Ticagrelor With Aspirin or Alone In High-Risk Patients After Coronary Intervention: Thrombogenicity Substudy

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Icahn School of Medicine at Mount Sinai, New York, NY

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Declaration of Interest

The TWILIGHT Trial

Sponsoring organization: Icahn School of Medicine at Mount Sinai, NY

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Coordinated by Icahn School of Medicine at Mount Sinai, NY
## Disclosures

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tbody>
<tr>
<td>Advisory board/personal fees</td>
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</tr>
<tr>
<td>Research Funding to Institution</td>
<td>AstraZeneca</td>
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</tbody>
</table>
• Several trials have shown that monotherapy with a P2Y$_{12}$ inhibitor alone results in similar rates of adverse ischemic events as compared with dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI).\textsuperscript{1-4}

• However, most studies were characterized by relatively infrequent\textsuperscript{1,2} or lower than expected rates of ischemic events\textsuperscript{3,4}, thus compromising power to detect signals of harm upon withdrawal of aspirin.

• Examining the direct effect of aspirin withdrawal on human endovascular thrombosis may provide a mechanistic basis for these observations and additional support for a clinical strategy of P2Y$_{12}$ inhibition alone after PCI.

\textsuperscript{1}Hahn et al., JAMA 2019 \textsuperscript{2}Watanabe et al., JAMA 2019 \textsuperscript{3}Vranckx et al., Lancet 2018 \textsuperscript{4}Mehran et al., NEJM 2019
Objective

To compare the antithrombotic potency of ticagrelor alone versus ticagrelor plus aspirin on ex-vivo whole blood thrombogenicity among high-risk patients undergoing PCI with drug eluting stents (DES)
Design

• TWILIGHT enrolled patients undergoing PCI with DES discharged on ticagrelor plus aspirin for at least 3 months. Event-free patients were randomized to aspirin or placebo (double-blind) and continued ticagrelor.

• Mechanistic-oriented substudy was nested within TWILIGHT and conducted at a single enrolling site (Mount Sinai Hospital, New York)

• Substudy participants were enrolled after randomization in the main trial, at which time pharmacodynamic studies to establish baseline levels of blood thrombogenicity were performed.

• Patients then commenced randomized therapy and returned 1-6 months thereafter for repeat studies.
High-Risk PCI Patients (N=9006)

3 months
Short course DAPT with ticagrelor plus aspirin

Randomized at MSSM (N=128)

Enrolled in PD study (N=51)

First blood draw
- Perfusion assay
- Platelet aggregation

Second blood draw
- Perfusion assay
- Platelet aggregation

Ticagrelor + Aspirin

Ticagrelor + Placebo

Study Schema
Endpoints and Experimental Methods

• **Primary Endpoint**
  - **Blood thrombogenicity** (platelet-dependent thrombus area) at the post-randomization visit using the Badimon perfusion chamber\(^5\)
  - Validated, *ex-vivo* model that generates thrombus under dynamic flow conditions of shear stress that mimic moderate arterial stenosis (high shear; 1690 sec\(^{-1}\)).
  - Native, non-anticoagulated whole blood is perfused over disrupted porcine tunica media, which is then processed and quantified using digital planimetry (µm\(^2\)).

• **Secondary Endpoint**
  - Platelet reactivity in whole blood measured with impedance aggregometry (Multiplate Analyzer\(^\circledR\) DiaPharma - West Chester, OH)
  - Agonists included adenosine diphosphate (ADP), arachidonic acid (AA), collagen and thrombin receptor activator peptide-6 (TRAP).

\(^5\)Vilahur et al., Circulation 2004
• Treatment effect (ticagrelor monotherapy versus ticagrelor plus aspirin) examined using analysis of covariance (ANCOVA)

• Between-group difference in thrombus area was adjusted for baseline values, expressed as a mean difference with 95% CI

• A sample size of 40 was required to provide 80% power to detect at least 2200 µm² difference in thrombus area between groups with type I error 0.05 and a within-group standard deviation of 2500 µm²

• Effective antiplatelet and antithrombotic agents display reductions in thrombus area of at least ~ 2,000 µm²\(^2\)\(^6\,7\)

\(^6\text{Lev et al., ATVB 2002; Zafar et al., Thromb Haemost 2017}\)
WATER BATH (37°c)

Low shear rate  High shear rate

Peristaltic pump

Discard bin

Thrombus area is quantified

Badimon Perfusion Chamber

Thrombogenic substrate
Randomized in TWILIGHT at Mount Sinai (N=128)

Platelet Substudy Enrolled (N = 51)

Ticagrelor + Placebo (N = 23)
- Baseline PD study
  Perfusion Assay (N = 23)
  4 – No longer on therapy
- Follow-up PD study
  Perfusion Assay (N = 18)
  Paired Perfusion Assay (N = 42)

Ticagrelor + Aspirin (N = 28)
- Baseline PD study
  Perfusion Assay (N = 28)
  Median (IQR) days between visits 41 (31 – 61)
- Follow-up PD study
  Perfusion Assay (N = 24)
  2 – No longer on therapy
  1 – Lost to follow-up
  1 – Refused
## Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ticagrelor plus Placebo (n=18)</th>
<th>Ticagrelor plus aspirin (n=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>61.9 ± 9.9</td>
<td>64.6 ± 9.3</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Female Sex</strong></td>
<td>2 (11.1%)</td>
<td>3 (12.5%)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Nonwhite Race</strong></td>
<td>11 (61.1%)</td>
<td>12 (50%)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>28.9 ± 4.8</td>
<td>28.5 ± 5.4</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
<td>5 (27.8%)</td>
<td>10 (41.7%)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Current Smoker</strong></td>
<td>2 (11.1%)</td>
<td>5 (20.8%)</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>15 (83.3%)</td>
<td>21 (87.5%)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>18 (100.0%)</td>
<td>21 (87.5%)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Prior myocardial infarction</strong></td>
<td>1 (5.6%)</td>
<td>5 (20.8%)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Prior PCI</strong></td>
<td>12 (66.7%)</td>
<td>18 (75.0%)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Prior coronary artery bypass</strong></td>
<td>2 (11.1%)</td>
<td>2 (8.3%)</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Chronic kidney disease</strong></td>
<td>1 (5.6%)</td>
<td>3 (12.5%)</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Hemoglobin, g/dl</strong></td>
<td>12.9 ± 1.2</td>
<td>13.4 ± 1.9</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Platelet count (x10³/μL)</strong></td>
<td>243.1 ± 60.2</td>
<td>213.6 ± 56.1</td>
<td>0.11</td>
</tr>
</tbody>
</table>
## Procedural Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ticagrelor plus Placebo (n=18)</th>
<th>Ticagrelor plus aspirin (n=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for PCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>6 (33.3%)</td>
<td>10 (41.7%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>9 (50%)</td>
<td>14 (58%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>12 (66.7%)</td>
<td>11 (45.8%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Number of lesions treated</td>
<td>1.7 ± 0.8</td>
<td>1.6 ± 0.8</td>
<td>0.86</td>
</tr>
<tr>
<td>LAD</td>
<td>6 (33.3%)</td>
<td>11 (45.8%)</td>
<td>0.41</td>
</tr>
<tr>
<td>RCA</td>
<td>8 (44.4%)</td>
<td>8 (33.3%)</td>
<td>0.46</td>
</tr>
<tr>
<td>LCx</td>
<td>8 (44.4%)</td>
<td>8 (33.3%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>35.8 ± 24.5</td>
<td>35.1 ± 21.9</td>
<td>0.92</td>
</tr>
<tr>
<td>Target lesion morphology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombus (%)</td>
<td>2 (11.1%)</td>
<td>4 (16.7%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Calcification, moderate or severe (%)</td>
<td>3 (16.7%)</td>
<td>11 (45.8%)</td>
<td>0.047</td>
</tr>
<tr>
<td>Any bifurcation (%)</td>
<td>6 (33.3%)</td>
<td>5 (20.8%)</td>
<td>0.83</td>
</tr>
</tbody>
</table>
Ex-vivo Thrombus Area by Treatment Group

Mean Difference (95% CI) in Thrombus Area Between Groups:
218.2 µm² (-575.9 to 139.9); p=0.22
Within-Group Changes in Thrombus Area

Thrombus area (um²)

- **Baseline**
  - Ticagrelor Plus Placebo: 3130.7
- **Follow-up**
  - Ticagrelor Plus Placebo: 3152.4
  - Ticagrelor Plus Aspirin: 3741.5

**P-values**
- Baseline: 0.87
- Follow-up: 0.16
Post-Randomization Platelet Reactivity by Treatment Group

Platelet Aggregation (U)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Adenosine Diphosphate</th>
<th>Thrombin Receptor Activating Peptide</th>
<th>Arachidonic Acid</th>
<th>Collagen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor Plus Placebo</td>
<td>13</td>
<td>77</td>
<td>19.4</td>
<td>40.2</td>
</tr>
<tr>
<td>Ticagrelor Plus Aspirin</td>
<td>16.8</td>
<td>79.1</td>
<td>11.6</td>
<td>35.9</td>
</tr>
</tbody>
</table>

- Adenosine Diphosphate: $p = 0.47$
- Thrombin Receptor Activating Peptide: $p = 0.81$
- Arachidonic Acid: $p = 0.02$
- Collagen: $p = 0.03$
Limitations

• Baseline differences in parameters that can influence thrombotic potential. However, thrombus was generated under uniform conditions using a common substrate, partially isolating the treatment effect from confounding.

• Given the study design, inferences regarding P2Y_{12} inhibition with prasugrel or clopidogrel with respect to blood thrombogenicity are not possible.

• Patients were assessed after 3 months of DAPT; earlier time points after PCI may have yielded different results.
Conclusions

• Ticagrelor monotherapy provides a similar antithrombotic effect to that of ticagrelor plus aspirin as assessed by ex-vivo platelet-dependent thrombus formation.

• Platelet reactivity to collagen and AA is increased in the absence of aspirin while aggregation to ADP and thrombin is unchanged with or without aspirin.

• These findings suggest that aspirin withdrawal does not modulate ex-vivo blood thrombogenicity in the presence of strong P2Y$_{12}$ blockade with ticagrelor and corroborates the clinical observations of no incremental ischemic risk upon aspirin withdrawal seen in TWILIGHT.
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