Apixaban vs VKA and Aspirin vs Placebo in Patients with Atrial Fibrillation and ACS/PCI: The AUGUSTUS Trial

Renato D. Lopes, MD, PhD
on behalf of the AUGUSTUS Investigators
Background

- The optimal antithrombotic regimen for patients with atrial fibrillation (AF) who have an acute coronary syndrome (ACS) or require percutaneous coronary intervention (PCI) is unclear.
- Prior studies were designed to identify strategies to reduce the bleeding associated with triple antithrombotic therapy:
  - WOEST (n=573): less bleeding AND fewer ischemic events without aspirin compared with vitamin K antagonist (VKA) + dual antiplatelet therapy (DAPT).
  - PIONEER AF-PCI (n=2124): less bleeding with two reduced-dose rivaroxaban regimens compared with VKA + DAPT.
  - RE-DUAL PCI (n=2725): less bleeding with two standard-dose dabigatran regimens, without aspirin, compared with VKA + DAPT.
- There are limited data with apixaban in patients with AF requiring DAPT.
- Data on the independent effects of aspirin in this population are needed.

Two Independent Hypotheses

In patients with AF and ACS or PCI on a P2Y₁₂ inhibitor

1. Apixaban is non-inferior to VKA for International Society on Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major (CRNM) bleeding

2. Aspirin is inferior to placebo for ISTH major or CRNM bleeding in patients on oral anticoagulation (OAC)
Inclusion:
- Atrial fibrillation (prior, persistent, >6 hr)
  - Physician decision for OAC
- Acute coronary syndrome or PCI
  - Planned P2Y₁₂ inhibitor for ≥6 months

Exclusion:
- Contraindication to DAPT
- Other reason for VKA (prosthetic valve, moderate / severe mitral stenosis)

Randomize n=4600 patients

Primary outcome: ISTH major / CRNM bleeding
Secondary outcome(s): death / hospitalization, death / ischemic events

# Trial Organization

## EXECUTIVE COMMITTEE
- John Alexander (Chair)
- Renato Lopes (PI)
- Roxana Mehran (USA)
- Christopher Granger (USA)
- Shaun Goodman (Canada)
- Harald Darius (Germany)
- Stephan Windecker (Switzerland)
- Ronald Aronson (BMS)

## DATA SAFETY MONITORING BOARD
- Lars Wallentin (Chair)
- Robert Harrington
- Stuart Pocock
- Statistical Support—Uppsala Clinical Research

## CLINICAL EVENTS CLASSIFICATION (CEC) COMMITTEE
- Duke Clinical Research Institute

## ACADEMIC COORDINATING CENTER
- Duke Clinical Research Institute

## CONTRACT RESEARCH ORGANIZATION
- Pharmaceutical Product Development (PPD)

## SPONSORS
- Bristol-Myers Squibb/Pfizer
Participating Countries and Number of Patients
Primary Outcome

• ISTH major bleeding
  – Results in death
  – Occurs in critical area or organ
  – Results in hemoglobin drop ≥2 g/dL
  – Requires transfusion of ≥2 units of whole blood or packed red blood cells

• Clinically relevant non-major bleeding
  – Results in hospitalization
  – Requires medical / surgical evaluation or intervention
  – Requires physician-directed change in antithrombotic regimen

Secondary Outcomes

• Death or Hospitalization

• Death or Ischemic Events
  – Stroke, myocardial infarction, stent thrombosis (definite or probable), urgent revascularization

Statistical Analysis—Hierarchical Testing

Apixaban vs. VKA:
- Major / CRNM Bleeding\(^{\text{NI then Sup}}\)
- Death / Hospitalization\(^{\text{Sup}}\)
- Death / Ischemic Events\(^{\text{Sup}}\)

Placebo vs. Aspirin:
- Major / CRNM Bleeding\(^{\text{Sup}}\)
- Death / Hospitalization\(^{\text{Sup}}\)
- Death / Ischemic Events\(^{\text{Sup}}\)

NI = non-inferiority; Sup = superiority
CONSORT Diagram

Total Randomized
N=4614

OAC

- Randomized to Apixaban
  N=2306
  - Study Drug Discontinuation: 291 (12.6%)
  - Lost to Follow-up: 6 (0.3%)
  - Withdrawal of Consent: 29 (1.3%)

- Randomized to VKA
  N=2308
  - Study Drug Discontinuation: 311 (13.5%)
  - Lost to Follow-up: 7 (0.3%)
  - Withdrawal of Consent: 46 (2.0%)

Aspirin/Placebo

- Randomized to Aspirin
  N=2307
  - Study Drug Discontinuation: 385 (16.7%)
  - Lost to Follow-up: 5 (0.2%)
  - Withdrawal of Consent: 43 (1.9%)

- Randomized to Placebo
  N=2307
  - Study Drug Discontinuation: 337 (14.6%)
  - Lost to Follow-up: 8 (0.3%)
  - Withdrawal of Consent: 30 (1.3%)
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=4614)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (25th, 75th), years</td>
<td>70.7 (64.2, 77.2)</td>
</tr>
<tr>
<td>Female, %</td>
<td>29.0</td>
</tr>
<tr>
<td>CHA\textsubscript{2}DS\textsubscript{2}-VASc score, mean (SD)</td>
<td>3.9 (1.6)</td>
</tr>
<tr>
<td>HAS-BLED score, mean (SD)</td>
<td>2.9 (0.9)</td>
</tr>
<tr>
<td>Prior OAC, %</td>
<td>49.0</td>
</tr>
<tr>
<td>P2Y\textsubscript{12} inhibitor, %</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>92.6</td>
</tr>
<tr>
<td>Qualifying index event, %</td>
<td></td>
</tr>
<tr>
<td>ACS and PCI</td>
<td>37.3</td>
</tr>
<tr>
<td>ACS and no PCI</td>
<td>23.9</td>
</tr>
<tr>
<td>Elective PCI</td>
<td>38.8</td>
</tr>
</tbody>
</table>
No Significant Interactions Between Randomization Factors

Apixaban / VKA vs. Aspirin / Placebo

- Major / CRNM Bleeding: $P_{\text{interaction}} = 0.64$
- Death / Hospitalization: $P_{\text{interaction}} = 0.21$
- Death / Ischemic Events: $P_{\text{interaction}} = 0.28$
**Major / CRNM Bleeding**

Apixaban vs. VKA

- **HR 0.69, 95% CI 0.58–0.81**
- *P* < 0.001 for non-inferiority
- *P* < 0.001 for superiority
- **ARR=4.2%**
- **NNT=24**

**Cumulative Incidence of Event (%)**

- **VKA: 14.7%**
- **Apixaban: 10.5%**

`ARR: absolute risk reduction
NNT: number needed to treat`
Major / CRNM Bleeding
Aspirin vs. Placebo

HR 1.89, 95% CI 1.59–2.24
P<0.001
ARI=7.1%
NNH=14

Aspirin: 16.1%
Placebo: 9.0%

ARI: absolute risk increase
NNH: number needed to harm
Major / CRNM Bleeding

Apixaban + Placebo vs. VKA + Aspirin:
11.4% absolute risk reduction (NNT=9)
Apixaban: 23.5%
VKA: 27.4%

Death / Hospitalization
Apixaban vs. VKA

HR 0.83, 95% CI 0.74–0.93
P=0.002
ARR=3.9%
NNT=26

ARR: absolute risk reduction
NNT: number needed to treat
Death / Hospitalization
Aspirin vs. Placebo

HR 1.08, 95% CI 0.96–1.21
P=0.20

Aspirin: 26.2%
Placebo: 24.7%
Death / Hospitalization

VKA + Placebo (27.3%)  
Apixaban + Placebo (22.0%)  
Apixaban + Aspirin (24.9%)  
VKA + Aspirin (27.5%)  

Apixaban + Placebo vs. VKA + Aspirin:  
5.5% absolute risk reduction (NNT=18)
## Ischemic Outcomes
### Apixaban vs. VKA

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Apixaban (N=2306)</th>
<th>VKA (N=2308)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death / Ischemic Events (%)</td>
<td>6.7</td>
<td>7.1</td>
<td>0.93 (0.75–1.16)</td>
</tr>
<tr>
<td>Death (%)</td>
<td>3.3</td>
<td>3.2</td>
<td>1.03 (0.75–1.42)</td>
</tr>
<tr>
<td>CV Death (%)</td>
<td>2.5</td>
<td>2.3</td>
<td>1.05 (0.72–1.52)</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td><strong>0.6</strong></td>
<td><strong>1.1</strong></td>
<td><strong>0.50 (0.26–0.97)</strong></td>
</tr>
<tr>
<td>Myocardial Infarction (%)</td>
<td>3.1</td>
<td>3.5</td>
<td>0.89 (0.65–1.23)</td>
</tr>
<tr>
<td>Definite or Probable Stent Thrombosis (%)</td>
<td>0.6</td>
<td>0.8</td>
<td>0.77 (0.38–1.56)</td>
</tr>
<tr>
<td>Urgent Revascularization (%)</td>
<td>1.7</td>
<td>1.9</td>
<td>0.90 (0.59–1.38)</td>
</tr>
<tr>
<td>Hospitalization (%)</td>
<td><strong>22.5</strong></td>
<td><strong>26.3</strong></td>
<td><strong>0.83 (0.74–0.93)</strong></td>
</tr>
</tbody>
</table>
## Ischemic Outcomes
### Aspirin vs. Placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Aspirin (N=2307)</th>
<th>Placebo (N=2307)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death / Ischemic Events (%)</td>
<td>6.5</td>
<td>7.3</td>
<td>0.89 (0.71–1.11)</td>
</tr>
<tr>
<td>Death (%)</td>
<td>3.1</td>
<td>3.4</td>
<td>0.91 (0.66–1.26)</td>
</tr>
<tr>
<td>CV Death (%)</td>
<td>2.3</td>
<td>2.5</td>
<td>0.92 (0.63–1.33)</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>0.9</td>
<td>0.8</td>
<td>1.06 (0.56–1.98)</td>
</tr>
<tr>
<td>Myocardial Infarction (%)</td>
<td>2.9</td>
<td>3.6</td>
<td>0.81 (0.59–1.12)</td>
</tr>
<tr>
<td>Definite or Probable Stent Thrombosis (%)</td>
<td>0.5</td>
<td>0.9</td>
<td>0.52 (0.25–1.08)</td>
</tr>
<tr>
<td>Urgent Revascularization (%)</td>
<td>1.6</td>
<td>2.0</td>
<td>0.79 (0.51–1.21)</td>
</tr>
<tr>
<td>Hospitalization (%)</td>
<td>25.4</td>
<td>23.4</td>
<td>1.10 (0.98–1.24)</td>
</tr>
</tbody>
</table>
Conclusion

In patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a P2Y\textsubscript{12} inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in ischemic events than regimens that included a vitamin K antagonist, aspirin, or both.
Acknowledgement

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Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

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