Ticagrelor vs Aspirin in Patients undergoing Coronary-Artery Bypass Grafting

*Heribert Schunkert, MD*

on behalf of

the TiCAB Investigators
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• **Event Adjudication Committee**
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After CABG Surgery

• Graft failure peaks in first year and is related to major adverse events

• Graft failure and other ischemic events may be prevented by more intensive platelet inhibition
Ticagrelor, as compared to aspirin, reduces major adverse cardiovascular events within one year after CABG operation.
Aspirin vs Ticagrelor after CABG - TiCAB Trial

Study Design

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

An investigator initiated trial partially funded through a grant by AstraZeneca
Primary Endpoint @ 12 months*

• Incidence of:
  – Cardiovascular death
  – Myocardial infarction
  – Stroke
  – Recurrent revascularization

* Supported by a power calculation and incidence rates observed in STICH, SYNTAX and PLATO-CABG
Safety Endpoint @ 12 months*

- Incidence of major bleeding events

* Periprocedural CABG and hospital stay-related: BARC 4 & 5
  Post-discharge: BARC ≥Type 3
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%)
Exclusion Criteria

1. Cardiogenic shock, haemodynamic instability
2. Indication for oral anticoagulation or dual antiplatelet therapy
3. Concomitant non-coronary surgery (e.g. valve replacement)
4. Contraindication for Aspirin or Ticagrelor use (e.g. known allergy)
5. ...
TiCAB Trial - Recruitment

Recruitment (cumulative)
04/2013 – 03/2017

- 3760 patients planned by power calculation
- Total recruitment: 1893 patients

- September 2016: cancelation of funding by the manufacturer of ticagrelor
- March 2018: DSMB suggested to stop the trial
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>
</tr>
<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
- Ticagrelor

HR 1.19
95% CI 0.87-1.62
P=0.27

8.2% after Aspirin
9.7% after Ticagrelor

Months after Enrollment

Primary End Point (%)

0 2 4 6 8 10 12
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**
- Aspirin
- Ticagrelor

HR 1.21
CI 0.70-2.08
P=0.49

**Revascularization**
- Aspirin
- Ticagrelor

HR 1.28
CI 0.82-2.00
P=0.28

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**Months after Enrollment**

- Stroke:
  - Aspirin: 2.6%
  - Ticagrelor: 3.2%

- Revascularization:
  - Aspirin: 3.9%
  - Ticagrelor: 5.0%
Aspirin vs Ticagrelor after CABG - TiCAB Trial

Results – MACE and Total mortality

*CV death, myocardial infarction or stroke
Aspirin vs Ticagrelor after CABG - TiCAB Trial

Results – Bleeding events

Bleeding (BARC 3, 4 and 5)

- Aspirin
- Ticagrelor

HR 1.17
CI 0.71-1.92
P=0.53

3.7%
3.2%

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

#### Results – Primary Endpoint

Subgroup analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Aspirin Group no. of events</th>
<th>Ticagrelor Group no. of events</th>
<th>Hazard Ratio (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value for Homogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>18/165</td>
<td>15/163</td>
<td>0.82 (0.41-1.63)</td>
<td>1.31 (0.92-1.86)</td>
<td>0.23</td>
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<tr>
<td>Age</td>
<td>55/763</td>
<td>71/768</td>
<td>1.36 (0.66-2.82)</td>
<td>0.68 (0.34-1.34)</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex</td>
<td>Female 11/143</td>
<td>14/137</td>
<td>1.38 (0.63-3.10)</td>
<td>1.15 (0.82-1.62)</td>
<td>0.65</td>
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<tr>
<td></td>
<td>Male 62/785</td>
<td>72/794</td>
<td>1.26 (0.77-2.07)</td>
<td>1.11 (0.74-1.67)</td>
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<tr>
<td>Diabetes</td>
<td>Yes 28/330</td>
<td>36/338</td>
<td>0.90 (0.49-1.64)</td>
<td>0.91 (0.91-1.89)</td>
<td>0.44</td>
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<tr>
<td></td>
<td>No 45/593</td>
<td>49/490</td>
<td>1.31 (0.65-1.90)</td>
<td>1.28 (0.66-1.90)</td>
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<td>PCI</td>
<td>Yes 22/182</td>
<td>20/193</td>
<td>1.00 (0.14-7.11)</td>
<td>0.76 (0.17-3.51)</td>
<td>0.5</td>
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<tr>
<td></td>
<td>No 51/744</td>
<td>66/738</td>
<td>1.31 (0.49-1.64)</td>
<td>1.15 (0.83-1.59)</td>
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<tr>
<td>LVEF</td>
<td>&lt;30 2/16</td>
<td>2/17</td>
<td>2.16 (0.54-8.63)</td>
<td>1.11 (0.54-8.63)</td>
<td>1.39</td>
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<tr>
<td></td>
<td>&gt;50 43/646</td>
<td>55/659</td>
<td>1.28 (0.86-1.90)</td>
<td>1.28 (0.86-1.90)</td>
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<tr>
<td>Off-Pump</td>
<td>Yes 3/32</td>
<td>6/33</td>
<td>2.16 (0.54-8.63)</td>
<td>1.15 (0.83-1.59)</td>
<td>0.39</td>
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<tr>
<td></td>
<td>No 70/896</td>
<td>80/898</td>
<td>1.31 (0.49-1.64)</td>
<td>1.15 (0.83-1.59)</td>
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<tr>
<td>Arterial graft</td>
<td>≥2 37/486</td>
<td>35/512</td>
<td>0.90 (0.56-1.43)</td>
<td>0.90 (0.56-1.43)</td>
<td>0.06</td>
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<td>1 34/403</td>
<td>45/382</td>
<td>1.42 (0.91-2.22)</td>
<td>1.42 (0.91-2.22)</td>
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<tr>
<td></td>
<td>0 2/39</td>
<td>6/37</td>
<td>3.29 (0.66-16.3)</td>
<td>3.29 (0.66-16.3)</td>
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<tr>
<td>Vein graft</td>
<td>≥3 44/518</td>
<td>51/536</td>
<td>1.13 (0.76-1.70)</td>
<td>1.13 (0.76-1.70)</td>
<td>0.73</td>
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<tr>
<td></td>
<td>≤2 29/410</td>
<td>35/395</td>
<td>1.27 (0.78-2.10)</td>
<td>1.27 (0.78-2.10)</td>
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</tr>
<tr>
<td>Protocol</td>
<td>Old 12/122</td>
<td>9/123</td>
<td>0.74 (0.31-1.76)</td>
<td>0.74 (0.31-1.76)</td>
<td>0.25</td>
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<tr>
<td></td>
<td>New 61/806</td>
<td>77/808</td>
<td>1.28 (0.91-1.79)</td>
<td>1.28 (0.91-1.79)</td>
<td></td>
</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
- The DSMB suggested to stop recruitment
- Ticagrelor displayed no signal for better outcome
Conclusion of the Study

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!
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%

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 α 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
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
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
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
Follow-up

- **1st Visit:** CABG - Hospital visit
- **2nd Visit:** 3 months after CABG - Hospital visit
- **3rd Visit:** 6 months after CABG - Telephone visit
- **4th Visit:** 9 months after CABG - Telephone visit
- **5th Visit:** 12 months after CABG - Hospital visit