A Randomized, Open Label, Multicenter Study of Oral Anticoagulation with or without Clopidogrel after Transcatheter Aortic Valve Implantation

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on behalf of the POPULAR TAVI investigators
PI Dr. Jurrien ten Berg, MD, PhD, FACC, FESC
Disclosures Dr Nijenhuis

• None.
Background

• TAVI remains associated with frequent complications:
  – Major and life-threatening bleeding: 3-15%
  – Stroke: 1-8%
• Approximately 30% of patients have atrial fibrillation (AF)
• In these patients, the risk of thromboembolic events is higher

Background

- Patients with AF undergoing TAVI are in need of oral anticoagulation (OAC) to reduce stroke and thromboembolism.
- Antiplatelet therapy in addition to OAC may decrease thromboembolism after TAVI but increases bleeding.

Background

Guidelines on the management of valvular heart disease (version 2012)

The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Despite the lack of evidence, a combination of low-dose aspirin and a thienopyridine is used early after TAVI and percutaneous edge-to-edge repair, followed by aspirin or a thienopyridine alone. In patients in AF, a combination of vitamin K antagonist and aspirin or thienopyridine is generally used, but should be weighed against increased risk of bleeding.
Despite the lack of evidence, a combination of low-dose aspirin and a thienopyridine is used early after TAVI and percutaneous edge-to-edge repair, followed by aspirin or a thienopyridine alone. In patients in AF, a combination of vitamin K antagonist and aspirin or thienopyridine is generally used, but should be weighed against increased risk of bleeding.
Hypothesis

OAC alone vs. OAC + 3 months clopidogrel, is:

- Superior for bleeding (primary outcome),
- Non-inferior for the composite of CV death, stroke, MI, non-procedural bleeding (secondary outcome),
- Non-inferior for the composite of CV death, ischemic stroke, MI (secondary outcome).
Trial Organization

- Trial Design
  - Investigator initiated, randomised, open-label, blinded CEC
- Sponsor and coordinating center
  - St. Antonius Hospital, Nieuwegein, The Netherlands
- Funding and Support
  - Dutch Organization for Health Research and Development ZonMw (project no. 836031014)
Recruitment

- Participating Sites (17)
  - Netherlands
  - Belgium
  - Luxembourg
  - Czech Republic
Study Population

**Inclusion**
- Long-term indication for OAC
- Written informed consent

**Exclusion**
- DES within 3 months before TAVI
- BMS within 1 month before TAVI
- Allergy or contraindication to OAC or clopidogrel
PLANNED TAVI AND ON OAC (COHORT B)

RANDOMIZATION 1:1
PRIOR TO TAVI
N=326

OAC ALONE
N=164

7 EXCLUDED
4 withdrew consent
2 TAVI not initiated/completed
1 screen failure

Modified ITT ANALYSIS
N=157

OAC + 3M CLOPIDOGREL
N=162

6 EXCLUDED
1 withdrew consent
3 TAVI not initiated/completed
2 screen failure

Modified ITT ANALYSIS
N=156

FOLLOW-UP: 1 YEAR

CO-PRIMARY OUTCOMES:
1. All bleeding (VARC-2)
2. Non-procedural bleeding (BARC)

CO-SECONDARY OUTCOMES:
1. CV mortality, non-procedural bleeding, all-cause stroke, and MI
2. CV mortality, ischemic stroke, and MI
Study Power

• Primary outcomes:
  – Superiority, power 80%, alpha 0.05
  – Expected event rate OAC vs. OAC + clopidogrel: 18% vs. 36%

• Secondary outcomes:
  – Non-inferiority, non-inferiority margin: 7.5%
  – Expected event rate OAC vs. OAC + clopidogrel: 31% vs. 39%
Adherence and Cross-Overs

- Adherence for 3 months clopidogrel: 95.5%
- Duration clopidogrel: median 91 days [IQR 89-92]
- Cross-overs: one in each group
## Baseline

<table>
<thead>
<tr>
<th></th>
<th>OAC (N=157)</th>
<th>OAC + CLOPIDOGREL (N=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - yr</td>
<td>81±6</td>
<td>81±6</td>
</tr>
<tr>
<td>Female - no. (%)</td>
<td>69 (43.9)</td>
<td>73 (46.8)</td>
</tr>
<tr>
<td>NYHA class III or IV – no. (%)</td>
<td>119 (75.8)</td>
<td>110 (70.1)</td>
</tr>
<tr>
<td>STS risk score - % [IQR]</td>
<td>3.2 [2.2 - 4.8]</td>
<td>3.1 [2.3 - 4.5]</td>
</tr>
<tr>
<td>Atrial fibrillation - no. (%)</td>
<td>150 (95.5)</td>
<td>147 (94.2)</td>
</tr>
<tr>
<td>Coronary artery disease - no. (%)</td>
<td>65 (41.4)</td>
<td>69 (44.2)</td>
</tr>
<tr>
<td>Peripheral artery disease - no. (%)</td>
<td>30 (19.1)</td>
<td>28 (17.9)</td>
</tr>
<tr>
<td>Previous stroke - no. (%)</td>
<td>15 (9.6)</td>
<td>15 (9.6)</td>
</tr>
<tr>
<td>Estimated GFR - ml/min/1.73 m²</td>
<td>53±18</td>
<td>56±17</td>
</tr>
<tr>
<td>LVEF – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>91 (58.0)</td>
<td>97 (62.2)</td>
</tr>
<tr>
<td>30-50%</td>
<td>54 (34.4)</td>
<td>46 (29.5)</td>
</tr>
<tr>
<td>≤30%</td>
<td>12 (7.6)</td>
<td>13 (8.3)</td>
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</tbody>
</table>
## Anticoagulation

<table>
<thead>
<tr>
<th></th>
<th>OAC (N=157)</th>
<th>OAC + CLOPIDOGREL (N=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K antagonist – no. (%)</td>
<td>118 (75.2)</td>
<td>110 (70.5)</td>
</tr>
<tr>
<td>Acenocoumarol</td>
<td>97 (61.8)</td>
<td>91 (58.3)</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>18 (11.5)</td>
<td>16 (10.3)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>3 (1.9)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Direct oral anticoagulant – no. (%)</td>
<td>37 (23.6)</td>
<td>46 (29.5)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>14 (8.9)</td>
<td>25 (16.0)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>7 (4.5)</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>4 (2.5)</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>12 (7.6)</td>
<td>12 (7.6)</td>
</tr>
<tr>
<td>Low molecular weight heparin – no (%)</td>
<td>2 (1.3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
# Procedure

<table>
<thead>
<tr>
<th></th>
<th>OAC (N=157)</th>
<th>OAC + CLOPIDOGREL (N=156)</th>
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</thead>
<tbody>
<tr>
<td><strong>Approach</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfemoral</td>
<td>136 (86.6)</td>
<td>132 (84.6)</td>
</tr>
<tr>
<td>Other</td>
<td>21 (13.4)</td>
<td>24 (15.4)</td>
</tr>
<tr>
<td><strong>Unfractionated heparin – no. (%)</strong></td>
<td>157 (100)</td>
<td>156 (100)</td>
</tr>
<tr>
<td><strong>Prosthesis – no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sapien 3, Edwards Lifesciences</td>
<td>65 (41.4)</td>
<td>82 (52.6)</td>
</tr>
<tr>
<td>CoreValve Evolut R, Medtronic</td>
<td>45 (28.7)</td>
<td>36 (23.1)</td>
</tr>
<tr>
<td>Other</td>
<td>47 (29.9)</td>
<td>38 (24.3)</td>
</tr>
<tr>
<td><strong>Embolic protection device use – no. (%)</strong></td>
<td>4 (2.5)</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td><strong>VARC-2 vascular complication – no (%)</strong></td>
<td>20 (12.7)</td>
<td>35 (22.4)</td>
</tr>
<tr>
<td>Minor vascular complication</td>
<td>12 (7.6)</td>
<td>17 (10.9)</td>
</tr>
<tr>
<td>Major vascular complication</td>
<td>8 (5.1)</td>
<td>18 (11.5)</td>
</tr>
</tbody>
</table>
All Bleeding

RR 0.63
95% CI 0.43 to 0.90
P = 0.011

Cumulative event

Days since TAVI

OAC + clopidogrel
OAC alone

34.6%
21.7%
Non-Procedural Bleeding

For the calculation of RR 0.64, 95% CI 0.44 to 0.92, and p = 0.015, the data shows a cumulative event rate of 34.0% for OAC + clopidogrel and 21.7% for OAC alone.
CV Mortality, Non-Procedural Bleeding, Stroke, MI

RR 0.69
95% CI 0.51 to 0.92
-14.3% (-25.0 to -3.6)
Non-inferiority margin +7.5%
CV Mortality, Ischemic Stroke, MI

RR 0.77
95% CI 0.46 to 1.31
-3.9% (-11.9 to 4.0)
Non-inferiority margin +7.5%

Days since TAVI

Cumulative event

OAC + clopidogrel
OAC alone

0.3
0.2
0.1
0.0
17.3%
13.4%
0 45 90 135 180 225 270 315 360
## Secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OAC (N=157)</th>
<th>OAC + CLOPIDOGREL (N=156)</th>
<th>RISK RATIO (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>21 (13.4)</td>
<td>24 (15.4)</td>
<td>0.87 (0.51 to 1.50)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>13 (8.3)</td>
<td>20 (12.8)</td>
<td>0.65 (0.33 to 1.25)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>8 (5.1)</td>
<td>9 (5.8)</td>
<td>0.88 (0.35 to 2.23)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>1 (0.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>0.99 (0.06 to 15.75)</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major, life-threatening, or disabling</td>
<td>14 (8.9)</td>
<td>26 (16.7)</td>
<td>0.54 (0.29 to 0.99)</td>
</tr>
<tr>
<td>Minor</td>
<td>20 (12.7)</td>
<td>28 (17.9)</td>
<td>0.71 (0.42 to 1.21)</td>
</tr>
</tbody>
</table>
Conclusions POPULAR TAVI COHORT B

In patients with an established indication for OAC undergoing TAVI, OAC alone as compared to OAC + clopidogrel:

- Reduces the rate of bleeding events, including major, life-threatening, or disabling bleeding
- Does not increase the rate of thrombotic events
Acknowledgments

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Jorn Brouwer (Coordinating I.)
Ronak Delewi
Renicus S. Hermanides
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Arie P. Kappetein

**Funding**

ZonMW

**Endpoint Adjudication Committee**

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Bert Everaert
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