The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary 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/Conflict of interest Willem J.M. Dewilde: none
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 is not increasing thrombotic risk in a multicentre two-country study (The Netherlands and Belgium)
Study Design-1

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
1:1 Randomisation:

Double therapy group:
OAC + 75mg Clopidogrel qd

1 month minimum after BMS
1 year after DES

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

1 month minimum after BMS
1 year after DES

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

284 patients were included in Intention to treat analysis

289 were assigned to Triple therapy group

284 patients were included in Intention to treat analysis

No PCI (n=3)  No PCI (n=1)

Withdrawn informed consent (n=2)*  Withdrawn informed consent (n=2)*

Lost to follow up (n=1)  Lost to follow up (n=1)

Did not meet inclusion criteria (n=1)  Did not meet inclusion criteria (n=2)

279 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>
<tr>
<td><strong>Indication for OAC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AF/Aflutter</strong></td>
<td>164 (69.5%)</td>
<td>162 (69.2%)</td>
</tr>
<tr>
<td><strong>Mechanical valve</strong></td>
<td>24 (10.2%)</td>
<td>25 (10.7%)</td>
</tr>
<tr>
<td><strong>Other (pulmonary embolus,</strong></td>
<td>48 (20.3%)</td>
<td>47 (20.1%)</td>
</tr>
<tr>
<td><strong>EF&lt;30%, Apical thrombus...</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ACS at baseline</strong></td>
<td>69 (25.0%)</td>
<td>86 (30.6%)</td>
</tr>
</tbody>
</table>
## 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-produral 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 bleeding events (TIMI criteria)

Cumulative incidence of bleeding

- **Triple therapy group**: 44.9%
- **Double therapy group**: 19.5%

*Significance:* p<0.001

Hazard Ratio (HR): 0.36, 95% CI [0.26-0.50]

Days at risk:

- 0: 284
- 30: 279
- 60: 253
- 90: 244
- 120: 241
- 180: 241
- 270: 173
- 365: 140

- 0: 210
- 30: 219
- 60: 186
- 90: 181
- 120: 181
- 180: 241
- 270: 236
- 365: 140

n at risk:
Primary Endpoint: Bleeding events TIMI classification

- **TIMI Minimal**: Double therapy group (6.5%) vs. Triple therapy group (16.7%)
  - p < 0.001
- **TIMI Minor**: Double therapy group (11.2%) vs. Triple therapy group (27.2%)
  - p < 0.001
- **TIMI Major**: Double therapy group (3.3%) vs. Triple therapy group (5.8%)
  - p = 0.159
- **Any TIMI bleeding**: Double therapy group (19.5%) vs. Triple therapy group (44.9%)
  - p < 0.001

**WOEST**
Locations of TIMI bleeding: Worst bleeding per patient

GI=gastrointestinal; Other bleeding consists of eye, urogenital, respiratory tract, retroperitoneal, mouth, PMPocket bleeding.
## WOEST

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>284</td>
<td>279</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

double therapy better <=> triple therapy better
WOEST

Compliance to OAC, aspirin and clopidogrel

Double therapy group

Triple therapy group

Days 0 30 60 90 120 180 270 365

0 % 25 % 50 % 75 % 100 %

OAC
Clopidogrel
Aspirin
Bleeding in triple therapy group and aspirin compliance

Free from bleeding curve

Days

0 30 60 90 120 180 270 365

Triple therapy group

Double therapy group

Days

0 30 60 90 120 180 270 365

n at risk:
284 210 194 186 181 173 159 140
279 253 244 241 241 236 226 208

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

**Triple therapy group**

**Double therapy group**

- Cumulative incidence
- Days: 0, 30, 60, 90, 120, 180, 270, 365
- n at risk: 284, 272, 270, 266, 261, 252, 242, 223

- Cumulative incidence at 365 days:
  - Triple therapy group: 17.7%
  - Double therapy group: 11.3%

- Statistical significance:
  - p = 0.025
  - HR = 0.60, 95% CI [0.38–0.94]
MI=any myocardial infarction; TVR= target vessel revascularisation (PCI + CABG); ST= stent thrombosis
All-Cause Mortality

**Triple therapy group**

**Double therapy group**

Cumulative incidence of death

HR = 0.39, 95% CI [0.16-0.93]

\[ p = 0.027 \]

Days

Cumulative incidence of death

0 %

2.5 %

5 %

7.5 %

284 281 280 280 279 277 270 252

n at risk:

279 278 276 276 276 275 274 256

2.6 %

6.4 %
Limitations

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

- Open label trial design with its inherent bias

- Classification of smaller bleeding, although well defined and blindly adjudicated, may be subjective
Conclusions

1. First randomized trial to address the optimal antiplatelet therapy in patients on OAC undergoing coronary stenting

2. In this study which was specifically designed to detect bleeding events, the bleeding rate was higher than expected

3. Primary endpoint was met: OAC plus clopidogrel causes less bleeding than triple antithrombotic therapy, but now shown in a randomized way

4. Secondary endpoint was met: with double therapy there is no excess of thrombotic/thromboembolic events: stroke, stent thrombosis, target vessel revascularisation, myocardial infarction or death

5. Less all-cause mortality with double therapy
Implications

We propose that a strategy of oral anticoagulants plus clopidogrel, but without aspirin could be applied in this group of high-risk patients on OAC when undergoing PCI.
The WOEST investigators

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Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam: Jean-Paul Herrman, Freek Verheugt

Catholic University of Leuven, Leuven: Tom Adriaenssens

Hospital Oost-Limburg (ZOL), Belgium: Mathias Vrolix

Medical Center Alkmaar, Alkmaar: Ton Heestermans

Academic Medical Center, University of Amsterdam, Amsterdam: Marije Vis

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