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

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on behalf of the TWILIGHT Investigators
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

Funded by AstraZeneca

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

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant/ Exec committee/Advisory board/personal fees</td>
<td>Abbott Laboratories, Boston Scientific, Medscape, Siemens Medical Solutions, Phillips (Spectranetics), PLx Pharma, Roivant Sciences Inc, Volcano Corporation, Sanofi, Janssen,</td>
</tr>
<tr>
<td>Research Funding to Institution</td>
<td>Abbott Laboratories, Astra Zeneca, Bayer, Beth Israel Deaconess, BMS, CSL Behring, DSI, Medtronic, Boston Scientific, Novartis, OrbusNeich</td>
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<tr>
<td>Equity, &lt;1%</td>
<td>Claret Medical, Elixir Medical</td>
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<tr>
<td>DSMB membership paid to the institution</td>
<td>Watermark Research Partners</td>
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</table>
Background

• Balancing ischemic and bleeding complications post PCI is an important dilemma for clinicians.¹⁻³

• Addressing the clinical imperatives of lowering bleeding while preserving ischemic benefit requires therapeutic strategies that decouple thrombotic from hemorrhagic risk.

• Reducing the duration of aspirin after PCI may allow for more prolonged use of potent P2Y₁₂ inhibitors while avoiding aspirin-related bleeding risk.⁴

In patients undergoing PCI who are at high risk for ischemic or hemorrhagic complications and who have completed a 3-month course of dual antiplatelet therapy with ticagrelor plus aspirin, continued treatment with ticagrelor monotherapy would be superior to ticagrelor plus aspirin with respect to clinically relevant bleeding and would not lead to ischemic harm.
Study Design

Enrollment Period
3 Months

High-Risk PCI Patients (N=9006)

N = 7119

Not Randomized (N=1887)

Ticagrelor + Aspirin (Open label)

Randomization Period
12 Months

Ticagrelor + Aspirin

Ticagrelor + Placebo

Observation Period
3 Months

Standard of Care

Standard of Care
Includes 48 deaths

Lost to follow-up (106)
• Adverse events (243)
  - Death, MI or stroke (111)
  - Any revascularization (134)
  - BARC 3B or higher bleed (52)
• DAPT non-adherence (1148)
• Consent withdrawal/refusal (267)
• Other reasons (123)

1:1 Randomized
(N = 7119)

Ticagrelor + Placebo
(N = 3555)

15 Month Follow-up
(N = 3496; 98.3%)

15 M Vital status
(N = 3546; 99.7%)

Ticagrelor + Aspirin
(N = 3564)

15 Month Follow-up
(N = 3511; 98.5%)

15 M Vital status
(N = 3554; 99.7%)

Includes 34 deaths

18 withdrew consent
41 lost to follow-up

25 withdrew consent
27 lost to follow-up
1 physician withdrew

Mount Sinai

Twilight
Adherence to Study Medications

At 6-month Follow-up

- Ticagrelor + Placebo: 93.9%
- Ticagrelor + Aspirin: 92.8%
- Study Drug: 90.5%, 89.6%

At 12-month Follow-up

- Ticagrelor + Placebo: 87.1%, 85.9%
- Ticagrelor + Aspirin: 82.9%, 82.2%
- Study Drug: 89.6%, 90.5%
## Patient Characteristics

### Baseline Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tica + Placebo (N = 3555)</th>
<th>Tica + Aspirin (N = 3564)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years [Mean ± SD]</td>
<td>65.2 ± 10.3</td>
<td>65.1 ± 10.4</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>37.1%</td>
<td>36.5%</td>
</tr>
<tr>
<td>Insulin requiring</td>
<td>9.4%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>16.8%</td>
<td>16.8%</td>
</tr>
<tr>
<td>Anemia</td>
<td>19.8%</td>
<td>19.1%</td>
</tr>
<tr>
<td>ACS presentation</td>
<td>64.0%</td>
<td>65.7%</td>
</tr>
</tbody>
</table>

Previous MI                  | 28.7%                      | 28.6%                      |
Previous PCI                 | 42.3%                      | 42.0%                      |
Previous CABG                | 10.2%                      | 9.8%                       |
Previous major bleed         | 0.9%                       | 0.9%                       |
## Patient Characteristics

### Baseline Procedural Details

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tica + Placebo (N = 3555)</th>
<th>Tica + Aspirin (N = 3564)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial access</td>
<td>73.1%</td>
<td>72.6%</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>63.9%</td>
<td>61.6%</td>
</tr>
<tr>
<td>Lesion morphology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombus</td>
<td>10.4%</td>
<td>10.7%</td>
</tr>
<tr>
<td>Calcification, moderate/severe</td>
<td>14.0%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Any bifurcation</td>
<td>12.2%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Total stent length</td>
<td>40.1 ± 24.2</td>
<td>39.7 ± 24.3</td>
</tr>
</tbody>
</table>

Calculated from the data provided, the comparison shows slight differences in patient characteristics and procedural details between the two groups. The radial access rate was marginally higher in the Tica + Placebo group, while multivessel CAD was slightly more prevalent in the Tica + Aspirin group. Lesion morphology indications such as thrombus and calcification show comparable rates, with slight variations in bifurcation and total stent length.
Primary Endpoint: BARC 2, 3 or 5 Bleeding

ITT Cohort

Placebo vs Aspirin
HR (95%CI): 0.56 (0.45 to 0.68)
P <0.001

ARD = -3.08% (-4.15% to -2.01%)
NNT = 33

Cumulative incidence (%) vs Months since randomization

No. at risk
Ticagrelor + Aspirin 3564 3454 3357 3277 3213
Ticagrelor + Placebo 3555 3474 3424 3366 3321
BARC 3 or 5 Bleeding

**ITT Cohort**

- Cumulative incidence (%)
  - Ticagrelor + Aspirin
  - Ticagrelor + Placebo

**Placebo vs Aspirin**
- HR (95%CI): 0.49 (0.33 to 0.74)
- \( P = 0.0006 \)
- ARD = -0.99% (-1.55% to -0.43%)

**No. at risk**
- Ticagrelor + Aspirin: 3564, 3516, 3470, 3426, 3390
- Ticagrelor + Placebo: 3555, 3504, 3475, 3440, 3423
Prespecified Bleeding Endpoints (ITT Cohort)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ticagrelor + Placebo</th>
<th>Ticagrelor + Aspirin</th>
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<tbody>
<tr>
<td>BARC 3 or 5</td>
<td>1.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>TIMI major</td>
<td>0.5%</td>
<td>1.0%</td>
</tr>
<tr>
<td>GUSTO moderate or severe</td>
<td>0.7%</td>
<td>1.4%</td>
</tr>
<tr>
<td>ISTH major</td>
<td>1.1%</td>
<td>2.1%</td>
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HR [95%CI]:
- Ticagrelor + Placebo: 0.49 [0.33 - 0.74], p = 0.0006
- Ticagrelor + Aspirin: 0.50 [0.28 - 0.90], p = 0.02
- HR [95%CI]: 0.53 [0.33 - 0.85], p = 0.008
- HR [95%CI]: 0.54 [0.37 - 0.80], p = 0.002
Key Secondary Endpoint: Death, MI or Stroke

PP Cohort

Cumulative incidence (%)

Placebo vs Aspirin
HR (95%CI): 0.99 (0.78 to 1.25)
\( P_{\text{non-inferiority}} < 0.001 \)

ARD = -0.06% (-0.97% to 0.84%)

Months since randomization

No. at risk
Ticagrelor + Aspirin 3515 3466 3415 3361 3320
Ticagrelor + Placebo 3524 3457 3412 3365 3330
Conclusions

In *high-risk* patients who underwent PCI and were treated with ticagrelor and aspirin for 3 months without any major adverse (bleeding or ischemic) events, an antiplatelet strategy of continuing ticagrelor monotherapy resulted in:

- substantially *less bleeding* than ticagrelor plus aspirin
- without increasing ischemic events over a period of 1 year
Ticagrelor with or without Aspirin in High-Risk Patients after PCI