Apixaban versus Heparin/Vitamin K Antagonist in Anticoagulation-naïve Patients with Atrial Fibrillation Scheduled for Cardioversion: The EMANATE Trial

Michael D. Ezekowitz, Professor, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA and Lankenau Heart Center, Wynnewood, PA and Bryn Mawr Hospital, Bryn Mawr, PA; Co Chair Executive Committee EMANATE on behalf of co-authors Charles V. Pollack, Jonathan L. Halperin, Richard D. England, Sandra VanPelt Nguyen, Judith Spahr, Maria Sudworth, Nilo Cater, Andrei Breazna, Jonas Oldgren, Paulus Kirchhof, for the EMANATE investigators
Disclosures

• Michael D. Ezekowitz has received consulting fees from Boehringer Ingelheim, Armetheon, Pfizer, Sanofi, Bristol-Myers Squibb, Portola, Daiichi-Sankyo, Medtronic, Johnson & Johnson, and Janssen Scientific Affairs; grant support from Boehringer Ingelheim, Pfizer, and Bristol-Myers Squibb

• Co-PI PETRO, RE-LY, X-VeRT, EMANATE; Executive Committee ENSURE-AF, ENGAGE-AF.
The goal of anticoagulation in the setting of cardioversion is to prevent stroke and systemic embolism without causing bleeding.

Post hoc analyses of cardioversions in the RE-LY, ARISTOTLE, ROCKET-AF and ENGAGE-AF trials found low event rates.\textsuperscript{1-4} A limitation was the prolonged period of pre-cardioversion anticoagulation.

To evaluate more immediate cardioversion, prospective trials comparing rivaroxaban (X-VeRT)\textsuperscript{5} and edoxaban (ENSURE-AF)\textsuperscript{6} against heparin/VKA in patients undergoing cardioversion found comparable efficacy and safety with low event rates.

Objectives of EMANATE

• To prospectively compare the outcomes of stroke, systemic embolism, major bleeding, and clinically relevant non-major (CRNM) bleeding in patients with < 48 hrs anticoagulation who were randomized to apixaban or heparin/VKA in an open-label trial with blinded endpoint adjudication.

• To gain insight into the role of image guidance.

• To assess the value of a loading dose of apixaban in patients rapidly transitioned to cardioversion.
### Key Eligibility Criteria

#### Key Inclusion Criteria
- Anticoagulation-naïve patients with AF ( <48 hours of parenteral and/or oral anticoagulation) indicated for cardioversion.

#### Key Exclusion Criteria
- Contraindications to apixaban or heparin/VKA
- Mitral stenosis or previous valve surgery
- Other conditions requiring anticoagulation
- Dual antiplatelet therapy
Study Design

- **Study Design**

  - **Screening/randomization**: 1:1
  - **Cardioversion**: Apixaban 5.0 mg twice daily (2.5 mg BID if down-titrated)
  - **Treatment begins**: Heparin/VKA (usual care)
  - **Imaging**

**Follow-up**:
- If cardioverted: follow-up was 30+/- 7 days
- If not cardioverted: follow-up was 90 days
Apixaban Loading Dose Option

- In patients randomized to apixaban, cardioversion could be performed 2 hours after a loading dose of 10 mg (reduced to 5 mg if 2 of the following present: age ≥ 80, weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dl [133 micromol/L]).
Patient Disposition (ITT Population)

Randomized (N=1500)

Apixaban (n=753)
- Died (n=2)
- Lost to follow-up (n=0)
- Completed follow-up (n=736, 97.7%)
- Withdrew consent: refused follow-up* (n=15, 2.0%)

Mean Follow-up from randomization to withdrawal was 29 days, range 1-83 days

Heparin/VKA (n=747)
- Died (n=1)
- Lost to follow-up (n=1)
- Completed follow-up (n=730, 97.7%)
- Withdrew consent, refused follow-up* (n=15, 2.0%)

Mean Follow-up from randomization to withdrawal was 23 days, range 1-81 days

* No outcome events occurred.
## Key Baseline Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Apixaban</th>
<th>Apixaban</th>
<th>Heparin/VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=753)</td>
<td>5-mg loading dose (n=11)</td>
<td>10-mg loading dose (n=331)</td>
<td>(n=747)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>64.7 (12.2)</td>
<td>80.5 (7.4)</td>
<td>63.2 (12.2)</td>
<td>64.5 (12.8)</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>248 (32.9)</td>
<td>4 (36.4)</td>
<td>123 (37.2)</td>
<td>250 (33.5)</td>
</tr>
<tr>
<td>Race, white, n (%)</td>
<td>654 (86.9)</td>
<td>10 (90.9)</td>
<td>322 (97.3)</td>
<td>648 (86.7)</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>87.9 (20.6)</td>
<td>69.1 (15.5)</td>
<td>90.2 (21.0)</td>
<td>86.3 (19.8)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>496 (65.9)</td>
<td>9 (81.8)</td>
<td>221 (66.8)</td>
<td>481 (64.4)</td>
</tr>
<tr>
<td>LVEF &lt;40, n (%)</td>
<td>45 (6.0)</td>
<td>0</td>
<td>21 (6.3)</td>
<td>54 (7.2)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>154 (20.5)</td>
<td>1 (9.1)</td>
<td>75 (22.7)</td>
<td>140 (18.7)</td>
</tr>
<tr>
<td>CHA\textsubscript{2}DS\textsubscript{2}-VASc score, mean (SD)</td>
<td>2.4 (1.7)</td>
<td>4.4 (1.8)</td>
<td>2.3 (1.7)</td>
<td>2.4 (1.7)</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min, mean (SD)</td>
<td>79.2 (50.6)</td>
<td>41.0 (13.4)</td>
<td>91.7 (52.1)</td>
<td>78.5 (49.0)</td>
</tr>
</tbody>
</table>
One patient’s adjudicated stroke date was one day prior to randomization; thus at Day 0, only 1499 were at risk for stroke. No patients had SE.

### Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Heparin/VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>752</td>
<td>6145</td>
</tr>
<tr>
<td>Heparin/VKA</td>
<td>747</td>
<td>65</td>
</tr>
</tbody>
</table>

P = 0.0164

5 ischemic, 1 hemorrhagic stroke with 0 systemic embolic events
### Safety Outcomes (Safety Population*, N=1456)

<table>
<thead>
<tr>
<th></th>
<th>Apixaban Total (n=735)</th>
<th>Apixaban Loading Dose Subset (n=342)</th>
<th>Heparin/VKA Total (n=721)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeds</td>
<td>3</td>
<td>(1)</td>
<td>6</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeds</td>
<td>11</td>
<td>(4)</td>
<td>13</td>
</tr>
</tbody>
</table>

*Randomized and received ≥ 1 dose of study medication (by treatment received).
Image-Guided Strategy (n=840)

Thrombus-present (First Image) (n=61) complete follow up, no outcome events

- Apixaban (n=30)
- Heparin/VKA (n=31)

Actual treatment

- Apixaban (n=29)
- Heparin/VKA (n=1)
- Heparin/VKA (n=31)

Repeat Imaging was 37 ± 9 days (mean +/-1SD) after first image

2nd View

- Thrombus (+) (n=11/23)
- Thrombus (-) (n=12/23)
- No further imaging (n=6)
- No further imaging (n=1)
- Thrombus (+) (n=8/18)
- Thrombus (-) (n=10/18)
- No further imaging (n=13)
Summary and Conclusion

- EMANATE evaluated patients scheduled for cardioversion. All received < 48 hrs anticoagulation and 61% were not anticoagulated prior to randomization.

- There were 0 vs 6 strokes in the apixaban vs heparin/VKA group ($p=0.0164^*$), 3 vs 6 major bleeds, 2 vs 1 deaths, and no systemic embolic events in either group.

- Among 342 patients receiving the loading dose of apixaban, there were 0 strokes, 1 major bleed, and 1 death.

- Imaging identified left atrial appendage thrombi in 61 patients; all continued anticoagulation. There were no outcome events. Among those with repeat imaging (37 ± 11 days after the initial imaging) thrombi resolved in 52% vs 56% in the apixaban and heparin/VKA groups.

- Limitation: Like the other prospective cardioversion studies, EMANATE was underpowered.

- We believe the findings observed in EMANATE support the use of apixaban in patients with AF undergoing cardioversion.

*log-rank test
The Executive Committee Acknowledge:

- EMANATE patients and investigators from Belgium, Canada, Denmark, Germany, Israel, Italy, Japan, Korea, Romania, Spain, Sweden, and the United States
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BACK UP
Statistical Assumptions

- Using the ARISTOTLE hypothesis of a non-inferiority margin of 1.38 and accounting for the short follow-up of between 30 and 90 days, and the event rate of 0.75 – 1.00% we estimated that approximately 40,000 patients would have to be recruited to achieve a statistically valid study.