Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation (ISAR-TRIPLE Trial)

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All faculty disclosures are available on the CRF Events App and online at www.crf.org/tct
Background

**Coronary stent implantation**

Cardiac Events

- Oral Anticoagulation
- Dual Antiplatelet

Cumulative Incidence (%)

Days after Stenting

*ISAR, NEJM 1996*

**Atrial fibrillation**

- Dual Antiplatelet
- Oral Anticoagulation

Cumulative hazard rates

Years

*ACTIVE-W Lancet 2006*

= Dual Antiplatelet + Oral Anticoagulation

Such triple therapy increases the risk of bleeding however.

The optimal duration of triple therapy after drug-eluting stent (DES) implantation has not been defined. Two factors need to be considered in this regard:

1. The risk of stent thrombosis is highest in the early phase after PCI and declines over time
2. The risk of bleeding is dependent on length and intensity of OAC therapy
Objective

To evaluate clinical outcomes of a therapy duration of

6 weeks clopidogrel

versus

6 months clopidogrel

after DES implantation in patients receiving concomitantly aspirin and oral anticoagulation
ISAR-TRIPLE: Study Organization

DESIGN:
Prospective, randomized open-label trial

INCLUSION CRITERIA:
DES implantation and indication for oral anticoagulation

MAJOR EXCLUSION CRITERIA:
Previous stent thrombosis
DES in left main coronary artery

SPONSOR:
Deutsches Herzzentrum Munich,
(ClinicalTrials.gov # NCT00776633)

614 patients with DES implantation
3 European centers
(September 2008 – December 2013)

Aspirin and VKA

6-week Clopidogrel (n=307)
6-month Clopidogrel (n=307)

Clinical follow up at 9 months in 606 patients (98.7%)

VKA: Vitamin K Antagonist
ISAR-TRIPLE: Study Organization

TEST HYPOTHESES:
6-week superior to 6-month therapy; 
Primary Endpoint 10%, Risk reduction 60% with 6-week therapy; Power = 80%, alpha = 0.05; 283 patients per group

PRIMARY ENDPOINT:
• Death, myocardial infarction, definite stent thrombosis, stroke or TIMI major bleeding at 9 months

SECONDARY ENDPOINTS:
• Ischemic complications: Cardiac death, myocardial infarction, definite stent thrombosis or ischemic stroke
• Bleeding complications (TIMI major)

614 patients with DES implantation
3 European centers
(September 2008 – December 2013)

Aspirin and VKA

6-week Clopidogrel (n=307) 6-month Clopidogrel (n=307)

Clinical follow up at 9 months in 606 patients (98.7%)

VKA: Vitamin K Antagonist
Randomization

PCI Randomization

Stop clopidogrel Group A

Stop clopidogrel Group B

Aspirin and oral anticoagulation

Clopidogrel

A: 6-week group

B: 6-month group

6-week Follow-up

6-month Follow-up

9-month Follow-up

Time (months)

0

ISAR-TRIPLE Investigators

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• **Aarhus University Hospital, Aarhus, Denmark**: Michael Maeng, Steen D. Kristensen

• **Klinikum rechts der Isar, Munich, Germany**: Petra Hoppmann, Simon Schneider, Tareq Ibrahim, Karl-Ludwig Laugwitz

• **Klinikum der Ludwig Maximilians Universität, Munich, Germany**: Julinda Mehilli, Dirk Sibbing, Steffen Massberg, Nikolaus Sarafoff
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>6-week group (n=307)</th>
<th>6-month group (n=307)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>74 ± 8</td>
<td>73 ± 9</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>25 %</td>
<td>21 %</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>28 %</td>
<td>23 %</td>
</tr>
<tr>
<td><strong>History of myocardial infarction</strong></td>
<td>29 %</td>
<td>25 %</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>33 %</td>
<td>31 %</td>
</tr>
<tr>
<td>Stable Angina</td>
<td>67 %</td>
<td>69 %</td>
</tr>
<tr>
<td><strong>Indication for OAC</strong> *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>83 %</td>
<td>85 %</td>
</tr>
<tr>
<td>Mechanical valve</td>
<td>5 %</td>
<td>9 %</td>
</tr>
<tr>
<td>VTE</td>
<td>7 %</td>
<td>4 %</td>
</tr>
<tr>
<td>other</td>
<td>4 %</td>
<td>2 %</td>
</tr>
</tbody>
</table>

*p=0.03; OAC= Oral Anticoagulation; VTE= Venous Thrombembolism
# Antithrombotic therapy

**ASPIRIN:**
75-200 mg per day

**CLOPIDOGREL:**
75 mg per day

**PHENPROCOUMON or WARFARIN:**
Target INR 2.0 or 2.5 in patients with mechanical valves

<table>
<thead>
<tr>
<th>Compliance</th>
<th>6-week FU</th>
<th>6-month FU</th>
<th>9-month FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin*</td>
<td>97 %</td>
<td>95 %</td>
<td>96 %</td>
</tr>
<tr>
<td>OAC*</td>
<td>94 %</td>
<td>91 %</td>
<td>88 %</td>
</tr>
<tr>
<td>INR (median)*</td>
<td>2.2</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Time in therapeutic range *</td>
<td>64 %</td>
<td>69 %</td>
<td>66 %</td>
</tr>
<tr>
<td>Clopidogrel 6-week group</td>
<td>97 %</td>
<td>26 %</td>
<td>23 %</td>
</tr>
<tr>
<td>Clopidogrel 6-month group</td>
<td>98 %</td>
<td>87 %</td>
<td>35 %</td>
</tr>
</tbody>
</table>

*No significant differences between groups; FU = Follow Up time point
## Stent type

<table>
<thead>
<tr>
<th>Stent Type</th>
<th>6-week group (417 lesions)</th>
<th>6-month group (409 lesions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd gen. permanent polymer DES</td>
<td>203 (48.7)</td>
<td>206 (50.4)</td>
</tr>
<tr>
<td>Biodegradable polymer DES</td>
<td>131 (31.4)</td>
<td>134 (32.8)</td>
</tr>
<tr>
<td>Polymer free DES</td>
<td>45 (10.8)</td>
<td>46 (11.2)</td>
</tr>
<tr>
<td>1st gen. permanent polymer DES</td>
<td>29 (6.9)</td>
<td>16 (3.9)</td>
</tr>
<tr>
<td>BVS</td>
<td>4 (1.0)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>BMS*</td>
<td>2 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>DEB/PTCA**</td>
<td>3 (0.7)</td>
<td>4 (1.0)</td>
</tr>
</tbody>
</table>

DES = Drug-eluting stent; BMS = Bare-metal stent; BVS = Bioresorbable vascular scaffold; DEB = Drug-eluting balloon; *One patient had 1 DES and 1 BMS and 1 patient had 1 BMS only. **These patients were treated with drug eluting balloons (DEB) except for 1 patient in the 6-week group and 1 patient in the 6-month group.
Primary Endpoint

Death, myocardial infarction, stent thrombosis, stroke or TIMI major bleeding

HR 1.14 (95%, CI 0.68 – 1.91), p=0.63
Secondary Endpoints

Cardiac death, myocardial infarction, stent thrombosis or ischemic stroke

HR 0.93 (0.43 - 2.05), p=0.87

TIMI major bleeding

HR 1.35 (0.64 - 2.84), p=0.44

6-month group

6-week group
### Results

<table>
<thead>
<tr>
<th></th>
<th>6-week group (n=307)</th>
<th>6-month group (n=307)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>12 (4.0)</td>
<td>16 (5.2)</td>
<td>0.75 (0.35 - 1.59)</td>
<td>0.45</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>5 (1.7)</td>
<td>9 (3.0)</td>
<td>0.56 (0.19 - 1.66)</td>
<td>0.29</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6 (2.0)</td>
<td>0</td>
<td>-</td>
<td>0.03</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td>2 (0.7)</td>
<td>0</td>
<td>-</td>
<td>0.50</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (1.3)</td>
<td>6 (2.0)</td>
<td>0.67 (0.14 - 2.78)</td>
<td>0.75</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>3 (1.0)</td>
<td>4 (1.3)</td>
<td>0.75 (0.11 - 4.40)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

**Temporal distribution of MIs in 6-week group:**
- 4 within 24h of PCI
- 1 at 2.5 weeks
- 1 at 7 months

} Both groups on triple therapy

} Both groups on aspirin and OAC
Any BARC Bleeding (type 1-5)

Any BARC Bleeding

HR 0.94 (0.73 - 1.21), p=0.63

Post-hoc landmark analysis of any BARC Bleeding before and after 6 weeks (6w)

HR 0.68 (0.47 – 0.98), p=0.04

Cumulative Incidence (%) vs Months After Randomization

6-month group
6-week group
Conclusion

• The main finding was that a 6-week triple therapy is not superior to a 6-month triple therapy with regard to net clinical outcomes.

• Shortening the duration of triple therapy neither reduced the incidence of major bleeding nor increased the incidence of ischemic events.
Conclusion

- ISAR TRIPLE is the largest randomized trial to date investigating triple therapy after stenting and the first trial evaluating duration of triple therapy
Thank You For Your Attention