The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing PCI with stenting

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The WOEST Trial = What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting (clinicaltrials.gov NCT00769938)
Conflict of interest

Investigator-initiated study

Funding:
- Centre of platelet function research, Sint Antonius Hospital Nieuwegein, The Netherlands
- Stichting Strect, Tilburg, The Netherlands

Disclosures for JM ten Berg

Consultant
- Merck & Co., Inc

Speakers’ bureau
- Eli Lilly and Company and Merck & Co., Inc.

Scientific advisory board
- AstraZeneca and Eli Lilly Daiichi Sankyo and Merck & Co., Inc and
Background

1/ Long term oral anticoagulant therapy (OAC) is obligatory (class I) in:
   - most patients with atrial fibrillation
   - patients with mechanical heart valves

2/ Over 30% of these patients have concomitant ischemic heart disease. When these patients need to undergo percutaneous coronary stenting, there is also an indication for aspirin and clopidogrel.

3/ Triple therapy (OAC, aspirin and clopidogrel) is recommended according to the guidelines but is also known to increase the risk of major bleeding. Major bleeding increases mortality.

4/ No prospective data available.
Aim of the study

To test the hypothesis that in patients on OAC undergoing PCI, clopidogrel alone is superior to the combination aspirin and clopidogrel with respect to bleeding but does not increase the thrombotic risk in a multicentre two-country study (The Netherlands and Belgium)
Inclusion criteria:
1/ Indication for OAC for at least 1 year
2/ One coronary lesion eligible for PCI
3/ Age over 18

Exclusion criteria:
1/ History of intracranial bleeding
2/ Cardiogenic shock during hospitalisation
3/ Peptic ulcer in the previous 6 months
4/ TIMI major bleeding in the previous year
5/ Contra-indication for aspirin or clopidogrel
6/ Thrombocytopenia (platelet count less than 50,000 per ml)
7/ Pregnancy
8/ Age >80
**Study Design-2**

**1:1 Randomisation:**

**Double therapy group:**
- OAC + 75mg Clopidogrel qd

1 month minimum after BMS
1 year after DES and/or ACS

**Triple therapy group**
- OAC + 75mg Clopidogrel qd + 80mg Aspirin qd

1 month minimum after BMS
1 year after DES and/or ACS

**Follow up:** 1 year

**Primary Endpoint:** The occurrence of all bleeding events (TIMI criteria)

**Secondary Endpoints:**
- Combination of stroke, death, myocardial infarction, stent thrombosis and target vessel revascularisation
- All individual components of primary and secondary endpoints
Study Design-3

- Power calculation was based on the largest retrospective study by Karjalainen\(^1\) addressing this issue.
- We anticipated a 12% bleeding rate in the triple therapy group and a 5% bleeding rate in the double therapy group.
- Power was chosen to be 80% and \(\alpha\) level 5%. The total patient number is estimated at \(n = 496\).
- The study is designed as a superiority trial.
- All events were adjudicated by a committee blinded to treatment allocation.

\(^1\) Eur Heart J 2007;28:726-32
573 patients underwent 1:1 randomization

284 were assigned to Double therapy group

No PCI (n=3)

Withdrawn informed consent (n=2)*

Lost to follow up (n=1)

Did not meet inclusion criteria (n=1)

279 patients were included in Intention to treat analysis

289 were assigned to Triple therapy group

No PCI (n=1)

Withdrawn informed consent (n=2)*

Lost to follow up (n=1)

Did not meet inclusion criteria (n=2)

284 patients were included in Intention to treat analysis

* withdrawn informed consent; in double group 2 patients and triple group 1 patient were included in intention to treat analysis until the day of withdrawal
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Double therapy n=279 (%)</th>
<th>Triple therapy n=284 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>70.3 (±7.3)</td>
<td>69.5 (±8.0)</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>214 (76.7%)</td>
<td>234 (82.4%)</td>
</tr>
<tr>
<td><strong>BMI (kg/m2)</strong></td>
<td>27.5 (±4.3)</td>
<td>27.9 (±4.2)</td>
</tr>
<tr>
<td><strong>Current Smoker</strong></td>
<td>60 (21.5%)</td>
<td>42 (14.8%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>68 (24.4%)</td>
<td>72 (25.4%)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>193 (69.2%)</td>
<td>193 (68.0%)</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>191 (68.5%)</td>
<td>205 (72.2%)</td>
</tr>
<tr>
<td><strong>History of MI</strong></td>
<td>96 (34.4%)</td>
<td>100 (35.2%)</td>
</tr>
<tr>
<td><strong>History of Heart Failure</strong></td>
<td>71 (25.4%)</td>
<td>70 (24.6%)</td>
</tr>
<tr>
<td><strong>History of Stroke</strong></td>
<td>49 (17.6%)</td>
<td>50 (17.6%)</td>
</tr>
<tr>
<td><strong>History of PCI</strong></td>
<td>86 (30.8%)</td>
<td>101 (35.6%)</td>
</tr>
<tr>
<td><strong>History of CABG</strong></td>
<td>56 (20.1%)</td>
<td>74 (26.1%)</td>
</tr>
<tr>
<td><strong>History of GI bleeding</strong></td>
<td>14 (5.0%)</td>
<td>14 (4.9%)</td>
</tr>
</tbody>
</table>

**Indication for OAC...**

- **AF/Aflutter**
  - 164 (69.5%)
  - 162 (69.2%)
- **Mechanical valve**
  - 24 (10.2%)
  - 25 (10.7%)
- **Other (pulmonary embolus, EF<30%, Apical thrombus...)**
  - 48 (20.3%)
  - 47 (20.1%)
- **ACS at baseline**
  - 69 (25.0%)
  - 86 (30.6%)
## Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Double therapy n=279 (%)</th>
<th>Triple therapy n=284 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI vessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>111 (39.9%)</td>
<td>118 (41.8%)</td>
</tr>
<tr>
<td>RCX</td>
<td>59 (21.2%)</td>
<td>76 (27.0%)</td>
</tr>
<tr>
<td>RCA</td>
<td>92 (33.1%)</td>
<td>72 (25.5%)</td>
</tr>
<tr>
<td>Arterial/Venous Graft</td>
<td>16 (5.7%)</td>
<td>16 (5.6%)</td>
</tr>
<tr>
<td>INR on the day of PCI</td>
<td>1.86 (±0.9)</td>
<td>1.94 (±1.1)</td>
</tr>
<tr>
<td>LVEF &lt;=30%</td>
<td>40 (21.1%)</td>
<td>37 (18.1%)</td>
</tr>
<tr>
<td>Stent type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5 (1.8%)</td>
<td>4 (1.4%)</td>
</tr>
<tr>
<td>BMS</td>
<td>89 (32.0%)</td>
<td>86 (30.3%)</td>
</tr>
<tr>
<td>DES</td>
<td>181 (65.1%)</td>
<td>183 (64.4%)</td>
</tr>
<tr>
<td>BMS + DES</td>
<td>3 (1.0%)</td>
<td>11 (3.8%)</td>
</tr>
<tr>
<td>Femoral access</td>
<td>204 (73.4%)</td>
<td>208 (74.6%)</td>
</tr>
<tr>
<td>Radial access</td>
<td>74 (26.6%)</td>
<td>71 (25.4%)</td>
</tr>
<tr>
<td>Angioseal</td>
<td>166 (59.5%)</td>
<td>167 (59.4%)</td>
</tr>
<tr>
<td>Other closure device</td>
<td>43 (15.4%)</td>
<td>29 (10.3%)</td>
</tr>
<tr>
<td>Peri-procedural OAC continuation</td>
<td>128 (45.9%)</td>
<td>113 (39.8%)</td>
</tr>
<tr>
<td>Peri-procedural LMWH</td>
<td>66 (23.7%)</td>
<td>68 (23.9%)</td>
</tr>
<tr>
<td>Peri-Procedural GPIIbIIIa</td>
<td>25 (8.9%)</td>
<td>26 (9.1%)</td>
</tr>
<tr>
<td>Peri-Procedural Fondaparinux</td>
<td>3 (1.0%)</td>
<td>2 (0.7%)</td>
</tr>
</tbody>
</table>
Primary Endpoint: Total number of TIMI bleeding events

**Triple therapy group**

**Double therapy group**

Cumulative incidence of bleeding

- **44.9%**
- **19.5%**

* p<0.001

HR=0.36  95%CI[0.26-0.50]
Primary Endpoint: Bleeding events TIMI classification

- **Double therapy group**
  - TIMI Minimal: 6.5%
  - TIMI Minor: 11.2%
  - TIMI Major: 3.3%
  - Any TIMI bleeding: 19.5%

- **Triple therapy group**
  - TIMI Minimal: 16.7%
  - TIMI Minor: 27.2%
  - TIMI Major: 5.8%
  - Any TIMI bleeding: 44.9%

- Multiple bleeds: 2.2% vs 12%
- Transfusion: 3.9% vs 9.7%
Locations of TIMI bleeding: Worst bleeding per patient

GI=gastro intestinal; Other bleeding consists of eye, urogenital, respiratory tract, retroperitoneal, mouth, PMPocket bleeding
## Forest plot of primary endpoint Hazard Ratios

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group</th>
<th>Triple</th>
<th>Double</th>
<th>P-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>&lt;75 years</td>
<td>79</td>
<td>82</td>
<td>0.9157</td>
</tr>
<tr>
<td></td>
<td>&gt;75 years</td>
<td>200</td>
<td>194</td>
<td></td>
</tr>
<tr>
<td>gender</td>
<td>female</td>
<td>50</td>
<td>65</td>
<td>0.8217</td>
</tr>
<tr>
<td></td>
<td>male</td>
<td>234</td>
<td>214</td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>no</td>
<td>195</td>
<td>207</td>
<td>0.7210</td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>86</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>indication</td>
<td>AF/AFlut</td>
<td>162</td>
<td>164</td>
<td>0.1116</td>
</tr>
<tr>
<td>OAC</td>
<td>Mechanical valve</td>
<td>25</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>47</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Stent type</td>
<td>BMS</td>
<td>90</td>
<td>94</td>
<td>0.7894</td>
</tr>
<tr>
<td></td>
<td>DES</td>
<td>194</td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>284</td>
<td>279</td>
<td></td>
</tr>
</tbody>
</table>

Forest plot of primary endpoint Hazard Ratios of double therapy better versus triple therapy better.
Compliance to OAC, aspirin and clopidogrel

Double therapy group

Triple therapy group

- **OAC**
- **Clopidogrel**
- **Aspirin**
Secondary Endpoint (Death, MI, TVR, Stroke, ST)

**Triple therapy group**

**Double therapy group**

Cumulative incidence over time with Kaplan-Meier survival curves. The graph shows the cumulative incidence of the secondary endpoint for each therapy group over the course of 365 days. The numbers at risk are listed below the graph:

- **Triple therapy group**: 284, 272, 270, 266, 261, 252, 242, 223
- **Double therapy group**: 279, 276, 273, 270, 266, 263, 258, 234

The graph indicates a statistically significant difference between the two groups with a p-value of 0.025. The hazard ratio (HR) is 0.60 with a 95% confidence interval (CI) of [0.38, 0.94].
MI=any myocardial infarction; TVR= target vessel revascularisation (PCI + CABG); ST= stent thrombosis
Limitations

- Open label trial design which has its inherent bias

- The study was powered to show superiority on the primary bleeding endpoint, but not to show non-inferiority on the secondary endpoint

- Classification of self reported bleedings for which the patient did not consult a health-care professional may be subjective
Conclusions

1. In this first randomized trial to address the optimal antiplatelet therapy in patients on OAC undergoing PCI, the bleeding rate was higher than expected.

2. OAC plus clopidogrel causes less bleeding than triple antithrombotic therapy. Now shown in a randomized way.

3. Double therapy did not lead to an excess of thrombotic/thromboembolic events: stroke, stent thrombosis, target vessel revascularisation, myocardial infarction or death.

4. Less all-cause mortality with double therapy.
Implications

We propose that clopidogrel alone, without aspirin, is the optimal treatment in high-risk patients on OAC when undergoing PCI.
The WOEST investigators

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