ANTITHROMBOTIC THERAPY IN PATIENTS WITH ATRIAL FIBRILLATION POST CORONARY ANGIOPLASTY

Azfar Zaman
Freeman Hospital and Newcastle University
United Kingdom
DECLARATION OF INTERESTS

Relevant to this meeting, I have received consulting and/or lecture fees from:
Bayer
BMS
Pfizer
Boehringer
Sanofi
AFib: a high cost to society

The presence of AF independently increases the risk of mortality and morbidity due to:

- Stroke and thromboembolism\(^1\)
- Congestive heart failure\(^1\)
- Impaired quality of life\(^2\)

Direct cost of AF represented 0.9–2.4% of the UK health-care budget in 2000 and had almost doubled over the previous 5 years.\(^3\)

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Background – AFib + PCI

- AFib prevalence – 1% in under 60 years old, 10% if > 80 years

- of all ACS patients undergoing PCI, up to 20% (range 5-20) have AFib

- strokes in patients with AFib have worse outcomes

Management of patients with AF who undergo PCI must balance the need for thromboprophylaxis with the risk of bleeding.

ACS, acute coronary syndrome; AF, atrial fibrillation; CAD, coronary artery disease; PCI, percutaneous coronary intervention.

Access to PCI in older people is changing over time

PCI = percutaneous coronary intervention.
Different conditions with different outcomes

- atrial fibrillation - thrombus is *fibrin rich*

- PCI - acute coronary syndromes/stent thrombosis – thrombus is *platelet rich*
Known knowns and known unknowns

- OAC superior than DAPT in preventing ischaemic and embolic events in AFib
- DAPT superior to OAC in preventing stent thrombosis
- Triple therapy increases bleeding risk but untested

Connolly et al Lancet 2006;367:1903
Leon et al NEJM 1998;339:1665
What combination of therapy is optimal for patients with AF undergoing PCI?

**AF\(^1\)**
Anticoagulant therapy

For prevention of stroke in patients with additional risk factors\(^1\)

**PCI\(^2\)**
Antiplatelet therapy

For prevention of stent thrombosis following PCI\(^2\). Dual antiplatelet therapy superior to aspirin alone

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**AF and PCI\(^1,2\)**

**Dual therapy:**

anticoagulant + single antiplatelet

**OR**

**Triple therapy:**

anticoagulant + dual antiplatelet

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PCI, percutaneous coronary intervention

An Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention PIONEER AF-PCI

Published on November 14, 2016, at NEJM.org.
DOI: 10.1056/NEJMoa1611594
Primary Endpoint: First Occurrence of Clinically Significant Bleeding Events

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug. Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA.

Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.

Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

Riva + DAPT v. VKA + DAPT
HR=0.59 (95% CI: 0.47-0.76)
p <0.000013
ARR=9.9
NNT=11

Riva + P2Y_{12} v. VKA + DAPT
HR=0.59 (95% CI: 0.47-0.76)
p <0.000013
ARR=9.9
NNT=11

Gibson et al. AHA 2016
Secondary Endpoint: First Occurrence of CV Death, MI or Stroke

- **Cardiovascular Death, Myocardial Infarction, or Stroke (%)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0 Days</th>
<th>30 Days</th>
<th>60 Days</th>
<th>90 Days</th>
<th>180 Days</th>
<th>270 Days</th>
<th>360 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riva + P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
<td>694</td>
<td>648</td>
<td>633</td>
<td>621</td>
<td>590</td>
<td>562</td>
<td>430</td>
</tr>
<tr>
<td>Riva + DAPT</td>
<td>704</td>
<td>662</td>
<td>640</td>
<td>628</td>
<td>596</td>
<td>570</td>
<td>457</td>
</tr>
<tr>
<td>VKA + DAPT</td>
<td>695</td>
<td>635</td>
<td>607</td>
<td>579</td>
<td>543</td>
<td>514</td>
<td>408</td>
</tr>
</tbody>
</table>

- **Riva + P2Y<sub>12</sub> v. VKA + DAPT**
  - HR = 1.08 (95% CI: 0.69-1.68)
  - p = 0.750

- **Riva + DAPT v. VKA + DAPT**
  - HR = 0.93 (95% CI: 0.59-1.48)
  - p = 0.765

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Composite of adverse CV events is composite of CV death, MI, and stroke.

Hazard ratios as compared to VKA group are based on the stratified Cox proportional hazards model.

Log-Rank P-values as compared to the VKA group are based on the stratified two-sided log rank test.

6 Subjects were excluded from all efficacy analyses because of violations in Good Clinical Practice guidelines.

Gibson et al. AHA 2016
Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

Christopher P. Cannon, M.D., Deepak L. Bhatt, M.D., M.P.H., Jonas Oldgren, M.D., Ph.D., Gregory Y.H. Lip, M.D., Stephen G. Ellis, M.D., Takeshi Kimura, M.D., Michael Maeng, M.D., Ph.D., Bela Merkely, M.D., Uwe Zeymer, M.D., Savion Gropper, M.D., Ph.D., Matias Nordaby, M.D., Eva Kleine, M.Sc., Ruth Harper, Ph.D., Jenny Manassie, B.Med.Sc., James L. Januzzi, M.D., Jurrien M. ten Berg, M.D., Ph.D., P. Gabriel Steg, M.D., and Stefan H. Hohnloser, M.D., for the RE-DUAL PCI Steering Committee and Investigators*

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DOI: 10.1056/NEJMoa1708454
RE-DUAL PCI®: composite efficacy endpoint

Probability of event (%)

Time to first event (days)

Pradaxa (combined doses) dual therapy
Warfarin triple therapy

HR: 1.04 (95% CI: 0.84–1.29)
Non-inferiority p = 0.005

* Unplanned revascularization was percutaneous coronary intervention or coronary-artery bypass grafting
**A** Primary End Point in Dual-Therapy Group (110 mg) vs. Triple-Therapy Group

Hazard ratio, 0.52 (95% CI, 0.42–0.63)

P<0.001 for noninferiority

<table>
<thead>
<tr>
<th>Days to First Event</th>
<th>Cumulative Incidence of Event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>90</td>
<td>10</td>
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<tr>
<td>180</td>
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<tr>
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<tr>
<td>540</td>
<td>60</td>
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<tr>
<td>630</td>
<td>70</td>
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<tr>
<td>720</td>
<td>80</td>
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</table>

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Dual therapy (110 mg)</th>
<th>Triple therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>981</td>
<td>898</td>
<td>981</td>
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<td>162</td>
<td>86</td>
<td>124</td>
</tr>
<tr>
<td>86</td>
<td></td>
<td>63</td>
</tr>
</tbody>
</table>
RE-DUAL PCI®: ISTH major or CRNM bleeding

HR: 0.52 (95% CI: 0.42–0.63)
Non-inferiority p < 0.001
Superiority p < 0.001

ARR: 11.5%
Pradaxa 110mg BD dual therapy (n=981)
151 (15.4%)

Warfarin triple therapy (n=981)
264 (26.9%)

ARR, absolute risk reduction; BD, twice daily; CI, confidence interval; CRNM, clinically relevant non-major; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis
RE-DUAL PCI®: ISTH major or CRNM bleeding

HR: 0.72 (95% CI: 0.58–0.88)

Non-inferiority p < 0.001
Superiority p = 0.002

ARR: 5.5%

Pradaxa 150mg BD dual therapy (n=763)

154 (20.2%)

Warfarin triple therapy (n=764)

196 (25.7%)

ARR, absolute risk reduction; BD, twice daily; CI, confidence interval; CRNM, clinically relevant non-major; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis
Decision making

• choice of anticoagulant – data for rivaroxaban and dabigatran

• choice of antiplatelet

• duration of dual strategy

• cessation of antiplatelet therapy
Which antiplatelet?

- Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.

ESC Guidelines 2015
Duration of therapy
Patients with an indication for oral anticoagulation undergoing PCI

Concerns about ischaemic risk prevailing

Concerns about bleeding risk prevailing

Time from treatment initiation

1 mo.

3 mo.

6 mo.

12 mo.

Beyond 12 mo.

A = Aspirin  
C = Clopidogrel  
O = Oral anticoagulation
Strategies to minimise bleeding

- Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA\textsubscript{2}DS\textsubscript{2}-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.

- Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.

- Consider the use of NOACs instead of VKA.

- Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. > 65–70%) when VKA is used.

- Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.\textsuperscript{a}

- Clopidogrel is the P2Y\textsubscript{12} inhibitor of choice.

- Use low-dose (\leq 100 mg daily) aspirin.

- Routine use of PPIs.

\textsuperscript{a} ESC 2017
Summary

• changing demographics will see an increase in AFib in patients with ACS ± PCI
• dual strategy proven to be effective at reducing ischaemic and stroke risk
• important to carefully assess bleeding risk – therapy duration dependent on this
• no role for VKA in this patient population