Guided de-escalation of antiplatelet treatment in ACS patients undergoing PCI

Results of the TROPICAL-ACS study: a randomised, investigator-initiated, open-label, multicentre-trial

Background I – Platelet inhibition in ACS patients

- Current guidelines\(^1\) recommend **uniform & potent platelet inhibition** with prasugrel or ticagrelor for 12 months after PCI for ACS
- However, **risk patterns** (early vs. late risk) for ischaemic and bleeding complications **differ over time**\(^2,3\)

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\(^1\)Roffi et al., ESC ACS Guidelines, EHJ 2016, \(^2\)Antman et al., JACC 2008; \(^3\)Becker et al., EHJ 2011
Background II – Early anti-ischaemic benefit of potent inhibition

Wiviott et al., NEJM 2007
Background III – Late excess & growing bleeding risk over time

Antman et al., JACC 2008
Background IV – Concept of de-escalation

- Conceptually, a stage-adapted treatment with **de-escalation from potent drugs to the less potent clopidogrel** early after an ACS may be beneficial.

- To date, **solid evidence showing safety of de-escalation** is lacking.

- Despite of this, **DAPT de-escalation is commonly done** for clinical (e.g. bleeding, side-effects) and economic (generic clopidogrel) reasons (TRANSLATE-ACS\(^1\)).

- A potential obstacle for de-escalation could be **clopidogrel’s large response variability**\(^2\) - any de-escalation regimen should account for this issue

\(^1\)Zettler et al., AHJ 2017, \(^2\)Gurbel et al., Circulation 2003
Background V – Levels of platelet inhibition & outcomes

Collaborative meta analysis:
- 17 studies
- 20,839 patients

- Platelet function testing (PFT) could serve to make de-escalation safer by identifying low responders to clopidogrel.

Aradi, ..., Sibbing, EHJ 2015
In the TROPICAL-ACS* trial we aimed to investigate the safety and efficacy of early de-escalation of antiplatelet treatment from prasugrel to clopidogrel guided by platelet function testing (PFT).

* TROPICAL-ACS: Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes
Trial Conduct (33 study sites in Europe)

**Academic Sponsor**
Klinikum der Universität München, LMU Munich

**Steering Committee**
Steffen Massberg (Chair), Dirk Sibbing (CI), Daniel Aradi, Lukasz Koltowski, Kurt Huber, Franz-Josef Neumann, Julinda Mehilli, Jörg Hausleiter

**Coordinating Center**
CSCLMU, Clinical Study Center, LMU Munich

**Study Monitoring and Data Management**
Monitoring: Münchner Studienzentrum (MSZ)
Data Management: Technische Universität Dresden (KKS)

**Data Safety and Monitoring Board (DSMB)**
Albert Schömig, Helmut Schühlen, Martin Hadamitzky

**Independent Event Adjudication Committee (EAC)**
Dritan Poci, Jürgen Pache, Ute Wilbert Lampen
**Inclusion Criteria**

- Biomarker positive ACS
- Successful PCI
- Planned DAPT for 12 months after PCI
- Written informed consent

**Key Exclusion Criteria**

- Age <18 years and >80 years
- Contraindications to study drugs
- Active bleeding
- History of TIA or stroke
- Concomitant treatment with anticoagulants (e.g. VKA, NOACS)
- Indication for major surgery
Primary study endpoint

Composite endpoint consisting of:
- Death from cardiovascular cause
- Myocardial infarction
- Stroke
- Bleeding events grade 2 or above (BARC criteria)

„Net-clinical benefit“: assessed for non-inferiority @ 1 year follow-up
Secondary study endpoints

- **Bleeding events 2 or above according to BARC criteria**
  - = key secondary EP: assessed for superiority
- Death from any cause
- Stent thrombosis according to ARC criteria
- Ischemic components (combined & singular) of the primary endpoint
- Urgent revascularization

@ 1 year follow-up
**Trial Design**

**Biomarker positive ACS patients with successful PCI**

**Control group**
- 14 days prasugrel

**Guided de-escalation group**
- 7 days prasugrel
- 7 days clopidogrel

PFT (Multiplate analyser) @ 2 weeks after discharge

- **Low Responders (HPR*)**
  - 11½ months prasugrel
- **Good Responders (no HPR*)**
  - 11½ months clopidogrel

**Uniform antiplatelet therapy with prasugrel**

*HPR denotes high platelet reactivity

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For further details on TROPICAL-ACS trial design see: Sibbing et al., Thromb Haemost. 2017;117:188-195 -
Sample size calculation

Primary hypothesis:
Non-inferiority of PFT-guided de-escalation vs. standard 1-year prasugrel treatment

Statistical assumptions:
- Incidence for the primary endpoint @ 1 year follow-up: 10.5%
- Non-inferiority margin of 30%
- Power: 80%, alpha-level: 5%
- Sample size: 1197 patients per group
- 1300 planned to compensate for losses to follow-up
Biomarker positive ACS patients (n=2610) with successful PCI

Control (n=1306)
- 14 days prasugrel

Guided de-escalation (n=1304)
- 7 days prasugrel
- 7 days clopidogrel

PFT (Multiplate analyser) @ 2 weeks after discharge
- Low Responders (40%)
- Good Responders (60%)

Follow-up:
- 98% @ 2 weeks
- 96% @ 12 months

Adherence to treatment: >94% in both groups

R*: 1:1

Dec 2013 – May 2016

Study patients & follow-up data
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group (n = 1306)</th>
<th>Guided de-escalation group (n = 1304)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59 (SD 10)</td>
<td>59 (SD 10)</td>
</tr>
<tr>
<td>Female sex</td>
<td>283 (22%)</td>
<td>275 (21%)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>186 (14%)</td>
<td>173 (13%)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>46 (4%)</td>
<td>39 (3%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>153 (12%)</td>
<td>140 (11%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>287 (22%)</td>
<td>240 (18%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>591 (45%)</td>
<td>591 (45%)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>806 (62%)</td>
<td>793 (61%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>529 (41%)</td>
<td>546 (42%)</td>
</tr>
</tbody>
</table>
## Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 1306)</th>
<th>Guided de-escalation group (n = 1304)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>722 (55%)</td>
<td>731 (56%)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>584 (45%)</td>
<td>573 (44%)</td>
</tr>
<tr>
<td>Access site:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial</td>
<td>3 (&lt;1%)</td>
<td>--</td>
</tr>
<tr>
<td>Femoral</td>
<td>541 (41%)</td>
<td>523 (40%)</td>
</tr>
<tr>
<td>Radial</td>
<td>762 (58%)</td>
<td>781 (60%)</td>
</tr>
<tr>
<td>Diseased vessels:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>682 (52%)</td>
<td>659 (51%)</td>
</tr>
<tr>
<td>2</td>
<td>345 (26%)</td>
<td>359 (28%)</td>
</tr>
<tr>
<td>3</td>
<td>279 (21%)</td>
<td>286 (22%)</td>
</tr>
<tr>
<td>Anticoagulant for PCI:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>55 (4%)</td>
<td>54 (4%)</td>
</tr>
<tr>
<td>LMWH</td>
<td>70 (5%)</td>
<td>72 (6%)</td>
</tr>
<tr>
<td>UFH</td>
<td>1181 (90%)</td>
<td>1178 (90%)</td>
</tr>
<tr>
<td>Stent type:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DES</td>
<td>1002 (77%)</td>
<td>1003 (77%)</td>
</tr>
<tr>
<td>BMS</td>
<td>208 (16%)</td>
<td>224 (17%)</td>
</tr>
<tr>
<td>BVS</td>
<td>83 (6%)</td>
<td>68 (5%)</td>
</tr>
<tr>
<td>None (POBA)</td>
<td>13 (1%)</td>
<td>9 (1%)</td>
</tr>
</tbody>
</table>
Primary Endpoint (CVD, MI, stroke, BARC ≥2)

Event probability (%)

No. at risk
Control 1306 1238 1220 1190 1132 1124 924
De-escalation 1304 1234 1213 1189 1129 1124 942

HR 0.81 (0.62-1.06)
p = 0.0004 for non-inferiority
(p = 0.1202 for superiority)

-- Control group
-- Guided de-escalation group

ESC CONGRESS
BARCELONA 2017
#esccongress
www.escardio.org/ESC2017
Key Secondary endpoint
Bleeding BARC ≥2

All bleeding events (BARC 1 to 5)
Ischemic events at 12 months follow-up

- All-cause mortality: 12 events (1%) in control vs. 11 (1%) in guided de-escalation group, p=0.85

- Definite ST: 3 events (0.2%) in control vs. 2 (0.2%) in guided de-escalation group, p=0.66

HR 0.77 (0.48-1.21) p=0.0115 for non-inferiority
### Subgroup Analyses (primary endpoint)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>$p$ value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.81 (0.62-1.06)</td>
<td></td>
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<tr>
<td>ACS-Presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI (n=1453)</td>
<td>0.54 (0.35-0.83)</td>
<td>0.01</td>
</tr>
<tr>
<td>NSTEMI (n=1157)</td>
<td>1.10 (0.77-1.58)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (n=2052)</td>
<td>0.78 (0.57-1.06)</td>
<td>0.60</td>
</tr>
<tr>
<td>Women (n=558)</td>
<td>0.92 (0.63-1.62)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 70 years (n=370)</td>
<td>1.17 (0.69-2.01)</td>
<td>0.11</td>
</tr>
<tr>
<td>$\leq$ 70 years (n=2240)</td>
<td>0.70 (0.51-0.96)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=527)</td>
<td>1.17 (0.71-1.93)</td>
<td>0.10</td>
</tr>
<tr>
<td>No (n=2083)</td>
<td>0.71 (0.52-0.99)</td>
<td></td>
</tr>
</tbody>
</table>

Guided de-escalation better

Uniform prasugrel better
Conclusions

- A stage-adapted and individualized antiplatelet treatment with initial potent platelet inhibition (prasugrel), followed by guided DAPT de-escalation to clopidogrel proved to be feasible and safe when compared to conventional 12-month prasugrel therapy in ACS patients undergoing PCI.

- PFT-guided DAPT de-escalation should be considered as an alternative DAPT strategy in ACS patients undergoing PCI.
Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial

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Summary

Background Current guidelines recommend potent platelet inhibition with prasugrel or ticagrelor for 12 months after an acute coronary syndrome managed with percutaneous coronary intervention (PCI). However, the greatest anti-ischaemic benefit of potent antiplatelet drugs over the less potent clopidogrel occurs early, while most excess bleeding events arise during chronic treatment. Hence, a stage-adapted treatment with potent platelet inhibition in the acute phase and de-escalation to clopidogrel in the maintenance phase could be an alternative approach. We aimed to investigate the safety and efficacy of early de-escalation of antiplatelet treatment from prasugrel to clopidogrel guided by platelet function testing (PFT).
Thanks for your attention!