Ticagrelor versus Clopidogrel in Troponin-negative Patients with Acute Coronary Syndrome Undergoing Ad-Hoc Percutaneous Coronary Intervention: Results of a Prospective, Randomized, Multicenter Pharmacodynamic Study

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Conflicts of interest
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• J.M. Sweeny and G. Raveendran have no conflicts of interest to declare
• R. Teng and G. Carlson are employees of AstraZeneca
• Y. Zhao is a consultant to AstraZeneca
Ad-Hoc PCI Study Sites and PIs

15 US sites randomized patients

- Dominick J. Angiolillo: University of Florida, Jacksonville, FL – High Enroller
- Joseph M. Sweeny: Mount Sinai Medical Center, New York, NY
- Barry Bertolet: North Mississippi Medical Center, Tupelo, MS
- Ron Waksman: Washington Hospital Center, Washington, DC
- Thomas Stuckey: LeBauer CV Research Foundation, Greensboro, NC
- Robert Levitt: Sarah Cannon Research Institute, Richmond, VA
- Zakir Sahul: Michigan Heart PC, Ypsilanti, MI
- Ganesh Raveendran: University of Minnesota, Minneapolis, MN
- Zafir Hawa: North Kansas City Hospital, North Kansas City, MO
- Jeffrey Carr: Trinity Medical Center, Tyler, TX
- Frank Iacovone: Clara Maass Medical Center, Belleville, NJ
- Mohamed Effat: University of Cincinnati, Cincinnati, OH
- Mark Sasse: University of Alabama, Birmingham, AL
- Jose Exaire: Oklahoma VA Medical Center, Oklahoma City, OK
- Yerem Yeghiazarians: University of California, San Francisco, CA
Background

- Ticagrelor is an oral, direct-acting, reversible-binding platelet P2Y\textsubscript{12} receptor inhibitor
- The US Food and Drug Administration approval of ticagrelor for the treatment of ACS patients was based on efficacy in patients pretreated with a P2Y\textsubscript{12} inhibitor, irrespective of invasive or noninvasive management strategy\textsuperscript{1,2}
- Many low-risk, troponin-negative ACS patients do not receive pretreatment with a P2Y\textsubscript{12} inhibitor
- Over half of all elective PCI procedures in the US are done on an ad-hoc basis in low-risk ACS patients – i.e., immediately after diagnostic coronary angiography\textsuperscript{3}
- No previous study has assessed the effect of ticagrelor versus clopidogrel at the time of ad-hoc PCI

Aim and Hypothesis

Aim
• Evaluate the effect of ticagrelor versus clopidogrel loading dose (LD) on platelet reactivity in troponin-negative ACS patients undergoing ad-hoc PCI

Hypothesis
• Ticagrelor 180 mg LD (standard dose) will result in faster and greater inhibition of platelet reactivity compared with clopidogrel 600 mg LD in this patient population
Study Design

- Prospective, open-label, randomized, multicenter, US, Phase IV study

**Visit 1**
Screening period

**Visit 2**
Randomization 1:1, pre-LD platelet function testing,* first dose

- **Ticagrelor** 180 mg LD after diagnostic angiography, then 90 mg 12 h later + aspirin 160–500 mg LD, then 75–100 mg daily
- **Clopidogrel** 600 mg LD after diagnostic angiography + aspirin 160–500 mg LD, then 75–100 mg daily

**Visit 3**
Platelet function testing* (0.5, 2, and 8 h post-LD, and end of PCI)

*Measurement of P2Y$_{12}$ reaction units (PRU) with VerifyNow™
Inclusion and Exclusion Criteria

Inclusion criteria

• Age ≥18 years
• Women (post-menopausal or surgically sterile) and men
• Documented non-ST-segment elevation ACS
• ≥1 negative troponin test (Tnl, TnT or hsTn) 6–48 h after symptom onset
• On aspirin as antiplatelet medication

Key exclusion criteria

• Contraindication to study drug
• Use of any thienopyridine or ticagrelor within 7 days prior to randomization
• Any indication for chronic oral anticoagulation
• Concomitant therapy with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic index, or strong CYP3A inducers
Study Endpoints and Safety Evaluation

Primary endpoint
- Platelet reactivity 2 h after ticagrelor or clopidogrel LD, measured as PRU level using VerifyNow™

Secondary endpoints
- PRU levels at 0.5 h post dose, end of PCI (when guide catheter removed from body), and 8 h post dose
- Percentage reduction from baseline in PRU
- Percentage IPA from baseline

Exploratory endpoint
- Percentage of patients with high on-treatment PRU levels (≥208)

Safety evaluation
- Assessment of AEs (including bleeding), physical examination, and vital signs

IPA, inhibition of platelet aggregation, measured as P2Y_{12} receptor inhibition
Statistical Analysis

Statistical analysis

- The primary analysis of the difference between ticagrelor and clopidogrel in PRUs at 2 hours was analyzed using a two-sample $t$-test. Treatment level means and 2-sided 95% confidence intervals (CIs) were estimated. Tests were evaluated with a 2-sided alpha level of 0.05

Sample size

- Calculations using 90% power, detection of a difference of 100 PRUs, and a 2-sided alpha of 0.05 yielded a required sample size of 40 completed patients, with 20 per treatment group. This assumed a standard deviation (SD) of 93 PRUs based on a previous study. However, the administration of study treatment in a supine position was assumed to incur a 2- to 3-fold increase in variability, resulting in a sample size of approximately 100 patients
Results

Patient Disposition and Characteristics
Patient Disposition

Screened (n=343)

Did not meet inclusion/exclusion criteria (n=241)
Not randomized (n=2)
Progressive disease (n=1)
PI's decision (n=1)

Met inclusion/exclusion criteria (n=102)

Randomized (n=100)
Incorrectly randomized (n=4)

Did not meet inclusion/exclusion criteria (n=241)
Not randomized (n=2)
Progressive disease (n=1)
PI's decision (n=1)

Ticagrelor (n=51)
Safety population (n=51)
PD population (n=46)†
  Missing analyzable data (n=1)
  Protocol deviation (n=4)
Completed study (n=49)
Completed treatment (n=47)
  No PCI, patient had received 2 doses prior, discontinued, unable to place stent/wire (n=1 each)

Clopidogrel (n=49)
Safety population (n=49)
PD population (n=47)
  Missing analyzable data (n=0)
  Protocol deviation (n=2)
Completed study (n=48)
Withdrawn due to AE (n=1)
Completed treatment (n=49)

†One patient with pre-dose PRU <150 was excluded from primary and secondary endpoint analyses (n=45)
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (n=51)</th>
<th>Clopidogrel (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; mean (SD)</td>
<td>60.1 (10.7)</td>
<td>63.0 (9.1)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>17 (33.3)</td>
<td>13 (26.5)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>33 (71.7)</td>
<td>33 (71.7)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>11 (23.9)</td>
<td>11 (23.9)</td>
</tr>
<tr>
<td>Other†</td>
<td>2 (4.4)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Body mass index &gt;30 kg/m², n (%)‡</td>
<td>24 (48.0)</td>
<td>24 (49.0)</td>
</tr>
<tr>
<td>CV risk factors, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>38 (74.5)</td>
<td>42 (85.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44 (86.3)</td>
<td>48 (98.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (39.2)</td>
<td>16 (32.7)</td>
</tr>
<tr>
<td>Chronic kidney disease, GFR &lt;60 mL/min/1.73m²</td>
<td>7 (13.7)</td>
<td>7 (14.3)</td>
</tr>
<tr>
<td>Prior CVD and CV procedures, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>5 (9.8)</td>
<td>2 (4.1)</td>
</tr>
<tr>
<td>Peripheral arterial occlusive disease</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Stroke, ischemic</td>
<td>0</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>9 (17.6)</td>
<td>16 (32.7)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>19 (37.3)</td>
<td>22 (44.9)</td>
</tr>
<tr>
<td>Prior coronary artery bypass graft,</td>
<td>5 (9.8)</td>
<td>14 (28.6)</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate †Asian, American Indian, or Alaskan Native ‡Data missing for one patient
Results

Primary Endpoint
PRU at 2 h after LD
PD Population

Treatment difference (95% CI): -159.1 (-194.7, -123.5); p<0.001

Ticagrelor (n=45)
Clopidogrel (n=47)
Results

Secondary Endpoints
Time Course of PRU
PD Population

Mean PRU (95% CI)

- Ticagrelor (n=45)
- Clopidogrel (n=47)

Mean time to end of PCI 0.6 h
Percent Reduction from Baseline in PRU

PD Population

Mean (SD) percent reduction from baseline in PRU

- Ticagrelor (n=45)
- Clopidogrel (n=47)

<table>
<thead>
<tr>
<th>Time</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 h</td>
<td>1.5</td>
<td>0</td>
<td>p=0.702</td>
</tr>
<tr>
<td>End of PCI</td>
<td>5.5</td>
<td>-3.9</td>
<td>p=0.058</td>
</tr>
<tr>
<td>2 h</td>
<td>66.3</td>
<td>13.0</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>8 h</td>
<td>85.2</td>
<td>32.7</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
Device-defined IPA†
PD Population

Mean (SD) percent inhibition of P2Y₁² receptor from BASE
t Ticagrelor (n=45)  Clopidogrel (n=47)

- 0.5 h: 9.8 ± 3.8 vs. 16.0 ± 4.5, p=0.031
- End of PCI: 14.0 ± 4.5 vs. 65.8 ± 14.0, p=0.005
- 2 h: 85.2 ± 31.1, p<0.001
- 8 h: 31.1 ± 6.2, p<0.001

†VerifyNow™-determined percent inhibition from the reference base channel
Results

Exploratory Endpoint
High On-treatment PRU (≥208)

PD Population

Patients with high on-treatment PRU (%)

- Ticagrelor (n=45)
- Clopidogrel (n=47)

<table>
<thead>
<tr>
<th>Time</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>88.6</td>
<td>91.1</td>
<td>0.74</td>
</tr>
<tr>
<td>0.5 h</td>
<td>84.1</td>
<td>86.7</td>
<td>0.77</td>
</tr>
<tr>
<td>End of PCI</td>
<td>81.8</td>
<td>97.7</td>
<td>0.030</td>
</tr>
<tr>
<td>2 h</td>
<td>13.3</td>
<td>78.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8 h</td>
<td>2.4</td>
<td>53.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean time to end of PCI 0.6 h
Results

Safety Evaluation
Safety Summary

• No deaths or AEs leading to discontinuation of study drug
• Most frequently occurring AEs with ticagrelor vs clopidogrel were
  – Chest pain (4 vs 1 patient)
  – Unstable angina (0 vs 3 patients)
  – Hypotension (3 vs 0 patients)
  – Dyspnea (2 vs 1 patient)
  – Hematoma (2 vs 0 patients)
• All except 3 AEs (all in the ticagrelor group) and all except one SAE (duodenitis in 1 patient in the ticagrelor group) were considered unrelated to study drug
• Bleeding events considered related to study drug occurred in 3 (5.9%) ticagrelor patients, all of mild intensity, and 0 clopidogrel patients
• No notable findings for vital signs or physical examination
• No new clinically meaningful safety findings
Conclusions

• In low-risk ACS patients undergoing ad-hoc PCI, platelet reactivity as measured by VerifyNow™ was decreased to a greater extent at 2 h after ticagrelor LD, compared with clopidogrel LD, and was maintained up to the 8-h time point.

• The number of patients with high on-treatment PRU at 2 h was significantly lower with ticagrelor (p<0.001).

• Ticagrelor was well tolerated, with no notable safety findings, as assessed by AEs, bleeding events, physical examination, and vital signs.

• These findings suggest that a ticagrelor LD may be more effective than clopidogrel for inhibition of platelet activity in low-risk, troponin-negative ACS patients undergoing ad-hoc PCI.