NOAC in Patients with PCI

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Introduction

- Between 5–15% of AF patients will undergo PCI in their lives.
- Among patients undergoing PCI, 5 to 8% have AF.
- Oral anticoagulation (OAC) has not been shown to prevent stent thrombosis and dual antiplatelet therapy (DAPT) is ineffective to prevent cardioembolic stroke.
Introduction

- The combination of antithrombotic agents, particularly triple therapy with OAC and DAPT, substantially increases the risk of bleeding.

- Thus, antithrombotic regimen with an acceptable benefit–risk profile would be the best strategy in AF patients with concomitant ACS or PCI.

- In the era of NOAC, several RCTs demonstrated excellent efficacy and safety of dual therapy with NOAC and P2Y12 inhibitor in AF patients undergoing PCI.
Population: patients with paroxysmal, persistent or permanent NVAF undergoing PCI with stent

Decision for DAPT duration: 1, 6 or 12 months

Rivaroxaban 15 mg + P2Y₁₂

Rivaroxaban 2.5 mg BID + DAPT

Rivaroxaban 15 mg OD + low-dose ASA

VKA (INR 2.0–3.0) + DAPT

VKA + low-dose ASA

DAPT duration (1, 6 or 12 months)

End of treatment (12 months)

Primary end point: clinically significant bleeding
Underpowered for comparing the ischemic events

P2Y₁₂ inhibitor → Clopidogrel: 94.4%

DAPT
1 m: 15%
6 m: 35%
12 m: 50%

DAPT
1 m: 16%
6 m: 35%
12 m: 49%
PIONEER AF-PCI

Primary endpoint: clinically significant bleeding

- Triple with VKA 26.7%
- Triple with R 2.5mg bid 18.0%
- Dual with R15mg qd 16.8%

Hazard ratio for group 1 vs. group 3,
0.59 (95% CI, 0.47–0.76)
P<0.001

Hazard ratio for group 2 vs. group 3,
0.63 (95% CI, 0.50–0.80)
P<0.001

PIioneer AF-PCI

Secondary endpoint: major adverse cardiovascular event

- Triple with VKA 6.0%
- Triple with R 2.5mg bid 5.6%
- Dual with R15mg qd 6.5%

Hazard ratio for group 1 vs. group 3:
1.08 (95% CI, 0.69–1.68)
P=0.75

Hazard ratio for group 2 vs. group 3:
0.93 (95% CI, 0.59–1.48)
P=0.76

In subgroup analysis with patients assigned to DAPT for 6 months, there were higher stroke events in the 2.5mg bid rivaroxaban arm compared to triple therapy group with VKA (2.7% vs 0%, p=0.02, data not shown).
**RE-DUAL PCI**

- Primary end point: major or clinically relevant nonmajor bleeding
- Tested for the noninferiority of dual therapy to triple therapy with respect to the incidence of a composite efficacy end point of thromboembolic events (MI, stroke, or systemic embolism), death, or unplanned revascularization.

**Patients with AF undergoing PCI with stenting**

- **Randomization ≤120 hours post-PCI**

**N=2725**

**Dabigatran 150 mg BID + P2Y12 inhibitor**

**Dabigatran 110 mg BID + P2Y12 inhibitor**

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

6-month minimum treatment duration with visits every 3 months for the first year, then visits and telephone contact alternating every 3 months and a 1-month post-treatment visit

**Mean duration of follow-up: ~14 months**
RE-DUAL PCI
Primary Endpoint: ISTH major or clinically relevant non-major bleeding event

HR: 0.52 (95% CI: 0.42–0.63)
Non-inferiority P<0.0001
P<0.0001

HR: 0.72 (95% CI: 0.58–0.88)
Non-inferiority P<0.0001
P=0.002

RE-DUAL PCI
Secondary Endpoint: death, thromboembolic event, or unplanned revascularization

HR: 1.04 (95% CI: 0.84–1.29)
Non-inferiority P=0.0047

Dabigatran (combined doses) dual therapy (n=1744)
Warfarin triple therapy (n=981)

Time to first event (days)

Patients with outcome event (%)
# RE-DUAL PCI

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg dual therapy (n=981)</th>
<th>Warfarin triple therapy (n=981)</th>
<th>D110 DT vs warfarin TT</th>
<th>Dabigatran 150 mg dual therapy (n=763)</th>
<th>Warfarin triple therapy (n=764)</th>
<th>D150 DT vs warfarin TT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>HR (95% CI)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>55 (5.6)</td>
<td>48 (4.9)</td>
<td>1.12 (0.76–1.65)</td>
<td>0.56</td>
<td>30 (3.9)</td>
<td>35 (4.6)</td>
</tr>
<tr>
<td>Stroke</td>
<td>17 (1.7)</td>
<td>13 (1.3)</td>
<td>1.30 (0.63–2.67)</td>
<td>0.48</td>
<td>9 (1.2)</td>
<td>8 (1.0)</td>
</tr>
<tr>
<td>Unplanned revascularization</td>
<td>76 (7.7)</td>
<td>69 (7.0)</td>
<td>1.09 (0.79–1.51)</td>
<td>0.61</td>
<td>51 (6.7)</td>
<td>52 (6.8)</td>
</tr>
<tr>
<td>MI</td>
<td>44 (4.5)</td>
<td>29 (3.0)</td>
<td>1.51 (0.94–2.41)</td>
<td>0.09</td>
<td>26 (3.4)</td>
<td>22 (2.9)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>15 (1.5)</td>
<td>8 (0.8)</td>
<td>1.86 (0.79–4.40)</td>
<td>0.15</td>
<td>7 (0.9)</td>
<td>7 (0.9)</td>
</tr>
</tbody>
</table>
AUGUSTUS

INCLUSION
- Atrial fibrillation (prior, persistent, >6 hr)
  - Physician decision for OAC
- Acute coronary syndrome or PCI
  - Planned P2Y$_{12}$ inhibitor for ≥6 months

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

VKA (INR 2–3)

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

Aspirin
Double Blind
Placebo

Primary outcome: ISTH major / CRNM bleeding
Secondary outcome(s): death / hospitalization, death / ischemic events
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Primary endpoint: major or clinically relevant nonmajor bleeding.

Event rate per 100 patient-yr:
- VKA + Aspirin + P2Y12 inhibitor: 49.1
- Apixaban + Aspirin + P2Y12 inhibitor: 33.6
- VKA + P2Y12 inhibitor: 26.7
- Apixaban + P2Y12 inhibitor: 16.8

P2Y12 inhibitor: clopidogrel 93%
Patients in the apixaban group had a lower incidence of death or hospitalization than those in the vitamin K antagonist group (23.5% vs. 27.4%; hazard ratio, 0.83; 95% CI, 0.74 to 0.93; P = 0.002).
## AUGUSTUS

### Outcomes

#### Anticoagulant-Regimen Comparison

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Apixaban</th>
<th>VKA</th>
<th>HR (95% CI)</th>
<th>Aspirin + P2Y12</th>
<th>P2Y12</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISTH major bleeding</td>
<td>69 (3.0)</td>
<td>104 (4.6)</td>
<td>0.64 (0.47-0.86)</td>
<td>108 (4.7)</td>
<td>65 (2.9)</td>
<td>1.7 (1.25-2.31)</td>
</tr>
<tr>
<td>Death</td>
<td>77 (3.3)</td>
<td>74 (3.2)</td>
<td>1.03 (0.75-1.42)</td>
<td>72 (3.1)</td>
<td>79 (3.4)</td>
<td>0.91 (0.66-1.26)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>518 (22.5)</td>
<td>607 (26.3)</td>
<td>0.83 (0.74-0.93)</td>
<td>585 (25.4)</td>
<td>540 (23.4)</td>
<td>1.10 (0.98-1.24)</td>
</tr>
<tr>
<td>Stroke</td>
<td>13 (0.6)</td>
<td>26 (1.1)</td>
<td>0.50 (0.26-0.97)</td>
<td>20 (0.9)</td>
<td>19 (0.8)</td>
<td>1.06 (0.56-1.98)</td>
</tr>
<tr>
<td>MI</td>
<td>72 (3.1)</td>
<td>80 (3.5)</td>
<td>0.89 (0.65-1.23)</td>
<td>68 (2.9)</td>
<td>84 (3.6)</td>
<td>0.81 (0.59-1.12)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>14 (0.6)</td>
<td>18 (0.8)</td>
<td>0.77 (0.38-1.56)</td>
<td>11 (0.5)</td>
<td>21 (0.9)</td>
<td>0.52 (0.25-1.08)</td>
</tr>
</tbody>
</table>
Network meta-analysis

A TIMI major bleeding

Odds ratio (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Nonreference Strategy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA + DAPT (reference)</td>
<td>0.58 (0.31-1.08)</td>
<td></td>
</tr>
<tr>
<td>VKA + P2Y12 inhibitor</td>
<td>0.70 (0.38-1.23)</td>
<td></td>
</tr>
<tr>
<td>NOAC + DAPT</td>
<td>0.49 (0.30-0.82)</td>
<td></td>
</tr>
</tbody>
</table>

B TIMI major and minor bleeding

Odds ratio (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Nonreference Strategy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA + DAPT (reference)</td>
<td>0.49 (0.26-0.92)</td>
<td></td>
</tr>
<tr>
<td>VKA + P2Y12 inhibitor</td>
<td>0.63 (0.33-1.17)</td>
<td></td>
</tr>
<tr>
<td>NOAC + DAPT</td>
<td>0.43 (0.25-0.76)</td>
<td></td>
</tr>
</tbody>
</table>

C Trial-defined primary safety outcome

Odds ratio (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Nonreference Strategy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA + DAPT (reference)</td>
<td>0.45 (0.21-0.92)</td>
<td></td>
</tr>
<tr>
<td>VKA + P2Y12 inhibitor</td>
<td>0.64 (0.31-1.31)</td>
<td></td>
</tr>
<tr>
<td>NOAC + DAPT</td>
<td>0.47 (0.25-0.85)</td>
<td></td>
</tr>
</tbody>
</table>

D Intracranial hemorrhage

Odds ratio (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Nonreference Strategy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA + DAPT (reference)</td>
<td>1.44 (0.40-5.22)</td>
<td></td>
</tr>
<tr>
<td>VKA + P2Y12 inhibitor</td>
<td>0.54 (0.15-1.92)</td>
<td></td>
</tr>
<tr>
<td>NOAC + P2Y12 inhibitor</td>
<td>0.26 (0.08-0.79)</td>
<td></td>
</tr>
</tbody>
</table>
Meta-analysis in patients with stable CAD and AF

(A) Major adverse cardiovascular events

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Log HR</th>
<th>Log SE</th>
<th>HR (95% CI)</th>
<th>%Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamberts</td>
<td>2014</td>
<td>0.1133</td>
<td>0.0904</td>
<td>1.12 (0.94, 1.34)</td>
<td>31.81</td>
</tr>
<tr>
<td>(Aspirin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamberts</td>
<td>2014</td>
<td>0.4253</td>
<td>0.2543</td>
<td>1.53 (0.93, 2.52)</td>
<td>9.39</td>
</tr>
<tr>
<td>(Clopidogrel)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamon</td>
<td>2014</td>
<td>0.1398</td>
<td>0.3481</td>
<td>1.15 (0.58, 2.28)</td>
<td>5.51</td>
</tr>
<tr>
<td>Lemesle</td>
<td>2017</td>
<td>-0.1625</td>
<td>0.1473</td>
<td>0.85 (0.64, 1.13)</td>
<td>20.25</td>
</tr>
<tr>
<td>Fischer</td>
<td>2018</td>
<td>0.0853</td>
<td>0.1604</td>
<td>1.10 (0.80, 1.51)</td>
<td>18.27</td>
</tr>
<tr>
<td>Patti</td>
<td>2018</td>
<td>0.7419</td>
<td>0.3752</td>
<td>2.10 (1.01, 4.38)</td>
<td>4.82</td>
</tr>
<tr>
<td>Matsumura</td>
<td>2018</td>
<td>-0.1570</td>
<td>0.2454</td>
<td>0.85 (0.53, 1.38)</td>
<td>9.05</td>
</tr>
<tr>
<td>Overall (I² = 31.6%, p = 0.187)</td>
<td></td>
<td></td>
<td></td>
<td>1.09 (0.93, 1.29)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.

(B) Major bleeding

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Log HR</th>
<th>Log SE</th>
<th>HR (95% CI)</th>
<th>%Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamberts</td>
<td>2014</td>
<td>0.4055</td>
<td>0.1000</td>
<td>1.50 (1.23, 1.82)</td>
<td>59.34</td>
</tr>
<tr>
<td>(Aspirin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamberts</td>
<td>2014</td>
<td>0.0098</td>
<td>0.2597</td>
<td>1.84 (1.11, 3.06)</td>
<td>8.86</td>
</tr>
<tr>
<td>(Clopidogrel)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamon</td>
<td>2014</td>
<td>1.4531</td>
<td>0.7731</td>
<td>4.32 (0.95, 19.66)</td>
<td>0.09</td>
</tr>
<tr>
<td>Lemesle</td>
<td>2017</td>
<td>0.6259</td>
<td>0.3221</td>
<td>1.87 (0.69, 3.53)</td>
<td>5.71</td>
</tr>
<tr>
<td>Fischer</td>
<td>2018</td>
<td>0.5876</td>
<td>0.2161</td>
<td>1.80 (1.18, 2.75)</td>
<td>12.69</td>
</tr>
<tr>
<td>Patti</td>
<td>2018</td>
<td>0.8242</td>
<td>0.4201</td>
<td>2.28 (1.00, 5.16)</td>
<td>3.36</td>
</tr>
<tr>
<td>Matsumura</td>
<td>2018</td>
<td>0.3147</td>
<td>0.2559</td>
<td>1.37 (0.83, 2.26)</td>
<td>9.05</td>
</tr>
<tr>
<td>Overall (I² = 0.0%, p = 0.682)</td>
<td></td>
<td></td>
<td></td>
<td>1.61 (1.38, 1.87)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
2018 Korean AF Guideline

- Oral anticoagulant with VKA (TTR: 70%) or NOAC
- Aspirin
- Clopidogrel

A. Balanced thrombotic/bleeding risk

B. High bleeding risk/low thrombotic risk

C. High thrombotic risk/low bleeding risk
In AF patients, undergoing PCI,

1. Dual therapy with NOAC and clopidogrel is much safer than triple therapy with warfarin.

2. Although NOAC based dual therapy may potentially increase small risk of coronary ischemic events, huge reduction of major bleeding risk is evident.
The guideline recommendations of OAC monotherapy in patients with stable CAD, are based on the underpowered observational studies and small RCT. However NOAC monotherapy is a reasonable strategy for patients with stable CAD and AF as a default antithrombotic therapy.

Among the NOACs, only apixaban was tested as a component of triple therapy with stroke prevention dose in a RCT.
Thank you for your attention