Genotype-guided oral P2Y12 inhibition in patients with ST-segment elevation myocardial infarction undergoing primary PCI: a randomized, open-label, multicentre trial

POPular Genetics

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Declaration of interest

- I have nothing to declare
Background

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

1: Ibanez et al. ESC STEMI guidelines, EHJ2018,
Background

• 30% of Caucasians show an inadequate response to clopidogrel resulting in more stent thrombosis

• CYP2C19 Wild type (*1/*1) = normal response
• *2 and *3 loss-of-function alleles = inadequate response

• In wild type patients, clopidogrel demonstrated similar efficacy compared to potent P2Y12 inhibitors²,³

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Background

• Reduction in thrombotic events such as stent thrombosis in past decade\textsuperscript{4-6}

• Bleeding is very common and strongly associated with mortality\textsuperscript{7}

\textsuperscript{4} Wallentin et al. PLATO, NEJM 2009, \textsuperscript{5} Wiviott et al. TRITON-TIMI 38, NEJM 2007, \textsuperscript{6} Sibbing et al. TROPICAL ACS, Lancet 2017, \textsuperscript{7} Généreux et al. ADAPT DES JACC 2015
Hypothesis

• In primary PCI patients genotype-guided oral P2Y12 inhibition is as effective in preventing thrombotic events as the stronger ticagrelor and prasugrel but leads to less bleeding
Trial organisation

• **Trial design**
  – Investigator initiated, randomised, open-label, blinded CEC

• **Sponsor & coordinating centre**
  – St. Antonius Hospital, Nieuwegein, The Netherlands

• **Funding & study support**
  – ZonMw (Efficiency research project no. 171102022)
  – Spartan Bioscience Inc.

**Participating sites**

- St. Antonius Hospital Nieuwegein – J.M. ten Berg
- Isala Hospital Zwolle – A.W.J. van’t Hof
- University Medical Centre Groningen – P. van der Harst
- University Federico II Hospital, Naples – E. Barbato
- Onze Lieve Vrouw Hospital, Aalst – J. Bartunek
- Rijnstate Hospital Arnhem – R.M. Tjon Joe Gin
- University Medical Centre Utrecht Asselbergs – F.W.
- Meander Medical Centre Amersfoort – A. Mosterd
- OLVG Amsterdam – J.P.R. Herman
Protocol change 2012

• **Original protocol:**
  - Standard treatment arm received clopidogrel

• **Protocol May 2012:**
  - Standard treatment arm received ticagrelor or prasugrel
  - The POPular Genetics only evaluates the patients included from May 2012
Inclusion criteria

• Age ≥21 years old
• Signs & symptoms of STEMI >30 minutes, < 12 hours
• Primary PCI + stent implantation

Key exclusion criteria

• Unable to obtain IC <48 hours after primary PCI
• Treatment with oral anticoagulants
• Contraindication to study drugs
• Cardiogenic shock or severe hypertension
Trial design

STEMI patients undergoing primary PCI with stent implantation

R* (1:1)

Standard treatment group

- No genetic testing
  - Prasugrel/ticagrelor for at least 12 months

Genotype-guided group

- Genetic testing for CYP2C19*2 & *3
  - Carrier of CYP2C19 *2 or *3 Prasugrel/ticagrelor for at least 12 months
  - (CYP2C19 *1/*1) Clopidogrel for at least 12 months

<48 hours after primary PCI
Genetic testing

Spartan RX point-of-care system in the cath lab

TaqMan StepOnePlus system
Primary outcomes

• Primary thrombotic & bleeding outcome:
  – All-cause death, recurrent MI, definite stent thrombosis, stroke & PLATO major bleeding at 12 months

• Co-primary bleeding outcome:
  – PLATO major & minor bleeding at 12 months
Sample size calculation

• **Expected event rate primary outcome:**
  – 16.9% in genotype-guided arm\(^1\) vs. 18.8% in standard treatment arm\(^2\)

• **Expected event rate co-primary bleeding outcome:**
  – 14.5% in genotype-guided arm\(^1\) vs. 18.9% in standard treatment arm\(^2\)

• Power 80%, alpha 0.05

• Absolute non-inferiority margin 2%

• 2 x 1250 patients for non-inferiority primary outcome

• Less patients for superiority co-primary bleeding outcome

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Trial patients and follow-up data

Primary PCI
N= 2488

R* (1:1)

No genetic testing (N = 1246)
prasugrel/ticagrelor for at least 12 months
Rate of adherence 82.0%

Genetic testing (N= 1242)
Carrier of CYP2C19 *2 or *3 prasugrel/ticagrelor for at least 12 months
Rate of adherence 84.5%
(CYP2C19 *1/*1) clopidogrel for at least 12 months

May 2012 – April 2018

T = 0
T = 14H
Genetic results: +3H
T = 365 days

99.9% complete follow-up available

99.9% complete follow-up available
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Genotype-guided</th>
<th>Standard treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Age - years</strong></td>
<td>61.9</td>
<td>61.4</td>
</tr>
<tr>
<td><strong>Age ≥75 years - %</strong></td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td><strong>Female - %</strong></td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td><strong>Mean Body-Mass Index</strong></td>
<td>27.5</td>
<td>27.0</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors - %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>History of CAD</td>
<td>11</td>
<td>10</td>
</tr>
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</table>
### Procedural characteristics

<table>
<thead>
<tr>
<th></th>
<th>Genotype-guided</th>
<th>Standard treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin before PCI - %</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitor before PCI - %</td>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>Radial artery access - %</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>Drug Eluting Stent - %</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Diseased coronary vessels ≥50% - %</td>
<td>51</td>
<td>54</td>
</tr>
<tr>
<td>1</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vessels treated during index PCI - %</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Left main</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>Bypass graft</td>
<td>0.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>
## Genetic results & discharge medication

### Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>67.2</td>
</tr>
<tr>
<td>Carriers of *2 or *3 LoF</td>
<td>31.4</td>
</tr>
<tr>
<td>Not available</td>
<td>1.4</td>
</tr>
</tbody>
</table>

### Therapy after randomization & genotyping

<table>
<thead>
<tr>
<th>P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitor - %</th>
<th>Genotype-guided</th>
<th>Standard treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>61</td>
<td>7</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>38</td>
<td>91</td>
</tr>
</tbody>
</table>
Primary outcome

All-cause death, MI, definite stent thrombosis, stroke, PLATO major bleeding

- Standard treatment: 5.9%
- Genotype-guided: 5.1%

HR (95%CI) = 0.86 (0.62 – 1.21)

P_{non-inf} = 0.0002

Time since index PCI (days)
Co-primary outcome

PLATO Major & minor bleeding

- Standard-treatment
- Genotype-guided

Cumulative PLATO major & minor bleeding

Time since index PCI (days)

- Standard-treatment: 12.5%
- Genotype-guided: 9.8%

P=0.04

HR (95%CI) = 0.78 (0.61 – 0.98)
**Secondary bleeding outcomes**

**PLATO minor bleeding**
- HR (95%CI) = 0.72 (0.55 – 0.94)
- Cumulative PLATO minor bleeding:
  - Standard treatment: 10.5%
  - Genotype-guided: 7.6%

**Time since index PCI (days)**

**PLATO major bleeding**
- HR (95%CI) = 0.97 (0.58 – 1.63)
- Cumulative PLATO major bleeding:
  - Standard treatment: 2.3%
  - Genotype-guided: 2.3%

**PLATO minor**: Requiring medical intervention

**PLATO major**: Requiring ≥2U RBC transfusion, intrapericardial Hb drop >3g/dl, significantly disabling, intracranial, fatal
Thrombotic outcome

Vascular death, MI, stent thrombosis & stroke

Cumulative thrombotic events

- Standard treatment
- Genotype-guided

HR (95%CI) = 0.83 (0.53 – 1.31)

Time since index PCI (days)
Conclusion

• POPular Genetics trial demonstrates:
  – Genotyping is easy to use, fast results
  – Almost 2/3 of the patients treated with clopidogrel
  – No difference in thrombotic event rates
  – Reduction in bleeding event rates
Conclusion

• A simple-to-use CYP2C19 genotype-guided strategy to guide treatment early after primary PCI, resulted in less bleeding without increasing the thrombotic risk compared to standard treatment with ticagrelor or prasugrel
A Genotype-Guided Strategy for Oral P2Y$_{12}$ Inhibitors in Primary PCI

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  – Ben M. Swinkels
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  – Fatih Arslan
  – Thijs Plokker

• Investigators: