Combined Antithrombotic Therapy: Is There a Role for it in 2019?

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AF and CAD
Overlapping Patient Populations
Overlapping Indications for Antithrombotic Therapy

Challenging

CAD (ACS, PCI/Stent, CABG)

Aspirin (drop?)
Clopidogrel
New P2Y12s
NOACs?

Doses
Stent type
Duration
Bleeding
Subgroups
Genetics
Cost

The art of medicine

Atrial Fibrillation

VKA
Antiplatelets
NOACs

Stroke risk
Bleeding risk
Renal function
Subgroups
Monitoring
Reversal
Cost

Practice guidelines largely based on clinical trials that exclude patients with other diseases / indication

Duke Clinical Research Institute
Coronary stenting in patient with AF and high risk of stroke

The problem: You can not simultaneously prevent all three!

- **Stent thrombosis**
- **Stroke**
- **DAPT**
- **OAC**
- **Major Bleeding**
Bewildering Number of Strategies in the ACS Patient with Atrial Fibrillation

- **ASA Dose**: None Low High 2 \(1+8 = 9\) ASA
- **ASA Duration (mos)**: 1 3 6 12 4
- **Thienopyridine**: None Clop Ticlid Pras Ticag 4 \(1+16 = 17\) Thieno
- **Thienopyridine duration (mos)**: 1 3 6 12 4
- **AC**: None Warf Dabi Riva Apix Edox 5 \(1+10 = 11\) ACs
- **AC INR/Dose**: Low High 2

Permutations of Single, Dual or Triple Therapy as *Early Initial Therapy* (0,1,3,6 mos) following ACS: \(9 \times 17 \times 11 = 1,683\)

Permutations of Single or Dual Therapy *Late After Early Therapy* (0,1,3,6 mos) following ACS: 1,683

Total Permutations *throughout one year*: 2.8 Million

*Slide by C. Michael Gibson, M.S., M.D.*
CONCLUSIONS AND RELEVANCE  Among recommendations in major cardiovascular society guidelines, only a small percentage were supported by evidence from multiple RCTs or a single, large RCT. This pattern does not appear to have meaningfully improved from 2008 to 2018.
What evidence is there for NOACs in AF + ACS?

<table>
<thead>
<tr>
<th>Study</th>
<th>Enrollment</th>
<th>Year</th>
<th>Study Type</th>
<th>Anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIONEER AF-PCI¹</td>
<td>N=2,124</td>
<td>2016</td>
<td>Parallel assignment</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>RE-DUAL PCI²</td>
<td>N=2,725</td>
<td>2017</td>
<td>Parallel assignment</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>AUGUSTUS ACS/PCI³</td>
<td>N=4,600*</td>
<td>2018</td>
<td>2x2 factorial</td>
<td>Apixaban</td>
</tr>
<tr>
<td>ENTRUST AF-PCI⁴</td>
<td>N=1,500*</td>
<td>2019</td>
<td>Parallel assignment</td>
<td>Edoxaban</td>
</tr>
</tbody>
</table>


*Target enrolment. ACC: American College of Cardiology; AHA: American Heart Association.*
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
INCLUSION
• Atrial fibrillation (prior, persistent, >6 hr)
  – Physician decision for OAC
• Acute coronary syndrome or PCI
  – Planned P2Y<sub>12</sub> inhibitor for ≥6 months

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

Randomize n=4600 patients

EXCLUSION
• Contraindication to DAPT
• Other reason for VKA (prosthetic valve, moderate / severe mitral stenosis)

Apixaban 5 mg BID
Apixaban 2.5 mg BID in selected patients

Aspirin for all on the day of ACS or PCI
Aspirin versus placebo after randomization

Apixaban 2.5 mg BID

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

Participating Countries and Number of Patients

- United States: 507
- Brazil: 318
- Argentina: 285
- Canada: 194
- Mexico: 91
- Colombia: 8
- Peru: 20
- Sweden: 53
- Ukraine: 333
- Russia: 762
- Norway: 27
- Denmark: 36
- Germany: 319
- Poland: 336
- Netherlands: 9
- United Kingdom: 51
- Belgium: 39
- France: 60
- Portugal: 71
- Spain: 67
- Switzerland: 9
- Austria: 19
- Czech Republic: 11
- Croatia: 99
- Slovakia: 189
- Romania: 64
- Israel: 104
- Bulgaria: 154
- Serbia: 136
- Hungary: 95
- India: 24
- South Korea: 106
- Australia: 18
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

Lopes RD, et al. NEJM, 2019
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=4614)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (25&lt;sup&gt;th&lt;/sup&gt;, 75&lt;sup&gt;th&lt;/sup&gt;), years</td>
<td>70.7 (64.2, 77.2)</td>
</tr>
<tr>
<td>Female, %</td>
<td>29.0</td>
</tr>
<tr>
<td>CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-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&lt;sub&gt;12&lt;/sub&gt; 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>

Lopes RD, et al. NEJM, 2019
No Significant Interactions Between Randomization Factors

Apixaban / VKA vs. Aspirin / Placebo

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

Lopes RD, et al. NEJM, 2019
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%

Lopes RD, et al. NEJM, 2019

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

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

Major / CRNM Bleeding

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

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Death / Hospitalization
Apixaban vs. VKA

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

VKA: 27.4%
Apixaban: 23.5%

ARR: absolute risk reduction
NNT: number needed to treat

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Death / Hospitalization
Aspirin vs. Placebo

HR 1.08, 95% CI 0.96–1.21
P=0.20

Aspirin: 26.2%
Placebo: 24.7%

Lopes RD, et al. NEJM, 2019
Death / Hospitalization

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

Lopes RD, et al. NEJM, 2019
## 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>

Lopes RD, et al. NEJM, 2019
## 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>

Lopes RD, et al. NEJM, 2019
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.
Clinical Implications for Clinical Practice

In most patients with atrial fibrillation and a recent acute coronary syndrome or PCI the use of apixaban plus clopidogrel without aspirin should be the preferred antithrombotic regimen whereas regimens that include a VKA plus DAPT should generally be avoided.
Treating Patients with AF and ACS/PCI

- Triple Therapy is not needed for most patients: one antiplatelet plus a new anticoagulant (aspirin out)

- Duration of Combination Therapy for AF patients is key

- Patient management options will be better clarified:
  - Randomized trials
“In medicine, therapeutic decisions should be based on science; the ‘art’ of medicine is in how you interact with the patient.”

- Robert M. Califf MD
Thank you!