Is There a Role For Pharmacokinetic/Pharmacodynamics Guided Dosing For Novel Anticoagulants?

Christopher Granger
Disclosures

- Research contracts: Armetheon, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Janssen, Novartis, GSK, Pfizer, The Medicines Company, AHA, FDA, NIH

- Consulting/Honoraria: AstraZeneca, GSK, BMS, Janssen, Pfizer, Lilly, Daiichi Sankyo, Novartis, Boehringer Ingelheim, The Medicines Company, and Sanofi-Aventis

- For full listing see www.dcri.duke.edu/research/coi.jsp
Setting the stage

- Lessons from warfarin experience
- Lessons from NOAC trials
  - It is possible to dose too low
  - PK-directed dosing does not assure success
- What is happening in practice?
“Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. ... What if figuring out the right dose of medicine was as simple as taking our temperature?”
“The best way to dose a drug is to use the dose as it was proven to be beneficial in large randomized outcome trials”
What have we learned from warfarin?
Background

- Anticoagulation with dose-adjusted warfarin is effective to prevent stroke among patients with atrial fibrillation
- There is a relationship between INR and risk of thrombosis and of bleeding
Efficacy and Safety with Warfarin

Narrow Therapeutic Window

Odds Ratio

International Normalized Ratio

Ischemic Stroke

Intracranial Bleeding

Duke Clinical Research Institute

ACC/AHA/ESC JACC 2006

Wan Y. Circ Outcomes 2008
Poor Control of INR with VKA Therapy in U.S.

Quest Diagnostics: 138,319 pts with 2,683,674 INRs, overall TTR 54%
In North America, non-rheumatic AF, CHADS\(_2\) ≥ 2, 52% on OAC
What have we learned from NOAC trials?
Overview of 4 Trials of Novel Agents vs Warfarin in 72,000 Patients (Lancet December 2013)

- Hemorrhagic Stroke: Risk Ratio (95% CI) 0.49 (0.38 - 0.64), p<0.0001
- All-Cause Mortality: Risk Ratio (95% CI) 0.90 (0.85 - 0.95), p=0.0003

Heterogeneity p=NS for all outcomes

What was done in the NOAC vs warfarin trials regarding NOAC dosing?
NOAC dosing strategies in trials

- Number of times a day (affects both peak and trough levels)
- Number of doses tested (in randomized comparison)
- Adjustment of dose for baseline factors related to
  - Anticipated (modeled) drug exposure
  - Risk of bleeding
- Adjustment of dose during the trial
## Dosing in NOAC vs Warfarin Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose(s)</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td></td>
<td>150 mg, 110 mg</td>
<td>20 mg</td>
<td>5 mg</td>
<td>60 mg, 30 mg</td>
</tr>
<tr>
<td>Frequency</td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>Dose Adjustment</td>
<td>No</td>
<td>20 $\rightarrow$ 15</td>
<td>5 $\rightarrow$ 2.5</td>
<td>60 $\rightarrow$ 30, 30 $\rightarrow$ 15</td>
</tr>
<tr>
<td>% reduced at baseline</td>
<td>0</td>
<td>21</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>% reduced after randomization</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>9</td>
</tr>
</tbody>
</table>

# Dose Adjustment Criteria in Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE AF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose Adjustment</strong></td>
<td>No</td>
<td>20 → 15</td>
<td>5 → 2.5</td>
<td>60 → 30</td>
</tr>
<tr>
<td><strong>Dose reduction criteria</strong></td>
<td>--</td>
<td>CrCl 30-49</td>
<td>2 of 3:</td>
<td>CrCl 30–50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age ≥ 80 years</td>
<td>wgt ≤60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>wgt ≤ 60 kg</td>
<td>Strong P-gp inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cr ≥ 1.5 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

Did the dose reduction “work”?
ENGAGE AF TIMI 48: Major Bleeding (% / Year)
High Dose Edoxaban vs Warfarin (on treatment)

No Dose Reduction: HR 0.88 (0.76 - 1.03)
Dose Reduction: HR 0.63 (0.50 - 0.81)  \( P_{int} = 0.02 \)
ENGAGE AF TIMI 48: Stroke or SE (% / Year)
High Dose Edoxaban vs Warfarin (on treatment)

No Dose Reduction: HR 0.78 (0.61 - 0.99)
Dose Reduction: HR 0.81 (0.58 - 1.13)  Pint = 0.85
Reduced-dose Apixaban in ARISTOTLE

Stroke/SE interaction p-value = 0.22
Major bleeding interaction p-value = 0.21

831 (4.6%)
Apixaban 2.5 mg BID vs Warfarin

17,370 (95.4%)
Apixaban 5 mg BID vs Warfarin

Dosing was specifically guided by PK in the RE-ALIGN trial
Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D.,

...tion of the initial dabigatran dose (150, 220, or 300 mg twice daily) was based on kidney function. Doses were adjusted to obtain a trough plasma level of at least 50 ng per milliliter. The warfarin dose was adjusted to obtain an international normali-

Trough plasma concentrations of dabigatran were measured using the Hemoclot® assay (Hyphen Biomed, France) at 1, 2, 4 and 12 weeks and thereafter at 6-monthly intervals. If a patient was found to have a level <50ng/mL during the first 1 to 2 weeks of treatment the dose of dabigatran was increased to the next higher dose. If a patient had a plasma level <50ng/mL (confirmed on repeat testing) despite receiving dabigatran at the highest dose of 300mg twice daily or a plasma level of 250ng/mL or higher despite receiving 150mg twice daily, the patient was switched to warfarin. Dosing was based on trough dabigatran concentrations because of
Under-dosing of oral anticoagulants is common
### NOAC Prescription Data

In practice, an unexpectedly high proportion of prescriptions for apixaban, rivaroxaban and dabigatran are given at lower doses.

<table>
<thead>
<tr>
<th>Country</th>
<th>Apixaban Q4 2014</th>
<th>Rivaroxaban Q4 2014</th>
<th>Dabigatran Q4 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>24% 76%</td>
<td>6% 21% 73%</td>
<td>16% 0% 84%</td>
</tr>
<tr>
<td>Japan</td>
<td>58% 42%</td>
<td>55% 45% 0%</td>
<td>40% 60% 0%</td>
</tr>
<tr>
<td>Germany</td>
<td>41% 59%</td>
<td>4% 34% 61%</td>
<td>2% 61% 37%</td>
</tr>
<tr>
<td>Canada</td>
<td>38% 62%</td>
<td>6% 26% 68%</td>
<td>1% 52% 47%</td>
</tr>
<tr>
<td>Australia</td>
<td>39% 61%</td>
<td>2% 30% 68%</td>
<td>0% 63% 37%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>42% 58%</td>
<td>6% 22% 71%</td>
<td>3% 51% 46%</td>
</tr>
<tr>
<td>Spain</td>
<td>37% 63%</td>
<td>5% 33% 63%</td>
<td>3% 60% 38%</td>
</tr>
<tr>
<td>France</td>
<td>46% 54%</td>
<td>0% 0% 0%</td>
<td>0% 0% 0%</td>
</tr>
<tr>
<td>Belgium</td>
<td>30% 70%</td>
<td>2% 42% 56%</td>
<td>0% 60% 40%</td>
</tr>
<tr>
<td>Italy</td>
<td>35% 65%</td>
<td>2% 37% 61%</td>
<td>0% 63% 36%</td>
</tr>
</tbody>
</table>

Data source: IMS MIDAS and CSD GERS(France) data.
Are lower doses of NOACs less effective at preventing stroke?
Stroke or Systemic Embolism

Dabigatran 110 vs. Warfarin

- Non-inferiority p-value: <0.001
- Superiority p-value: 0.34

Dabigatran 150 vs. Warfarin

- Non-inferiority p-value: <0.001
- Superiority p-value: <0.001

Margin = 1.46

HR (95% CI)

Dabigatran better

Warfarin better
ENGAGE AF TIMI 48: Outcomes by dose group

<table>
<thead>
<tr>
<th></th>
<th>Wafarin</th>
<th>Edox LD</th>
<th>Edox HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SE</td>
<td>1.8</td>
<td>2.04</td>
<td>1.57</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.25</td>
<td>1.77</td>
<td>1.25</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.43</td>
<td>2.75</td>
<td>1.61</td>
</tr>
</tbody>
</table>

low dose edoxaban vs warfarin, HR 1.41, p<0.001

- Warfarin is dose-adjusted using INR, but is systematically under dosed nonetheless
- NOACs are more safe and at least as effective as (well managed) warfarin, based on large trials without individual PK-guided dose adjustment
- There seems to be an irrational tendency to under dose NOACs in practice
- The biggest problem remains the use of very low dose anticoagulants (zero that is)