AUGUSTUS Trial

Friday, May 9, 2019, 12:00 PM ET

Guest Speaker: Renato Lopes, MD, PhD
AUGUSTUS Trial Chief Investigator

AC Forum Moderators:
Tracy Minichiello, MD
Diane Wirth, ANP, CACP
Presenters

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Professor of Medicine  
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Professor of Medicine  
Chief Anticoagulation & Thrombosis Service  
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**Diane Wirth, ANP, CACP**  
Manager Heart Failure Program  
Grady Memorial Hospital  
Atlanta, GA
Antithrombotic Therapy in AFIB and ACS/PCI

Anticoagulation to prevent this:

Dual Antiplatelet therapy after PCI or ACS to prevent this:

Why Dual Antiplatelet Therapy?

**ACS**
- Addition of P2Y12 inhibitor to ASA decreased death and ischemic events

**POST PCI**
- Early failure - stent thrombosis
  - Occurred in 25% of cases of early stents prior to DAPT
  - Results in STEMI usually and 20-30% mortality
  - DAPT reduced rates ≤ 3% at 3 years
- Late failure - instent restenosis
  - Neointimal hyperplasia (excessive healing)
  - < 5% at 12 months, ~ 50% reduction with DES vs BMS
Bleeding After Initiation of Multiple Antithrombotic Drugs, Including Triple Therapy, in Atrial Fibrillation Patients Following Myocardial Infarction and Coronary Intervention, Volume: 126, Issue: 10, Pages: 1185-1193, DOI: (10.1161/CIRCULATIONAHA.112.114967)
Practice Guideline: Full Text

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<tr>
<td>IIa</td>
<td>B-R</td>
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| 5. | In patients with AF at increased risk of stroke (based on CHA₂DS₂-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with a P2Y₁₂ inhibitor (clopidogrel or ticagrelor) and dose-adjusted vitamin K antagonist is reasonable to reduce the risk of bleeding as compared with triple therapy (S7.4-3, S7.4-6-S7.4-8).  
   **NEW:** New RCT data and data from 2 registries and a retrospective cohort study are available. |
| IIb | B-R |
| 6. | In patients with AF at increased risk of stroke (based on CHA₂DS₂-VASc risk score of 2 or greater) and with high-risk stent (drug eluting or bare metal) for ACS (oral anticoagulant and P2Y₁₂ inhibitor) at discrete sites (S7.4-9, S7.4-10).  
   **NEW:** New published data are available. |
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“Less than 10% of the treatment recommendations U.S. doctors rely on to manage care for heart patients are based on evidence gained RCTS”

January CT et al
Trial Design

**Inclusion**
- Atrial fibrillation (prior, persistent, >6 hr)
  - Physician decision for OAC
- Acute coronary syndrome or PCI
  - Planned P2Y_{12} inhibitor for ≥6 months

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

Randomize
n=4600 patients

- **Apixaban 5 mg BID**
  - Apixaban 2.5 mg BID in selected patients

- **VKA** (INR 2–3)
  - Aspirin for all on the day of ACS or PCI
  - Aspirin versus placebo after randomization

**Primary outcome**: ISTH major / CRNM bleeding

**Secondary outcome(s)**: death / hospitalization, death / ischemic events

Median time from the index event to randomization - 6 days

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

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>
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<th>Total (N=4614)</th>
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<tbody>
<tr>
<td>Age, median (25th, 75th), years</td>
<td>70.7 (64.2, 77.2)</td>
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<td>Female, %</td>
<td>29.0</td>
</tr>
<tr>
<td>CHA₂DS₂-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>P2Y₁₂ inhibitor, %</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>92.6</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>
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

VKA: 14.7%
Apixaban: 10.5%

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

**Aspirin: 16.1%**

**Placebo: 9.0%**

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

ARI: absolute risk increase
NNH: number needed to harm

NNT=14
Major / CRNM Bleeding

VKA + Aspirin (18.7%)
Apixaban + Aspirin (13.8%)
VKA + Placebo (10.9%)
Apixaban + Placebo (7.3%)

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

Difference driven by lower hospitalization

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

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><strong>Stroke (%)</strong></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><strong>Hospitalization (%)</strong></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>
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</tbody>
</table>
Conclusion

In patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a P2Y$_{12}$ 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.
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