Lessons Learned from DOAC Claims-based Observational Studies

Thursday | February 24, 2022 | 11:00am EST

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Disclosures & Notification of Support

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_The speakers have the following relevant financial relationships with commercial interests:_

Arthur Allen
Astra-Zeneca | Boehringer-Ingelheim | Janssen

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Katherine Murray
Metabolic Technologies Inc.

Wayne Ray
None

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Aspen Pharma | Bayer | BMS/Pfizer Alliance | Leo Pharma | Novartis | Portola | Servier
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Rivaroxaban vs. Apixaban in Atrial Fibrillation

JAMA | Original Investigation

Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation

Wayne A. Ray, PhD; Cecilia P. Chung, MD, MPH; C. Michael Stein, MB, ChB; Walter Smalley, MD, MPH; Eli Zimmerman, MD; William D. Dupont, PhD; Adriana M. Hung, MD, MPH; James R. Daugherty, MS; Alyson Dickson, MA; Katherine T. Murray, MD
• Apixaban and Rivaroxaban are most common oral anticoagulants
• Similar mechanism of action and elimination half-lives
  • Apixaban: 8-15hr
  • Rivaroxaban: 9-13hr

Do the relative peak concentration differences lead to different bleeding outcomes?
Methods – Data, Inclusion, Exclusion

- US Medicare Claims
  - Hospital stay, outpatient visits, pharmacy, nursing home claims
  - Must have Parts A & B (Fee-for-service) AND Part D (Prescription Drug)
  - Continuous enrollment for 1 year prior to prescription
- Age 65+ years of age with complete demographics
- 1+ fill of rivaroxaban or apixaban
  - Rivaroxaban 20mg daily, 15mg daily
  - Apixaban 5mg twice daily, 2.5mg twice daily
- Atrial fibrillation diagnosis code
- January 2013 through November 2018

Exclusions:
- Terminal illness
- Long-term care residence
- Mitral valve stenosis
- Severe kidney disease (stage 4-5 or ESRD)
- Prior use of oral anticoagulation in past 12 months
- Recent stroke or bleeding-related hospitalization (within 30 days)

JAMA 2021;326:2395-2404
Methods – Follow Up and Outcome Measures

- Cohort was followed for up to 4 years
  - Reasons to stop follow up (censor)
    - Any anticoagulation supply gap of 30+ days
    - Fill of different anticoagulant
    - Change in anticoagulant dose
    - Develop CKD stage 4, 5, ESRD
    - Loss of Medicare FFS coverage
    - Study outcome
    - Death

- Outcome Measures
  - Major ischemic or hemorrhagic events (primary)
    - Ischemic stroke
    - Systemic embolism
    - Hemorrhagic stroke
    - Intracranial bleed
    - Fatal extracranial bleed (death within 30 days)
  - Non-fatal bleeding
  - All-cause mortality
    - Including fatal ischemic or hemorrhagic events
  - Hospital principal discharge code

JAMA 2021;326:2395-2404
Methods – Statistical Analysis

• Propensity score analysis – inverse probability of treatment weights
  • 208 covariates included (demographics, comorbidities, medications)

JAMA 2021;326:2395-2404
Dtsch Arztebl Int 2016;113:597-603
## Results – Table 1 (Weighted)

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n=227,572)</th>
<th>Apixaban (n=353,879)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-reduced</td>
<td>23.2%</td>
<td>23.1%</td>
</tr>
<tr>
<td>Mean age</td>
<td>77 (7.1)</td>
<td>77 (7.0)</td>
</tr>
<tr>
<td>Men</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Non-white</td>
<td>7.6%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Cardiologist prescribed</td>
<td>49.8%</td>
<td>49.6%</td>
</tr>
<tr>
<td>Mean CHA₂DS₂-VASc</td>
<td>4.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Prior Stroke</td>
<td>9.3%</td>
<td>9.2%</td>
</tr>
<tr>
<td>CKD</td>
<td>16.3%</td>
<td>16.3%</td>
</tr>
<tr>
<td>PPI Use</td>
<td>31.0%</td>
<td>31.0%</td>
</tr>
<tr>
<td>NSAID Use</td>
<td>16.7%</td>
<td>16.7%</td>
</tr>
<tr>
<td>P2Y12 Use</td>
<td>16.0%</td>
<td>16.0%</td>
</tr>
</tbody>
</table>

JAMA 2021;326:2395-2404
## Results – Primary Outcome

### Figure 2. Primary Outcome in a Study of the Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Rivaroxaban (per 1000-pt-yr)</th>
<th>Apixaban (per 1000-pt-yr)</th>
<th>Rate Diff</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major ischemic or hemorrhagic event (primary)</td>
<td>16.1</td>
<td>13.4</td>
<td>2.7 (1.9-3.5)</td>
<td>1.18 (1.12-1.24)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>8.6</td>
<td>7.6</td>
<td>1.1 (0.5-1.7)</td>
<td>1.12 (1.04-1.20)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>7.5</td>
<td>5.9</td>
<td>1.6 (1.1-2.1)</td>
<td>1.26 (1.16-1.36)</td>
</tr>
<tr>
<td>Non-fatal Bleeding</td>
<td>39.7</td>
<td>18.5</td>
<td>21.1 (20.0-22.3)</td>
<td>2.07 (1.99-2.15)</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>44.2</td>
<td>41.0</td>
<td>3.1 (1.8-2.5)</td>
<td>1.06 (1.02-1.09)</td>
</tr>
</tbody>
</table>
Results – Outcomes by Medication Dose

Figure 3. Outcomes by Medication Dose in a Study of the Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Atrial Fibrillation

**Reduced Dose**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate per 1000 person-years</th>
<th>Rate difference (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>Favors rivaroxaban</th>
<th>Favors apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major ischemic/hemorrhagic event</td>
<td>27.4</td>
<td>21.0</td>
<td>6.4 (4.1 to 8.7)</td>
<td>1.28 (1.16 to 1.40)</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>15.5</td>
<td>11.9</td>
<td>3.6 (1.9 to 5.3)</td>
<td>1.27 (1.13 to 1.44)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>11.9</td>
<td>9.1</td>
<td>2.8 (1.3 to 4.3)</td>
<td>1.28 (1.11 to 3.00)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal extracranial bleeding</td>
<td>57.5</td>
<td>22.5</td>
<td>35.0 (31.9 to 38.1)</td>
<td>2.44 (2.26 to 34.0)</td>
<td></td>
</tr>
<tr>
<td>Total mortality</td>
<td>87.0</td>
<td>82.7</td>
<td>4.2 (-0.1 to 8.6)</td>
<td>1.02 (0.97 to 1.06)</td>
<td></td>
</tr>
<tr>
<td>Fatal ischemic/hemorrhagic event</td>
<td>8.5</td>
<td>6.2</td>
<td>2.3 (1.1 to 3.6)</td>
<td>1.35 (1.14 to 1.59)</td>
<td></td>
</tr>
<tr>
<td>Other death during follow-up</td>
<td>78.4</td>
<td>76.5</td>
<td>1.9 (-2.3 to 6.0)</td>
<td>1.00 (0.95 to 1.05)</td>
<td></td>
</tr>
</tbody>
</table>

**Standard Dose**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate per 1000 person-years</th>
<th>Rate difference (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>Favors rivaroxaban</th>
<th>Favors apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major ischemic/hemorrhagic event</td>
<td>13.2</td>
<td>11.4</td>
<td>1.8 (1.0 to 2.6)</td>
<td>1.13 (1.06 to 1.21)</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>6.8</td>
<td>6.4</td>
<td>0.5 (-0.1 to 1.0)</td>
<td>1.05 (.96 to 1.14)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>6.3</td>
<td>5.0</td>
<td>1.3 (0.8 to 1.8)</td>
<td>1.25 (1.14 to 1.37)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal extracranial bleeding</td>
<td>35.0</td>
<td>17.5</td>
<td>17.5 (16.3 to 18.7)</td>
<td>1.94 (1.85 to 2.03)</td>
<td></td>
</tr>
<tr>
<td>Total mortality</td>
<td>32.9</td>
<td>29.7</td>
<td>3.1 (1.9 to 4.4)</td>
<td>1.08 (1.04 to 1.12)</td>
<td></td>
</tr>
<tr>
<td>Fatal ischemic/hemorrhagic event</td>
<td>3.4</td>
<td>2.5</td>
<td>0.9 (0.5 to 1.3)</td>
<td>1.33 (1.17 to 1.51)</td>
<td></td>
</tr>
<tr>
<td>Other death during follow-up</td>
<td>29.4</td>
<td>27.2</td>
<td>2.2 (1.0 to 3.4)</td>
<td>1.06 (1.01 to 1.10)</td>
<td></td>
</tr>
</tbody>
</table>
• Initiation of rivaroxaban associated with higher risk of major ischemic and hemorrhagic events as compared to apixaban
  • Medicare beneficiaries 65+ years old with atrial fibrillation
• Largest cohort to compare DOACs to date in 65+yo Medicare population
• Increased risk of ischemic and hemorrhagic events with rivaroxaban was most pronounced for patients with reduced dose DOAC
Limitations

• Observational study, residual confounding
  • Very robust propensity score

• Claims-based analysis
  • Potential to misclassify exposure and outcomes
  • No data on medication adherence

• No actual drug level data

• Population limited to 65+ with Medicare Parts A/B/D
## RCT vs. Observational Study Interpretation

<table>
<thead>
<tr>
<th></th>
<th>Randomized Trials</th>
<th>Observational Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unmeasured Confounding</strong></td>
<td>Should not exist</td>
<td>Always a concern</td>
</tr>
<tr>
<td>- Selection bias</td>
<td>- Eligible for both treatments</td>
<td>- Why was a treatment given?</td>
</tr>
<tr>
<td><strong>Sample Size/Power</strong></td>
<td>Usually limited</td>
<td>Often larger</td>
</tr>
<tr>
<td><strong>Internal Validity</strong></td>
<td>Very high</td>
<td>May be a concern</td>
</tr>
<tr>
<td></td>
<td>- Known that treatment is given</td>
<td>- Did treatment actually happen?</td>
</tr>
<tr>
<td></td>
<td>- High quality comorbidity and medication data</td>
<td>- Are comorbidities &amp; other meds accurate?</td>
</tr>
<tr>
<td></td>
<td>- Available laboratory data</td>
<td>- Can claims assess severity? Are they accurate?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- No lab data for most claims</td>
</tr>
<tr>
<td><strong>External Validity/Generalizability</strong></td>
<td>Can be limited</td>
<td>May or may not be limited</td>
</tr>
<tr>
<td></td>
<td>- Many inclusion/exclusion criteria</td>
<td>- Often fewer inclusion/exclusion criteria</td>
</tr>
<tr>
<td><strong>Follow up/Loss to Follow Up</strong></td>
<td>Usually complete, can be longer-term</td>
<td>Average follow up often shorter</td>
</tr>
</tbody>
</table>

JACC: Cardiovasc Interv 2008;1:211-217
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- Antithrombotic Therapy after Open Revascularization

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**Faculty**
- Geoffrey Barnes, MD, MSc
- Snehal Bhatt, PharmD
- Brett Carroll, MD
- Naomi Hamburg, MD, MS
- Sonya Noor, MD
- Sahil Parikh, MD
- Deborah Siegal, MD, MSc, FRCPC
- Mitchell Weinberg, MD, MBA
- Diane Wirth, ANP, CACP

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- Updated twice monthly
- Most important articles starred
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- Abstract can be read on site
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http://acforum-excellence.org/
Non-Medical Switching

• AC Forum has been actively participating on this topic
  • Social media posts and reposts
  • Communicating with our members
  • Dr. Barnes has met with ACC & CVS

• Follow-up meeting between ACC and CVS March 8th

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- Common Indications: Venous thromboembolism
- Patient Education
- Invasive Procedure Planning
- VTE Prophylaxis
- Special Situations
- Cardiac Valves and Circulatory Support
- Managing Bleeding &: Other Unexpected Situations
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