Emerging Concepts in the Use of NOACs in AFib, CAD, and DVT

Daniel G. Blanchard, MD, FACC, FAHA
Professor of Medicine
Director, Cardiology Fellowship Program
Sulpizio Cardiovascular Center
UC San Diego
The NOACS & their studies, chronologically

- Dabigatran: Pradaxa (RE-LY)
- Rivaroxaban: Xarelto (ROCKET-AF)
- Apixaban: Eliquis (ARISTOTLE)
- Edoxaban: Savaysa (ENGAGE AF)
NOACs Compared to Warfarin

All have similar or lower risk of stroke vs warfarin

Most have HIGHER risk of GI Bleed

All have similar or lower risk of major bleeding

All have a LOWER risk of Intracranial Hemorrhage (!!)
Questions: Warfarin vs NOACs

• Do we want blood tests to monitor drug levels?
  • Anti-Xa assays detect presence of NOAC very accurately, but don’t yet have “therapeutic ranges”
  • PTT is usually elevated in patients taking a NOAC

• Are NOACs safe in valvular heart disease?

• Is aspirin safer in patients with high bleeding risk?

• What about antidotes?
NOACs and Valvular Disease: Stroke & Bleeding

NOACs and Valvular Disease

• NOACs appear safe in valvular heart disease EXCEPT
  • Mechanical valve replacement
  • Moderate-to-severe mitral stenosis (??)
    • Early registry data from Korea suggests no increase in events with NOAC
What about patients prone to falling and bleeding?

Should they be on aspirin instead of a NOAC?
AVERROES Substudy: Apixaban vs. ASA in older pts thought not to be good warfarin candidates

Risk of Major Bleeding

Similar Major Bleed Risk...

Risk of Stroke

Increased risk of Stroke with ASA!
NOAC Antidotes: For Major Bleeding

• Dabigatran:
  • Idarucizumab (Praxbind) – IV antibody fragment with very high affinity for dabigatran.
  • Reverses anticoag effect in minutes, decreases hemorrhage in bleeding pts & those needing urgent surgery

* Pollack CV et al. NEJM 2015;373.
Pollack CV et al. NEJM 2017;377(5).
NOAC Antidotes: For Major Bleeding

• FXa inhibitors: (apixaban, rivaroxaban, edoxaban)
  • PCC (K-centra, prothrombin complex concentrate) reverses hematologic effects. Recent observational studies have been encouraging

• Factor Xa protein “decoys”
  • Andexanet (Andexxa) – effective in preliminary studies, now FDA approved.
  • Currently expensive
### NOAC Antidotes: Andexanet for Major Bleeding

#### Figure 2. Subgroup Analysis of Hemostatic Efficacy.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Percent Adjudicated as Excellent or Good Hemostasis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with efficacy analyses</td>
<td>47</td>
<td>79 (64–89)</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>26</td>
<td>81 (61–93)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>20</td>
<td>75 (51–91)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24</td>
<td>71 (49–87)</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>87 (66–97)</td>
</tr>
<tr>
<td><strong>Site of bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>25</td>
<td>84 (64–96)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>20</td>
<td>80 (56–94)</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>7</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>65–75 yr</td>
<td>9</td>
<td>89 (52–100)</td>
</tr>
<tr>
<td>≥75 yr</td>
<td>31</td>
<td>77 (59–90)</td>
</tr>
<tr>
<td><strong>Andexanet dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>42</td>
<td>76 (61–88)</td>
</tr>
<tr>
<td>High</td>
<td>5</td>
<td>100 (48–100)</td>
</tr>
<tr>
<td>Anti–factor Xa &lt;75 ng/ml or &lt;0.5 IU/ml</td>
<td>17</td>
<td>82 (57–96)</td>
</tr>
</tbody>
</table>
### PCC for Intracranial Hemorrhage:

433 patients with ICH

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Percent With Excellent or Good Hemostasis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=433)</td>
<td>81.8 (77.9–85.2)</td>
</tr>
<tr>
<td>Factor Xa inhibitor</td>
<td></td>
</tr>
<tr>
<td>Apixaban (n=234)</td>
<td>79.5 (74.0–84.3)</td>
</tr>
<tr>
<td>Rivaroxaban (n=199)</td>
<td>84.4 (78.9–88.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male (n=231)</td>
<td>81.8 (76.5–86.4)</td>
</tr>
<tr>
<td>Female (n=202)</td>
<td>81.7 (75.9–86.5)</td>
</tr>
<tr>
<td>Primary intracranial hemorrhage site</td>
<td></td>
</tr>
<tr>
<td>Intracerebral (n=172)</td>
<td>73.3 (66.3–79.4)</td>
</tr>
<tr>
<td>Subarachnoid (n=68)</td>
<td>85.3 (75.5–92.2)</td>
</tr>
<tr>
<td>Subdural (n=193)</td>
<td>88.1 (83.0–92.1)</td>
</tr>
<tr>
<td>Hemorrhage mechanism</td>
<td></td>
</tr>
<tr>
<td>Traumatic (n=265)</td>
<td>81.9 (76.9–86.2)</td>
</tr>
<tr>
<td>Spontaneous (n=168)</td>
<td>81.5 (75.2–86.8)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>&lt;65 (n=54)</td>
<td>77.8 (65.4–87.2)</td>
</tr>
<tr>
<td>65–75 (n=106)</td>
<td>87.7 (80.5–92.9)</td>
</tr>
<tr>
<td>&gt;75 (n=273)</td>
<td>80.2 (75.2–84.6)</td>
</tr>
<tr>
<td>Prothrombin complex concentrate administered</td>
<td></td>
</tr>
<tr>
<td>Activated prothrombin complex concentrate (n=118)</td>
<td>88.1 (81.4–93.0)</td>
</tr>
<tr>
<td>Four-factor prothrombin complex concentrate (n=315)</td>
<td>79.4 (74.6–83.6)</td>
</tr>
<tr>
<td>Receiving concurrent antiplatelet agents before hospital presentation (n=171)</td>
<td>83.0 (76.9–88.1)</td>
</tr>
</tbody>
</table>
Do we still need warfarin?

• For now, yes
• Today, warfarin is still the anticoagulant of choice for patients with:
  • Mechanical heart valve replacement
  • Mitral stenosis

• Severe renal dysfunction/renal failure (??)
NOACs in End-Stage Renal Disease

The Bad News for Hemodialysis Patients

Oral Anticoagulation for Patients With Atrial Fibrillation on Long-Term Dialysis

The Better News for CKD Patients with AFib

• In patients with CKD but CrCl >25 mL/min, apixaban caused less bleeding than warfarin

• Apixaban 5 mg BID (as opposed to 2.5 mg BID) worked well in this population, with fewer events & no excessive bleeding

Dual vs Triple Therapy for Afib after PCI

Lower bleed risk with low-dose NOAC vs warfarin

- PIONEER AF-PCI
  - N=2124 pts with AF after PCI
    - Dual therapy: Low-dose rivaroxaban 15mg daily + P2Y12 (group 1)
    - Triple therapy: Very-low-dose rivaroxaban 2.5mg bid + DAPT (group 2)
    - Triple therapy: Warfarin + DAPT (group 3)
  - *Both rivaroxaban arms → lower risk of TIMI major + minor bleeding vs warfarin*
Risk of bleeding clearly lower with dual therapy (NOAC + Plavix) vs triple therapy (with ASA)

- OR 0.49 (95% CI 0.34-0.72, p<0.001)

Current recommendation: triple therapy for a month after PCI, then stop ASA. Consider stopping Plavix after 6-12 months.
ACS with Atrial Fibrillation

Pts on Plavix/Ticagrelor, ASA:

NOAC vs Warfarin?

*Apixaban is superior to Warfarin.* After 30 days, ASA increases bleeding events, but no longer decreases ischemic events (so should be stopped).

Continue with NOAC + Plavix/Ticagrelor

COMPASS: Use of NOACs in Stable CAD, without AFib

- N=27,395 pts, stable ischemic CAD or PAD
  - ASA 100 mg monotherapy vs low-dose rivaroxaban 5 mg bid monotherapy vs very-low-dose rivaroxaban 2.5 mg bid + ASA 100mg → clear winner, trial stopped early for “overwhelming efficacy”
- 1º endpoints: CV death, MI, stroke; bleeding

Eikelboom JW et al. NEJM 2017;377(14)
NOACs in Patients with Stable CAD

COMPASS

Eikelboom JW et al. NEJM 2017;377(14)
NOACs in Patients with Stable CAD & Diabetes

COMPASS: CV Death, MI, CVA

AFIRE Study: Effect of NOAC With vs. Without ASA in Pts with AFib and Stable CAD

• N=2236 pts with stable CAD, h/o PCI or CABG (>1 yr prior)
  • Randomized to Rivaroxaban alone vs. Riva + ASA or Plavix

• 1° efficacy endpoints: CV death, MI, stroke, CVA, revasc.
• 1° safety endpoint: major bleeding

AFib in Patients with stable CAD: Is a NOAC enough, or is ASA necessary?

Yasuda S, et al. NEJM 2019;381:1103
AFIRE Results

- **Primary Efficacy Endpoint:** Noninferior

- **Primary Safety Endpoint:** Superior for NOAC alone.

- (So why use ASA at all?)

Yasuda S, et al. NEJM 2019;381:1103
Rivaroxiban vs Enoxaparin after Orthopedic Surgery for Prevention of VTE Events

Risk ratio, 0.25 (95% CI, 0.09–0.75) P=0.01 for superiority

No. at Risk, According to Intended Treatment Period

<table>
<thead>
<tr>
<th></th>
<th>2 Wk to 1 mo</th>
<th>1 Mo to 2 mo</th>
<th>&gt;2 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enoxaparin</td>
<td>Enoxaparin</td>
<td>Enoxaparin</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Rivaroxaban</td>
<td>Rivaroxaban</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>No.</td>
<td>1070</td>
<td>677</td>
<td>51</td>
</tr>
<tr>
<td>Follow-up (days)</td>
<td>15</td>
<td>604</td>
<td>44</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>5</td>
<td>79</td>
<td>42</td>
</tr>
<tr>
<td>Patients</td>
<td>5</td>
<td>78</td>
<td>41</td>
</tr>
</tbody>
</table>

Samama CM, NEJM 2020;382:20
NOACs: Treatment for PE and VTE

Current standard of care:
- LMWH + warfarin > 5 d
  - LMWH 5 d
  - LMWH 5 d

LMWH initially then switch:
- LMWH 5 d
  - Dabigatran (150 mg BD)
  - Edoxaban daily (60 mg or 30 mg)

Single oral agent:
- Apixaban 10 mg BD 1 wk
  - Apixaban (5 mg BD)
  - Apixaban (2.5 mg BD)
- Rivaroxaban 15 mg BD 3 wk
  - Rivaroxiban (20 mg daily)
  - Rivaroxiban (20 mg daily)

Initial treatment Acute/long term treatment (3 mo) Extended treatment (12 mo)
Extended Duration Rivaroxaban Treatment After Hospitalization

28% reduction in fatal and major T-E events, including VTE, MI, stroke, and death. Patients were treated with Riva 10 mg qd for 45 days post discharge.

No increased risk of bleeding.

JACC 2020;75:3140-7
Conclusions

• NOACs have less intracranial bleeding than warfarin
• Equivalent or lower MACE compared to warfarin
• Not for mechanical heart valves/mod-severe MS (at this time)
• PCC & Andexanet appear useful to stem serious bleeding

• New and evolving regimens
  • post-PCI and also stable CAD with AFib (rivaroxaban)
  • post-PCI with CAD and also AFib with CKD (apixaban)
  • Long-term prevention of T-E events after hospitalization (Riva)
"I suppose, stranger, that flying for a major airline makes you think you’re something special"