Six versus Twelve Months of Clopidogrel Therapy After Drug-Eluting Stenting

– the Randomized, Double-Blind, Placebo-Controlled ISAR-SAFE Trial

The optimal duration of clopidogrel treatment as part of dual-antiplatelet therapy after drug-eluting stent (DES) implantation is still not known.
**Design**

- Investigator-initiated, international, multicenter, randomized, double-blind, placebo-controlled trial
- Recruitment period: October 2008 - April 2014

**Hypothesis**

- In patients with DES implantation, 6 months of clopidogrel is non-inferior to 12 months in terms of clinical outcomes
Endpoints

Primary endpoint:
Composite of death, myocardial infarction, stent thrombosis, stroke or TIMI major bleeding at 9 months after randomization, i.e. 15 months after DES implantation

Secondary endpoints:
Individual components of the primary endpoint
Inclusion and Exclusion Criteria

**Major Inclusion Criteria:**
- Patients on clopidogrel at 6 (-1/+2) months after DES
- Written informed consent

**Major Exclusion Criteria:**
- Clinically symptoms or signs of ischemia and/or angiographic lesions requiring revascularization
- Active bleeding; bleeding diathesis; history of intracranial bleeding
- STEMI and NSTEMI during the last 6 mo. after DES
- Previous stent thrombosis
- DES in left main coronary artery at index intervention
- Oral anticoagulation
- Planned major surgery within the next 6 mo. w/ need to discontinue antiplatelet therapy
40 Centers Worldwide
- 20 Highest-Enrolling Centers

- Deutsches Herzzentrum München, TU, Munich, Germany
- Klinikum rechts der Isar, Munich, Germany
- Herzzentrum Bad Krozingen, Germany
- St. Antonius Hospital, Nieuwegein, Netherlands
- Shenyang Northern Hospital, China
- Leuven University Hospital, Belgium
- Herzzentrum Bad Segeberg, Germany
- Helios Klinikum Wuppertal, Witten/Herdecke University, Germany
- Aarhus University Hospital, Denmark
- Krankenhaus Landshut-Achdorf, Germany
- University Hospital Göttingen, Germany
- Städt. Klinikum Neuperlach, Germany
- Herzzentrum Lahr/Baden, Germany
- Ulm University Hospital, Germany
- Regensburg University Hospital, Germany
- Klinikum Garmisch-Partenkirchen, Germany
- Städt. Klinikum Bogenhausen, Munich, Germany
- Regensburg Barmherzige Brüder, Germany
- Rostock University Hospital, Germany
- Isala Klinieken Zwolle, Netherlands
**Study Organisation**

**Steering Committee:**
- Adnan Kastrati (Chair)
- Julinda Mehilli (Coordinating Investigator)
- Jurrien M ten Berg (PI)
- Josef Dirschinger (PI)

**DSMB:**
- Johannes Mann
- Franz Hofmann
- Dieter Hauschke

**Event Adjudication Committee:**
- Claus Schmitt (Chairman)
- Dritan Poci
- Petra Barthel
- Nicolaus Sarafoff
- Andreas Stein
- Gjin Ndrepepa

**Coordinating Center:**
ISAResearch Center Munich

**Study grants**
from BMBF (FKZ 01KG0901) and Abbott Vascular
Sample Size Calculation

• Assumptions:
  - Incidence of the primary endpoint in the 12-month clopidogrel group: 10%
  - Margin of non-inferiority: 2% (absolute)
  - Power 80%
  - 1-sided α-Level 0.05

→ Enrolment of 6,000 patients required

• A planned, blinded interim analysis showed much lower than expected overall event rates. This, along with slow recruitment, induced the DSMB and the Steering Committee to terminate recruitment at a sample size of 4,000 patients
Study Flow

Randomization (n=4005)

Continuous clopidogrel therapy for 6 months

DES

6 months Placebo (n=1998)

- Study therapy not initiated (n=1)
  - immediate withdrawal of consent (n=1)

- Incomplete 9-month follow-up (n=127)

- Premature study drug discontinuation (n=255)

Included for analysis (n=1997)

6 months Clopidogrel (n=2007)

- Study therapy not initiated (n=4)
  - immediate withdrawal of consent (n=2)
  - physician decision due to erroneous enrolment (n=2)

- Premature study drug discontinuation (n=277)

Included for analysis (n=2003)
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Six months Clopidogrel (n=1997)</th>
<th>Twelve months Clopidogrel (n=2003)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>67.2 [59.3-73.3]</td>
<td>67.2 [59.1-73.7]</td>
</tr>
<tr>
<td>Women, %</td>
<td>19.3</td>
<td>19.5</td>
</tr>
<tr>
<td>Arterial hypertension, %</td>
<td>90.1</td>
<td>91.5</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>87.5</td>
<td>87.4</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>24.8</td>
<td>24.2</td>
</tr>
<tr>
<td>Family history of premature CAD, %</td>
<td>36.5</td>
<td>35.7</td>
</tr>
<tr>
<td>Active Smoker, %</td>
<td>14.6</td>
<td>15.3</td>
</tr>
<tr>
<td>Prior myocardial infarction, %</td>
<td>25.9</td>
<td>24.5</td>
</tr>
<tr>
<td>Prior CABG, %</td>
<td>7.7</td>
<td>7.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.2 [24.9-30.1]</td>
<td>27.5 [24.9-30.4]</td>
</tr>
</tbody>
</table>
### Angiographic and Procedural Characteristics (1/2)

<table>
<thead>
<tr>
<th>Clinical Presentation, %</th>
<th>Six months Clopidogrel (n=1997)</th>
<th>Twelve months Clopidogrel (n=2003)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48.6</td>
<td>47.8</td>
</tr>
<tr>
<td>- Stable CAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- NSTE-ACS</td>
<td>31.9</td>
<td>32.0</td>
</tr>
<tr>
<td>- STEMI</td>
<td>7.9</td>
<td>8.3</td>
</tr>
<tr>
<td>- Silent Ischemia</td>
<td>10.9</td>
<td>11.3</td>
</tr>
<tr>
<td>- Arrhythmia</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Reduced LVEF, %</td>
<td>25.7</td>
<td>26.9</td>
</tr>
<tr>
<td>Multivessel Disease, %</td>
<td>61.3</td>
<td>61.8</td>
</tr>
<tr>
<td>Target Vessel, %</td>
<td>39.8</td>
<td>40.6</td>
</tr>
<tr>
<td>- LAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- LCx</td>
<td>26.4</td>
<td>24.0</td>
</tr>
<tr>
<td>- RCA</td>
<td>31.8</td>
<td>34.0</td>
</tr>
<tr>
<td>- Left Main</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>- Bypass Graft</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Lesion characteristics, %</td>
<td>42.3</td>
<td>45.5</td>
</tr>
<tr>
<td>- Complex lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Chronic total occlusion</td>
<td>7.8</td>
<td>7.4</td>
</tr>
<tr>
<td>- Bifurcation lesion</td>
<td>19.3</td>
<td>19.2</td>
</tr>
</tbody>
</table>
### Angiographic and Procedural Characteristics (2/2)

<table>
<thead>
<tr>
<th></th>
<th>Six months Clopidogrel (n=1997)</th>
<th>Twelve months Clopidogrel (n=2003)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel size, mm</td>
<td>3.00 [2.75-3.50]</td>
<td>3.00 [2.75-3.50]</td>
</tr>
<tr>
<td>Multilesion intervention, %</td>
<td>37.5</td>
<td>37.6</td>
</tr>
<tr>
<td>Drug-eluting stent type, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Early gen. PES</td>
<td>2.2</td>
<td>2.3</td>
</tr>
<tr>
<td>- Early gen. SES</td>
<td>8.8</td>
<td>7.8</td>
</tr>
<tr>
<td>- New gen. SES</td>
<td>16.2</td>
<td>16.3</td>
</tr>
<tr>
<td>- Everolimus-eluting stent</td>
<td>47.5</td>
<td>49.3</td>
</tr>
<tr>
<td>- Zotarolimus-eluting stent</td>
<td>15.6</td>
<td>14.7</td>
</tr>
<tr>
<td>- Biolimus-eluting stent</td>
<td>8.3</td>
<td>8.5</td>
</tr>
<tr>
<td>- Bioresorbable EES</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>- Bare metal stent</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>- Drug-coated balloon</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>- Plain balloon angioplasty</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Number of stents</td>
<td>1.67 ±0.95</td>
<td>1.69 ±0.97</td>
</tr>
<tr>
<td>Total stented length, mm</td>
<td>28 [18-43]</td>
<td>28 [18-43]</td>
</tr>
</tbody>
</table>
Primary Endpoint

Composite of death, MI, stent thrombosis, stroke or TIMI major bleeding (%)

- 12 months of clopidogrel: 1.6%
- 6 months of clopidogrel: 1.5%

Δ -0.1%, 1-sided 95% CI 0.5%, \( P \) Noninferiority <0.001

Months after randomization
Composite of Death, Myocardial Infarction, Stent thrombosis or Stroke

HR 0.87 [95% CI 0.51-1.47]; P=0.59

12 months of clopidogrel: 1.5%
6 months of clopidogrel: 1.3%
TIMI Major or Minor Bleeding

HR 0.46 [95% CI 0.18-1.21]; p=0.12

Incidence (%) over time:
- 6 months of clopidogrel: 0.3%
- 12 months of clopidogrel: 0.7%
## Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Six months Clopidogrel (n=1997)</th>
<th>Twelve months Clopidogrel (n=2003)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>8 (0.4)</td>
<td>12 (0.6)</td>
<td>0.66 (0.27-1.63)</td>
<td>0.37</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13 (0.7)</td>
<td>14 (0.7)</td>
<td>0.93 (0.44-1.97)</td>
<td>0.85</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>5 (0.3)</td>
<td>4 (0.2)</td>
<td>1.25 (0.33-4.65)</td>
<td>0.74</td>
</tr>
<tr>
<td>(definite or probable)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>7 (0.4)</td>
<td>5 (0.3)</td>
<td>1.40 (0.44-4.41)</td>
<td>0.57</td>
</tr>
<tr>
<td>TIMI major Bleeding</td>
<td>4 (0.2)</td>
<td>5 (0.3)</td>
<td>0.80 (0.21-2.98)</td>
<td>0.74</td>
</tr>
</tbody>
</table>
### Additional Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Six months Clopidogrel (n=1997)</th>
<th>Twelve months Clopidogrel (n=2003)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite stent thrombosis</td>
<td>5 (0.3)</td>
<td>3 (0.2)</td>
<td>1.66 (0.40-6.96)</td>
<td>0.49</td>
</tr>
<tr>
<td>TIMI minor bleeding</td>
<td>2 (0.1)</td>
<td>8 (0.4)</td>
<td>0.25 (0.05-1.17)</td>
<td>0.08</td>
</tr>
<tr>
<td>BARC Bleeding ≥ Class 2</td>
<td>20 (1.0)</td>
<td>40 (2.0)</td>
<td>0.50 (0.29-0.85)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Subgroup Analysis

No. of events / total (%) | Hazard Ratio [95% Confidence Interval] | P for interaction
---|---|---
6 months Clopidogrel | 12 months Clopidogrel

**All patients**
- 29/1997 (1.5)
- 32/2003 (1.6)
- Hazard Ratio: 0.91 [0.55-1.50]

**Age**
- ≥67.2 years: 15/999 (1.5)
- <67.2 years: 14/998 (1.4)
- Hazard Ratio: 0.60 [0.31-1.13], P = 0.03

**Gender**
- Women: 2/386 (0.6)
- Men: 27/1611 (1.7)
- Hazard Ratio: 0.29 [0.06-1.38], P = 0.12

**Diabetes**
- Yes: 9/495 (1.9)
- No: 20/1501 (1.4)
- Hazard Ratio: 0.73 [0.31-1.73], P = 0.55

**ACS at Index PCI**
- Yes: 14/794 (1.8)
- No: 15/1200 (1.3)
- Hazard Ratio: 0.83 [0.41-1.68], P = 0.72

**Complex Lesion**
- Yes: 14/837 (1.7)
- No: 15/1140 (1.3)
- Hazard Ratio: 0.94 [0.46-1.92], P = 0.92

**Left Ventricular Ejection Fraction**
- ≥55%: 14/1374 (1.0)
- <55%: 12/476 (2.6)
- Hazard Ratio: 0.87 [0.43-1.79], P = 0.95

6 months Clopidogrel better | 12 months Clopidogrel better
Conclusion

• In the ISAR-SAFE trial, we did not observe a significant difference in net clinical outcome between 6 months and 12 months of clopidogrel therapy after DES implantation

• However, the results of the trial must be considered in view of its premature termination and lower than expected event rates
Thank you for your attention