Current Antithrombotic Strategy in AF Patients Undergoing PCI

Hyung Wook Park
Department of Cardiovascular Medicine
Chonnam National University Hospital, Gwangju, Korea
Coronary stenting in patient with AF and high risk of stroke

Stent thrombosis

Stroke

Antiplatelet + OAC

Bleeding

- Optimal combination (ASA + P2Y12 inhibitor + NOAC (VKA))
- Optimal duration (1, 3, 6, 12 months and life long)
Why is AF with concomitant ACS/PCI challenging to manage?

- Patients with AF and ACS are at high risk of cardiovascular mortality and morbidity
- Patients with AF who have undergone PCI often need DAPT and anticoagulation, which increases the risk of bleeding
- Unplanned PCI in AF patients is also associated with a worsened prognosis compared with patients who did not undergo PCI

Treatment recommendation for the management of NVAF patients with concomitant ACS or undergoing PCI

- Balancing the risk of thromboembolism with the risk of bleeding is particularly important in patients with ACS/PCI
- A number of guidelines provide treatment recommendations, however lack of clinical data has led to uncertainty in the optimal combinations of oral antithrombotic therapies in this population.
Expert consensus

- AF patients at risk for stroke, patients with mechanical valves, and patients with recent or recurrent deep vein thrombosis or pulmonary embolism should continue OAC during and after stenting.

- A short period of triple therapy (OAC, aspirin, clopidogrel) is recommended, followed by a period of dual therapy (OAC plus a single antiplatelet).

2016 ESC guideline – ACS

ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.

*Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients, especially those not receiving a stent or patients at a longer time from the index event.

*OAC plus single antiplatelet.

*Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

AF patient in need of OAC after elective PCI with stent

Bleeding risk low compared to risk for ACS or stent thrombosis

Time from PCI
0
1 month
3 months
6 months
12 months
lifelong

Bleeding risk high compared to risk for ACS or stent thrombosis

Triple therapy\(^a\) (IIaB)

Dual therapy\(^b\) (IIaC)

OAC monotherapy\(^c\) (IB)

OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.

\(^a\) Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients.

\(^b\) OAC plus single antiplatelet.

\(^c\) Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

Expert consensus

- NOAC - consensus recommendation is that the lowest dose effective for stroke prevention in AF

- Dose reduction beyond the approved dosing tested in phase III trials is not currently recommended.

Expert consensus – Prasugrel

Avoid unless there is a clear need for dual antiplatelets (e.g. stent thrombosis on aspirin plus clopidogrel)

Ongoing trials will inform about such combination therapies in the future.

Omit Aspirin; Clopidogrel + OAC

- WOEST (What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting) trial

Primary endpoint; Any bleeding

Secondary endpoint; Death, MI, stroke, TLR, Stent thrombosis

Omit Aspirin; Clopidogrel + OAC

- Although the trial was too small to assess ischaemic outcomes, dual therapy with OAC and clopidogrel may emerge in the future as an alternative to triple therapy in patients with AF and ACS and/or coronary intervention.

Unmet needs in the management of anticoagulation in NVAF patients with ACS/PCI

- There are a number of trials in these areas

<table>
<thead>
<tr>
<th>Trial</th>
<th>NOAC</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIONEER AF-PCI</td>
<td>Rivaroxaban</td>
<td>Completed</td>
</tr>
<tr>
<td>RE-DUAL PCI</td>
<td>Dabigatran</td>
<td>Ongoing</td>
</tr>
<tr>
<td>ENTRUST-AF PCI</td>
<td>Edoxaban</td>
<td>Ongoing</td>
</tr>
<tr>
<td>AUGUSTUS Trial</td>
<td>Apixaban</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

PIONEER AF-PCI, NCT01830543. Available at: www.clinicaltrials.gov
RE-DUAL, NCT02164864. Available at: www.clinicaltrials.gov
ENTRUST AF-PCI, NCT02866175. Available at: www.clinicaltrials.gov
AUGUSTUS, NCT02415400. Available at: www.clinicaltrials.gov
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
Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI

- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke

2100 patients with NVAF
- Coronary stenting
- No prior stroke/TIA, GI bleeding, Hb<10, CrCl<30

≤72 hours after sheath removal

1-1,6, or 12 months after randomization

- Pre randomization MD Choice
- Rivaroxaban 15 mg qd*
  Clopidogrel 75 mg qd†
  
- Rivaroxaban 2.5 mg bid
  Clopidogrel 75 mg qd†
  Aspirin 75-100 mg qd†

- Rivaroxaban 15 mg QD
  Aspirin 75-100 mg qd

- VKA (target INR 2.0-3.0)
  Clopidogrel 75 mg qd†
  Aspirin 75-100 mg qd

- VKA (target INR 2.0-3.0)
  Aspirin 75-100 mg qd

Gibson et al. AHA 2016.
PIONEER AF-PCI study: Bleeding was lower with rivaroxaban plus a P2Y12 inhibitor or DAPT than standard therapy

Rivaroxaban reduced the rates of clinically significant bleeding* compared with standard therapy in 2,124 randomised NVAF patients who had undergone PCI with stenting

<table>
<thead>
<tr>
<th>No. at risk:</th>
<th>Day</th>
<th>Warfarin OD (dose adjusted to achieve INR of 2.0–3.0)</th>
<th>Rivaroxaban (2.5 mg BID)</th>
<th>Rivaroxaban (15 mg OD) + clopidogrel (75 mg OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>30</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>Warfarin OD</td>
<td>696</td>
<td>628</td>
<td>606</td>
<td>585</td>
</tr>
<tr>
<td>Riva (2.5 mg BID)</td>
<td>636</td>
<td>600</td>
<td>579</td>
<td>521</td>
</tr>
<tr>
<td>Riva (15 mg OD)</td>
<td>697</td>
<td>593</td>
<td>555</td>
<td>521</td>
</tr>
</tbody>
</table>

HR for warfarin vs rivaroxaban (15 mg OD) 0.59 (95% CI: 0.47–0.76); p<0.001

HR for rivaroxaban (2.5 mg BID) vs rivaroxaban (15 mg OD) 0.63 (95% CI, 0.50–0.80); p<0.001

Kaplan-Meier Estimates of First Occurrence of CV Death, MI or Stroke

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. at risk</th>
<th>Days</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riva + P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
<td>694 648 633 621</td>
<td>590 562 430</td>
<td>1.08 (0.69-1.68)</td>
<td>0.750</td>
</tr>
<tr>
<td>Riva + DAPT</td>
<td>704 662 640 628</td>
<td>596 570 457</td>
<td>0.93 (0.59-1.48)</td>
<td>0.765</td>
</tr>
<tr>
<td>VKA + DAPT</td>
<td>695 635 607 579</td>
<td>543 514 408</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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, only for the Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.

Log-Rank P-values as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/115 mg QD comparing VKA) two-sided log rank test.

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

CONCLUSION

Among stented AF participants:

1) Rivaroxaban 15 mg daily + P2Y₁₂ monotherapy for one year
2) Rivaroxaban 2.5 mg BID + 1, 6, or 12 months of DAPT

Reduced the risk of clinically significant bleeding as compared with standard of care VKA plus 1, 6, or 12 months of DAPT and yielded comparable efficacy with broad confidence intervals
Interpretation of the PIONEER Results

- Clear signal of less bleeding with both reduced antithrombotic regimens
  - No aspirin (riva 15 + P2Y12)
  - Very low-dose OAC (riva 2.5 + P2Y12 + aspirin)

- Not powered for efficacy and effects on ischemic events were imprecise with wide confidence intervals
  - Stroke:  No Aspirin = HR 1.07, 95% CI 0.39-2.96
    Low-dose OAC = HR 1.36, 95% CI 0.52-3.58
  - Stent thrombosis: No aspirin = HR 1.20, 95% CI 0.32-4.45
    Low-dose OAC = HR 1.44, 95% CI 0.40-5.09

RE-DUAL PCI

Paroxysmal, persistent or permanent NVAF, PCI with stenting [BMS or DES] elective or ACS

Screening
0-120 hours post-PCI

1º End Point
Time to first ISTH major bleeding or clinically relevant non-major bleeding event
n= 2,500 patients (approx. 834 patients per arm)

Dabigatran etexilate 150 mg BID + P2Y12 inhibitor

Dabigatran etexilate 110 mg BID + P2Y12 inhibitor

Warfarin (INR 2.0 – 3.0) + P2Y12 inhibitor + ASA

Patients >80 years living outside of the USA will be assigned to 110mg dabigatran etexilate (BID) or warfarin in a 1:1 ratio

Apixaban Versus Warfarin in Patients with AF and ACS and/or PCI: The AUGUSTUS Trial

**Inclusion**
- AF (prior, persistent/permanent, paroxysmal)
- Physician decision that oral anticoagulation is indicated
- ACS and/or PCI with planned P2Y12 inhibitor for at least 6 months

**Randomize**

\[ n = 4,600 \]

**Patients**

**Exclusion**
- Contraindication to DAPT
- Other reason for warfarin (mechanical valve, mod/sev MS)

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**Apixaban**
- P2Y12 inhibitor for all patients x 6 months
- Aspirin for all on the day of ACS and/or PCI until randomization
- Aspirin versus placebo after randomization

**Warfarin**
- ASA versus placebo

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**Primary outcome:** major/clinically relevant non-major bleeding (through 6 months)
**Secondary objective:** Death, MI, stroke, stent thrombosis, urgent revascularization, re-hospitalization

Primary objectives:
To evaluate the safety and to explore the efficacy of an edoxaban-based antithrombotic regimen versus a VKA-based antithrombotic regimen in subjects with AF following PCI with stent placement

Primary endpoint: major/clinically relevant bleeding (for 12 months)
AF and CAD; Antithrombotic Therapy

CAD (ACS, PCI/Stent, CABG)  Atrial Fibrillation

Aspirin  Clopidogrel  New P2Y12 inhibitor

Doses  Stent type  Duration  Bleeding  Subgroups

VKA  NOACs