Ticagrelor vs Aspirin in Patients undergoing Coronary-Artery Bypass Grafting

Heribert Schunkert, MD
on behalf of
the TiCAB Investigators
TiCAB – an investigator initiated trial

Sponsor
Deutsches Herzzentrum München
Lazarettstr. 36
80636 Munich, Germany

Facilitated through a grant by AstraZeneca GmbH

A Randomized, Parallel Group, Double-Blind Study of Ticagrelor Compared with Aspirin for Prevention of Vascular Events in Patients Undergoing Coronary Artery Bypass Graft Operation*
April 2013 to May 2018

* de Waha et al Am Heart J. 2016;179:69-76
TiCAB Investigators

• Steering Committee
Prof. Dr. H. Schunkert, Prof. Dr. A. Böning, Prof. Dr. J. Cremer, Prof. Dr. C. Hamm, Prof. Dr. A. Kastrati, Prof. Dr. R. Lange, Prof. Dr. K. Laugwitz, Prof. Dr. S. Massberg, Prof. Dr. P. Radke, Ass.-Prof. Dr. S. Sandner, Prof. Dr. R. Schulz, Prof. Dr. H.-H. Sievers, Prof. Dr. U. Zeymer

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• Data Safety Monitoring Board
Prof. Dr. M. Gottwik (Chair), Prof. Dr. H. Oelert, Prof. Dr. S. Haigl, Prof. Dr. T. Meinert, Prof. Dr. K. Wegscheider

• Event Adjudication Committee
Prof. Dr. U. Tebbe (Chair), Prof. Dr. B. Nowak, Dr. J. Stritzke
• Graft failure is related to major adverse events

• Graft failure peaks in first year post surgery

• More intense platelet inhibition has been shown to prevent graft failure
Study Hypothesis

Ticagrelor, as compared to aspirin, reduces major adverse cardiovascular events within one year after CABG operation.
**TiCAB (3VG, LM, 2VD+EF<50% - stable CAD and ACS)**

Primary end point: CV death, MI, stroke and revascularisation

- estimated event rate: 13% in the control group
- Two-sided $\alpha$ level of 0.0492 (0.05 adjusted for a planned interim analysis)
- Power of 0.80
- Expected relative risk of 0.775 in the active group
- Total of 3760 patients required

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**STICH trial (CHF):**
Mortality 12% at 1 year

**SYNTAX trial (3VD and LM):**
MACCE rate 12.4% at 1 year

**PLATO-CABG (ACS):**
MACCE
- Ticagrelor/ Aspirin: 10.6%
- Clopidogrel/ Aspirin: 13.1%
Secondary Endpoints @ 12 months

• Safety endpoint: Incidence of major bleeding events

• Components of the primary endpoint:
  – Cardiovascular death
  – Myocardial infarction
  – Stroke
  – Recurrent revascularization
Study Design

• Randomized
• Double blind
• Parallel group
• International multicenter
• Phase III study
Inclusion Criteria

1. Patients 18 years of age or older – and
2. Informed, written consent by the patient – and
3. Indication for CABG surgery – and
   - coronary three vessel disease, or
   - left main stenosis, or
   - two vessel disease with impaired EF (< 50%)
1. Cardiogenic shock, haemodynamic instability
2. Indication for oral anticoagulation or dual antiplatelet therapy
3. Need for concomitant non-coronary surgery (e.g. valve replacement)
4. Contraindication for Aspirin or Ticagrelor use (e.g. known allergy)
5. ....
Aspirin vs Ticagrelor after CABG - TiCAB Trial

Follow-up

• 1\textsuperscript{st} Visit: CABG - Hospital visit

• 2\textsuperscript{nd} Visit: 3 months after CABG - Hospital visit

• 3\textsuperscript{rd} Visit: 6 months after CABG - Telephone visit

• 4\textsuperscript{th} Visit: 9 months after CABG - Telephone visit

• 5\textsuperscript{th} Visit: 12 months after CABG - Hospital visit
TiCAB Trial - Recruitment

Recruitment (cumulative)
04/2013 – 03/2017

Total recruitment: 1893 patients

September 2016 cancelation of funding by the manufacturer of ticagrelor
Aspirin vs Ticagrelor after CABG - TiCAB Trial

Follow-up

• The trial was continued with in-house funding of the German Heart Center
• The planned interim analysis by the DSMB was scheduled for March 2018
• The DSMB suggested the trial to be stopped
Aspirin vs Ticagrelor after CABG - TiCAB Trial

Trial Enrollment, Randomization and Follow-up

1,893 patients randomized

34 patients excluded
- withdrew consent before CABG
- surgery withheld

928 patients randomized to Aspirin
32 patients received no study med.:
3 Perioperative death or liver failure
4 CABG plus valve replacement
19 Indication for DAPT or OAC
6 Patients refused study medication

931 patients randomized to Ticagrelor
33 patients received no study med.:
5 Perioperative death or liver failure
2 CABG plus valve replacement
23 Indication for DAPT or OAC
3 Patients refused study medication
### Baseline Characteristics (I)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Aspirin Group (n=928)</th>
<th>Ticagrelor Gr. (n=931)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, no. (%)</td>
<td>785 (84.6)</td>
<td>794 (85.3)</td>
</tr>
<tr>
<td>Age – years</td>
<td>67.0 ± 10.2</td>
<td>66.4 ± 10.1</td>
</tr>
<tr>
<td>Stable angina, no. (%)</td>
<td>646 (69.6)</td>
<td>642 (69.0)</td>
</tr>
<tr>
<td>Unstable angina, no. (%)</td>
<td>117 (12.6)</td>
<td>126 (13.5)</td>
</tr>
<tr>
<td>Non-ST-elevation myocardial infarction, no. (%)</td>
<td>165 (17.8)</td>
<td>163 (17.5)</td>
</tr>
<tr>
<td>History of myocardial infarction, no. (%)</td>
<td>204 (22.0)</td>
<td>218 (23.4)</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>836 (90.1)</td>
<td>836 (89.8)</td>
</tr>
<tr>
<td>Hyperlipidemia, no. (%)</td>
<td>754 (81.3)</td>
<td>765 (82.2)</td>
</tr>
<tr>
<td>Smoking, no. (%)</td>
<td>187 (20.2)</td>
<td>200 (21.5)</td>
</tr>
<tr>
<td>Ex-Smoking, no. (%)</td>
<td>321 (34.6)</td>
<td>320 (34.4)</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>330 (35.6)</td>
<td>338 (36.3)</td>
</tr>
<tr>
<td><strong>Left ventricular ejection fraction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 %, no. (%)</td>
<td>16 (1.8)</td>
<td>17 (1.9)</td>
</tr>
<tr>
<td>30%-50%, no. (%)</td>
<td>232 (25.6)</td>
<td>225 (24.7)</td>
</tr>
<tr>
<td>&gt;50%, no. (%)</td>
<td>646 (71.1)</td>
<td>659 (72.4)</td>
</tr>
</tbody>
</table>
### Baseline Characteristics (II)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Aspirin Group (n=928)</th>
<th>Ticagrelor Gr. (n=931)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extent of coronary artery disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three vessel disease, no. (%)</td>
<td>858 (92.5)</td>
<td>855 (91.8)</td>
</tr>
<tr>
<td>Two vessel disease and EF (&lt; 50 %), no. (%)</td>
<td>60 (6.5)</td>
<td>67 (7.2)</td>
</tr>
<tr>
<td>Left main disease, no. (%)</td>
<td>365 (39.3)</td>
<td>387 (41.6)</td>
</tr>
<tr>
<td><strong>Medication use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin, no. (%)</td>
<td>731 (78.8)</td>
<td>727 (78.1)</td>
</tr>
<tr>
<td>P2Y12-Inhibitor, no. (%)</td>
<td>81 (8.7)</td>
<td>98 (10.5)</td>
</tr>
<tr>
<td>- Ticagrelor, no. (%)</td>
<td>26 (2.8)</td>
<td>37 (4.0)</td>
</tr>
<tr>
<td>- Prasugrel, no. (%)</td>
<td>0 (0.0)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>- Clopidogrel, no. (%)</td>
<td>55 (5.9)</td>
<td>57 (6.1)</td>
</tr>
<tr>
<td>Oral anticoagulant, no. (%)</td>
<td>4 (0.4)</td>
<td>1 (0.1)</td>
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<tr>
<td>β-blockers, no. (%)</td>
<td>606 (65.3)</td>
<td>635 (68.2)</td>
</tr>
<tr>
<td>ACEI or ARB, no. (%)</td>
<td>198 (21.3)</td>
<td>242 (26.0)</td>
</tr>
<tr>
<td>Calcium antagonist, no. (%)</td>
<td>202 (21.8)</td>
<td>199 (21.4)</td>
</tr>
<tr>
<td>Diuretics, no. (%)</td>
<td>288 (31.0)</td>
<td>286 (30.7)</td>
</tr>
<tr>
<td>Statins, no. (%)</td>
<td>779 (83.9)</td>
<td>776 (83.4)</td>
</tr>
<tr>
<td>Nitrates, no. (%)</td>
<td>53 (5.7)</td>
<td>50 (5.4)</td>
</tr>
<tr>
<td>Proton pump inhibitor, no. (%)</td>
<td>264 (28.4)</td>
<td>304 (32.7)</td>
</tr>
</tbody>
</table>
Results – CV death, MI, stroke, repeat revascularization

Aspirin vs Ticagrelor after CABG - TiCAB Trial

Primary End Point

Aspirin vs Ticagrelor after CABG - TiCAB Trial

Primary End Point

Aspirin
Ticagrelor

HR 1.19
95% CI 0.87-1.62
P=0.27

8.2%
9.7%

0 2 4 6 8 10 12

Months after Enrollment

Primary End Point (%)
Aspirin vs Ticagrelor after CABG - TiCAB Trial

Results – Secondary Endpoints

**Cardiovascular Death**

- Aspirin
- Ticagrelor

HR 0.85
CI 0.38-1.89
P=0.68

**Myocardial infarction**

- Aspirin
- Ticagrelor

HR 0.63
CI 0.36-1.12
P=0.12
Aspirin vs Ticagrelor after CABG - TiCAB Trial

Results – Secondary Endpoints

**Stroke**
- Hazard Ratio (HR): 1.21
- Confidence Interval (CI): 0.70-2.08
- P-value: 0.49

**Revascularization**
- Hazard Ratio (HR): 1.28
- Confidence Interval (CI): 0.82-2.00
- P-value: 0.28
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Results – MACE and Total mortality

**MACE**

- **Aspirin**
  - HR 0.99
  - CI 0.69-1.42
  - P=0.94

- **Ticagrelor**
  - 2.5%
  - 6.5%

**All Cause Death**

- **Aspirin**
  - HR 0.96
  - CI 0.53-1.72
  - P=0.89

- **Ticagrelor**
  - 2.4%
  - 6.3%

*CV death, myocardial infarction or stroke
Results – Bleeding events

Bleeding (BARC 3, 4 and 5)

- Aspirin vs Ticagrelor after CABG - TiCAB Trial

- Aspirin: 3.7%
- Ticagrelor: 3.2%

HR 1.17, CI 0.71-1.92, P=0.53
### Results – Primary Endpoint Subgroup analysis

#### Aspirin vs Ticagrelor after CABG - TiCAB Trial

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Aspirin Group</th>
<th>Ticagrelor Group</th>
<th>Hazard Ratio (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value</th>
<th>Homogeneity</th>
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</thead>
<tbody>
<tr>
<td><strong>no. of events (%)</strong></td>
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<tr>
<td><strong>ACS</strong></td>
<td></td>
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<tr>
<td>Yes</td>
<td>18/165</td>
<td>15/163</td>
<td>0.82 (0.41-1.63)</td>
<td></td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>55/763</td>
<td>71/768</td>
<td>1.31 (0.92-1.86)</td>
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</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 75</td>
<td>14/179</td>
<td>15/148</td>
<td>1.36 (0.66-2.82)</td>
<td></td>
<td>0.08</td>
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<tr>
<td>60-75</td>
<td>39/546</td>
<td>57/575</td>
<td>1.40 (0.93-2.10)</td>
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<tr>
<td>&lt; 60</td>
<td>20/203</td>
<td>14/208</td>
<td>0.68 (0.34-1.34)</td>
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<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>11/143</td>
<td>14/137</td>
<td>1.38 (0.63-3.10)</td>
<td></td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62/785</td>
<td>72/794</td>
<td>1.15 (0.82-1.62)</td>
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<td></td>
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<tr>
<td><strong>Diabetes</strong></td>
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<tr>
<td>Yes</td>
<td>28/330</td>
<td>36/338</td>
<td>1.26 (0.77-2.07)</td>
<td></td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>45/593</td>
<td>49/490</td>
<td>1.11 (0.74-1.67)</td>
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<tr>
<td><strong>PCI</strong></td>
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<tr>
<td>Yes</td>
<td>22/182</td>
<td>20/193</td>
<td>0.90 (0.49-1.64)</td>
<td></td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>51/744</td>
<td>66/738</td>
<td>1.31 (0.91-1.89)</td>
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<tr>
<td><strong>LVEF</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>2/16</td>
<td>2/17</td>
<td>1.00 (0.14-7.11)</td>
<td></td>
<td>0.82</td>
<td></td>
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<tr>
<td>30-50</td>
<td>26/232</td>
<td>28/225</td>
<td>1.11 (0.65-1.90)</td>
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<td></td>
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<tr>
<td>&gt; 50</td>
<td>43/646</td>
<td>55/659</td>
<td>1.28 (0.86-1.90)</td>
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<tr>
<td><strong>Off-Pump</strong></td>
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<tr>
<td>Yes</td>
<td>3/32</td>
<td>6/33</td>
<td>2.16 (0.54-8.63)</td>
<td></td>
<td>0.39</td>
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<tr>
<td>No</td>
<td>70/896</td>
<td>80/898</td>
<td>1.15 (0.83-1.59)</td>
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<tr>
<td><strong>Protocol</strong></td>
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<tr>
<td>Old</td>
<td>12/122</td>
<td>9/123</td>
<td>0.74 (0.31-1.76)</td>
<td></td>
<td>0.25</td>
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<tr>
<td>New</td>
<td>61/806</td>
<td>77/808</td>
<td>1.28 (0.91-1.79)</td>
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<tr>
<td><strong>Vein graft</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>44/518</td>
<td>51/536</td>
<td>1.13 (0.76-1.70)</td>
<td></td>
<td>0.73</td>
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<tr>
<td>≤ 2</td>
<td>29/410</td>
<td>35/395</td>
<td>1.27 (0.78-2.10)</td>
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<td><strong>Arterial graft</strong></td>
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<td></td>
</tr>
<tr>
<td>≥ 1</td>
<td>55/639</td>
<td>62/641</td>
<td>1.13 (0.78-1.62)</td>
<td></td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>18/289</td>
<td>24/290</td>
<td>1.37 (0.74-2.53)</td>
<td></td>
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</tr>
</tbody>
</table>
Limitations of the Study

- The event rates were lower than expected
- The study was terminated early after half of the anticipated patients were included
- A main source of funding terminated the contract
- Ticagralor displayed no signal for better outcome
- The DSMB suggested to stop recruitment
The use of ticagrelor monotherapy instead of aspirin monotherapy in patients undergoing CABG did not significantly impact the rates of major CV events nor major bleeding events.
Aspirin vs Ticagrelor after CABG - TiCAB Trial

Thank you for your attention!
THANK YOU!