugs, NSAIDs, excessive alcohol, labile INRs) and specifically bleeding risks for NOACs (low creatinine clearance, age ≥ 75, low body weight).†
    - **YES**
      - CAD or Arterial vascular disease (coronary, aortic, peripheral)
        - **YES**
          - ASA
        - **NO**
          - **NO**
            - No Antithrombotic
OAC for most patients 65 years of age or older or those with Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack (CHADS$_2$) score ≥ 1; acetylsalicylic acid (ASA) for patients younger than 65 years of age with CHADS$_2$ = 0 with arterial vascular disease (coronary, aortic, or peripheral); and no antithrombotic therapy for patients younger than 65 years of age with CHADS$_2$ = 0 and no arterial vascular disease. Bleeding risks should be modified when and if possible. The CCS also suggests that a novel direct oral anticoagulant (NOAC) be used in preference to warfarin for OAC therapy in nonvalvular AF patients.

Might require lower dosing.
Stroke Types and Incidence

Ischemic stroke 85-88%

Hemorrhagic stroke 12-15%

Cryptogenic 30%

Atherosclerotic cerebrovascular disease 20%

Cardiogenic embolism 20%

Small vessel disease “lacunes” 25%

Other 5%

Atherosclerotic cerebrovascular disease 20%
Timing issues non tPA; Stroke and VTE

• Ischemic stroke: ASA or Clopidogrel
• Hemiplegic stroke (large) VTE risk is high, hemorrhagic transformation usually occurs early (24-48 hours).
• Hemorrhagic stroke: VTE is OK within 48-72 hours but call someone.
• AF: anticoagulation timing depends on stroke size, first stroke, second stroke and all the phenotype questions.
• Big stroke: treat later (Generally 2 weeks). Call someone. timing
Inadequate anticoagulation in high risk patients with atrial fibrillation (Registry of Canadian Stroke Network)

- Preadmission medications in patients with known atrial fibrillation who were admitted with acute ischemic stroke (N=597)
  - Warfarin subtherapeutic: 29%
  - Warfarin therapeutic: 29%
  - Single antiplatelet agent: 10%
  - Dual antiplatelet therapy: 29%
  - No antithrombotics: 2%

- Preadmission medications in patients with known atrial fibrillation and a previous ischemic stroke/TIA who were admitted with acute ischemic stroke (N=323)
  - Warfarin therapeutic: 39%
  - Warfarin subtherapeutic: 3%
  - Dual antiplatelet therapy: 15%
  - Single antiplatelet agent: 25%
  - No antithrombotics: 18%

# Trials Comparing New Anticoagulants vs. Warfarin

<table>
<thead>
<tr>
<th></th>
<th>ROCKET AF&lt;sup&gt;1&lt;/sup&gt;</th>
<th>RE-LY&lt;sup&gt;2&lt;/sup&gt;</th>
<th>ARISTOTLE&lt;sup&gt;3,4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>14,264</td>
<td>18,113</td>
<td>18,201</td>
</tr>
<tr>
<td><strong>Statistical objective</strong></td>
<td>Non-inferiority</td>
<td>Non-inferiority</td>
<td>Non-inferiority</td>
</tr>
<tr>
<td><strong>Study drugs</strong></td>
<td>Double-blind rivaroxaban</td>
<td>Two doses of double-blind dabigatran</td>
<td>Double-blind apixaban</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>Double-blind warfarin (INR 2–3)</td>
<td>Open-label warfarin (INR 2–3)</td>
<td>Double-blind warfarin (INR 2–3)</td>
</tr>
<tr>
<td><strong>Primary Dose(s) Studied</strong></td>
<td>20 mg OD</td>
<td>110 mg BID and 150 mg BID</td>
<td>5 mg BID</td>
</tr>
<tr>
<td><strong>Adjusted Dose Studied</strong></td>
<td>15 mg OD For patients with CrCl = 30-49 mL/min</td>
<td>None</td>
<td>2.5 mg BID For patient with any two of the following: - Age ≥80 years - Body weight ≤60 kg - Serum creatinine ≥1.5 mg/dl (133 µmol/l)</td>
</tr>
</tbody>
</table>

## Known Risk Factors for Bleeding

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>ROCKET-AF</th>
<th>RE-LY</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension(^1)</td>
<td>90%</td>
<td>79%</td>
<td>87%</td>
</tr>
<tr>
<td>Prior Stroke/TIA(^1)</td>
<td>55%</td>
<td>20%</td>
<td>19%</td>
</tr>
<tr>
<td>Increasing Age(^1)</td>
<td>Age ≥ 75 years 44%</td>
<td>Age ≥ 75 years 40%</td>
<td>Age ≥ 75 years 31%</td>
</tr>
<tr>
<td>Diabetes mellitus(^2)</td>
<td>40%</td>
<td>23%</td>
<td>25%</td>
</tr>
<tr>
<td>CHF or low LVEF(^2)</td>
<td>63%</td>
<td>32%</td>
<td>36%</td>
</tr>
</tbody>
</table>

The new OAC agents are consistently associated with a significantly lower risk for intracranial hemorrhage compared to warfarin.†

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>OAC Agent</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban 20mg o.d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dabigatran 150mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td>RE-LY</td>
<td>Dabigatran 110mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Apixaban* 5mg b.i.d.</td>
<td></td>
</tr>
</tbody>
</table>

† Not intended as cross-trial comparison
*Not approved in Canada for stroke prevention in AF patients

Data obtained from intention-to-treat analysis

The new OAC agents are consistently associated with a numerically lower risk for all-cause mortality compared to warfarin.†

**TRIAL** | **OAC Agent** | **Relative Risk (95% CI)**
--- | --- | ---
**ROCKET-AF** | Rivaroxaban 20mg o.d. | |
**RE-LY** | Dabigatran 150mg b.i.d. | |
**ARISTOTLE** | Apixaban* 5mg b.i.d. | |

† Not intended as cross-trial comparison
*Not approved in Canada for stroke prevention in AF patients

Data obtained from intention-to-treat analysis

Which NOAC/DOAC?

- Probably all equivalent for stroke risk reduction
- Possible differences in bleeding risk
- All require caution in high risk patients including renal status
- None are indicated in mechanical heart valves
- Become familiar with 1-2 agents and use them.

[ANTICOAG_AF_STROKE_table.pdf](ANTICOAG_AF_STROKE_table.pdf)
### Ethnicity and anticoagulation

#### Table. NNT and NNH in Asians and non-Asians receiving dabigatran, apixaban and warfarin in clinical trials

<table>
<thead>
<tr>
<th></th>
<th>Asians</th>
<th>Non-Asians</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NNT</td>
<td>NNH</td>
<td>NNT</td>
</tr>
<tr>
<td>RE-LY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>75</td>
<td>91</td>
<td>37</td>
</tr>
<tr>
<td>Dabigatran 110 mg</td>
<td>53</td>
<td>435</td>
<td>35</td>
</tr>
<tr>
<td>Dabigatran 150 mg</td>
<td>33</td>
<td>222</td>
<td>32</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>123</td>
<td>53</td>
<td>35</td>
</tr>
<tr>
<td>Apixaban</td>
<td>60</td>
<td>149</td>
<td>32</td>
</tr>
</tbody>
</table>

NNH = number needed to harm; NNT = number needed to treat
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/Thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Maximum Score</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
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<td>Age ≥ 75</td>
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</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/Thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td>Maximum Score</td>
<td>9</td>
</tr>
</tbody>
</table>
### Patient Characteristics in ROCKET AF, RE-LY and ARISTOTLE Trials

<table>
<thead>
<tr>
<th></th>
<th>Subjects, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ROCKET AF (N=14,264)¹</td>
</tr>
<tr>
<td>CHADS₂ score (mean)</td>
<td>3.5</td>
</tr>
<tr>
<td>0 or 1</td>
<td>&lt;0.1*</td>
</tr>
<tr>
<td>2</td>
<td>13.0</td>
</tr>
<tr>
<td>3-6</td>
<td>86.9</td>
</tr>
<tr>
<td>Prior VKA use</td>
<td>62.4</td>
</tr>
<tr>
<td>CHF</td>
<td>62.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>90.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>40.0</td>
</tr>
<tr>
<td>Prior stroke/TIA/embolism</td>
<td>54.8</td>
</tr>
<tr>
<td>Prior MI</td>
<td>17.3</td>
</tr>
</tbody>
</table>

*Three subjects with a CHADS₂ score of 0 or 1 were enrolled in ROCKET AF in violation of the study protocol.*

Calculating Bleeding Risk:
HAS-BLED Scoring System

<table>
<thead>
<tr>
<th>LETTER</th>
<th>CLINICAL CHARACTERISTIC</th>
<th>POINTS AWARDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (&gt;65 yr old)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs (predisposing to bleeding such as NSAIDs or anti-platelets)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Calculating Bleeding Risk:
HAS-BLED Scoring System

![HAS-BLED Score vs. Annual Approximate Bleeding Risk](chart.png)