### Anticoagulation in Non-valvular AFib

<table>
<thead>
<tr>
<th></th>
<th>COUMADIN</th>
<th>PRADAXA Dabigatran 150mg</th>
<th>XARELTO Rivaroxaban</th>
<th>ELIQUIS Apixaban</th>
<th>LIXIANA SAVAYSA USA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke/Embolism</strong></td>
<td>✓ 1</td>
<td>✓ ✓? 2</td>
<td>✓? 3</td>
<td>✓? 4</td>
<td>✓? 5</td>
</tr>
<tr>
<td><strong>ICH</strong></td>
<td>x</td>
<td>✓ 6</td>
<td>✓ 7</td>
<td>✓ 8</td>
<td>✓ 9</td>
</tr>
<tr>
<td><strong>Major GI Bleed</strong></td>
<td>✓</td>
<td>x 10</td>
<td>x 11</td>
<td>✓ 12</td>
<td>x 13</td>
</tr>
<tr>
<td><strong>Major Bleed</strong></td>
<td>✓</td>
<td>✓ 14</td>
<td>✓ 15</td>
<td>✓ 16</td>
<td>✓ 17</td>
</tr>
<tr>
<td><strong>Manage Bleed</strong></td>
<td>✓ 14</td>
<td>✓ 18</td>
<td>x?</td>
<td>x?</td>
<td>x?</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>✓</td>
<td>x? 19</td>
<td>-?</td>
<td>-?</td>
<td>-?</td>
</tr>
<tr>
<td><strong>DC Rate / Dyspepsia</strong></td>
<td>-</td>
<td>x 20/↑GI</td>
<td>-</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td><strong>Low renal fx (CrCl)</strong></td>
<td>✓ ✓ 21</td>
<td>Cl&lt;30mL/min</td>
<td>Avoid&lt;30mL/min</td>
<td>Avoid&lt;15mL/min</td>
<td>Trial Cl&lt;25mL/min</td>
</tr>
<tr>
<td><strong>Cost: $40; ~ $115/mo</strong></td>
<td>✓ ✓ 22</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>? X NEW in Canada</td>
</tr>
<tr>
<td><strong>Half life Pros/Cons</strong></td>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Monitoring</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Certainty vs Uncertainty</strong></td>
<td>25</td>
<td>✓ ✓</td>
<td>+/- RE-LY</td>
<td>+/- ROCKET-AF</td>
<td>+/- ARISTOTLE</td>
</tr>
</tbody>
</table>

#### Dosing frequency, impact of missed dose, bleed management

#### Need for/ability to monitor INR has pros & cons.

#### An Advantage

#### Disadvantage

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**RCTs**

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Comparison of Warfarin and Direct or New/New Oral Anticoagulants (DOACs/NOACs) in Atrial Fibrillation (AFib)

Anticoagulation/Atrial Fibrillation (AFib): Notes on Outcome Comparison


Note, the RE-LY trial data for Canada found warfarin had a time in therapeutic range (TTR) >70%.

1) Stroke/Embolism: absolute differences minimal when INR control with warfarin reasonable (TTR=>65%).
2) Stroke/Embolism: Dabi 150mg BID vs Warf; NNT=88/~2yr; ITT (no difference with 110mg BID dose, but less bleeding); open label RCT. (Study pop: renal fx 30+, adherence likely better than normal conditions, etc.)
3) Stroke/Embolism: Riva 20mg daily vs Warf; non-inferiority trial design (ITT analysis favoured Riva but did not achieve superiority); double-blind RCT. (Study pop: limitations similar to RE-LY.)
4) Stroke/Embolism: Apix 5mg BID vs Warf; NNT=167/~2yrs; ITT; double-blind RCT. Also death NNT=132/~2yr. (Study pop: limitations similar to RE-LY.)
5) Stroke/Embolism: Edox 60mg daily vs Warf was noninferior (ITT analysis); superior NNT=141/~2.8yr (mITT analysis) (no difference with 30mg daily dose, but less bleeding); open label RCT. (Study pop: limitations similar to RE-LY.)
6) ICH: Dabi vs Warf; NNT=116/~2yr
7) ICH: Riva vs Warf; NNT=250/~2yr
8) ICH: Apix vs Warf; NNT=128/~2yr
9) ICH: Edox 60mg vs Warf;
   NNT=99/~2.8yr; 30mg vs Warf; NNT=77/~2.8yr
10) GI Bleed: Dabi vs Warf; NNH=100/~2yr
11) GI Bleed: Riva vs Warf; NNH=100/~2yrs
12) GI Bleed: Apix vs Warf; no difference
13) GI Bleed: Edox 60mg vs Warf; NNH=166/~2.8yr; 30mg vs Warf; NNT=115/~2.8yr
14) Major Bleed: Dabi 150mg BID vs Warfarin; no difference; however 110mg BID had reduced major bleeding (NNT=77/~2yr) but also less benefit.
15) Major Bleed: Riva vs Warf; no difference
16) Major Bleed: Apix vs Warf; NNT=67/~2yr
17) Major Bleed: Edox 60mg daily vs Warf; NNT=67/~2.8yr; 30mg daily; NNT=26/~2.8yr (but also less benefit).
18) Manage Bleeding: Warfarin - real world experience, & options include PCC & Vitamin K for reversal. New agents have less experience. Only Dabi has possible antidote (Idarucizumab (PRAZBIND CDN’16, FDA’15 ). Factor Xa inhibitors studies underway. Shorter half life of new agents means less time till anticoagulation status returns to normal. Life-threatening/fatal bleed was less in dabi / riva trials. However, ISMP Jan 2013 found that bleeds with Dabi 5x more fatal than bleeds with warfarin. Peri-procedural: less experience in managing DOACs.
19) MI Risk: Dabi vs Warf; initial ↑ risk of borderline significance (p=0.048); reanalysis slightly different & non-significant (p=0.06 both doses). (↑ rates of bleeding & thrombotic AE in AFib with mechanical valves RE-ALIGN) Concerns. Controversial. [Warf considered protective.]
20) Discontinuation rates vs Warf: lower with Apix (NNT=45/~2yrs); higher with Dabi (NNH=25/~2yr); also more dyspepsia with Dabi (NNH=18/2yr).
21) All new agents lack study & experience in patients with decreased renal Fx. Dabi is contraindicated (CI) if CrCl <30ml/min. Warfarin can be used. Since AFib patients often older, impaired renal Fx an issue.
22) Economic review found new anticoagulants more costly than warfarin even after consideration for cost of INR monitoring was built into. However, “soft” indirect costs (e.g. time/travel to the patient) not included & may be assessed individually. Direct cost/month: Warf $15, Dabi $116, Apix $104, Edoxaban $109, but is the newest in Canada.
23) Half life of new agents is shorter. “Cons” of this are that Dabi & Apix require BID dose; poor compliance (missed doses) will result in earlier loss of anticoagulation status; “Pros” are earlier achievement of anticoagulation after starting & return to normal after holding if over-coagulated.
24) INR “Con” - inconveniency factor; “Pro” - ability to assess anticoagulation status balance risk of stroke vs bleed. ? Dabi level.
25) Warfarin has 60yrs “real world” experience; new agents have about 5yrs & in limited populations. This factor will gradually change over the next few yrs.
26) If Valvular AFib: Warf OK, DOACs (NOACs) not indicated; Dabi C

(Note: Rate of ICH in AFib less in Canada than in trails. Gomes T, CMAJ 2012. Thus significance of this would be less in CDN context (ie. NNT would be much higher).

(This editorial synthesis based on interpretation of data from RCTs (RELY, ROCKET-AF, ARISTOTLE, ENGAGE-AF), CADTH reports, product monographs & clinical consultation. Only direct comparisons of individual DOACs (NOACs) with warfarin have been studied. Trials designed for non-inferiority, with option for superiority analysis. Comparisons between DOACs (NOACs) have the inherent limitations of indirect comparisons. However, indirect comparisons are often required when decisions need to be made & direct comparisons are not available, nor likely to be done in the near future.)