Long-Term Tolerability of Ticagrelor for Secondary Prevention: Insights from PEGASUS-TIMI 54 Trial

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on behalf of the PEGASUS-TIMI 54 Executive & Steering Committees and Investigators

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Disclosures

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• Consulting for AstraZeneca, Merck, Bayer, Roche Diagnostics
Primary Endpoint

21,162 patients with MI 1-3 years prior and treated with low-dose aspirin

CV Death, MI, or Stroke (%)

Months from Randomization

Ticagrelor 90 mg
HR 0.85 (95% CI 0.75 – 0.96)
P=0.008

Ticagrelor 60 mg
HR 0.84 (95% CI 0.74 – 0.95)
P=0.004

Bonaca MP et al. and Sabatine MS. NEJM 2015;372:1791-800
Enrollment began in 2010; therefore few patients (<1%) had already been treated with ticagrelor.

Premature discontinuation at 3 years was higher in those initiating ticagrelor (32% 90 mg BID, 29% 60 mg BID) vs. placebo (21%) with the majority due to adverse events.

However, translation of PEGASUS-TIMI 54 into clinical practice would more likely be in the form of continuing in patients already tolerating ticagrelor for 1 year after their MI.

We therefore investigated rates, reasons and timing of study drug discontinuation in PEGASUS-TIMI 54.
In outpatients with prior MI newly exposed to ticagrelor:

1. **Treatment discontinuation overall, and due to AEs, would be higher early after initiation and would be low in patients tolerating therapy for at least one year**

2. **The efficacy of ticagrelor would be robust for events occurring on treatment, particularly for patients continuing on P2Y₁₂ inhibition from their index MI**
Methods

- The rate and reasons for discontinuation compared between treatment groups

- Landmark evaluating discontinuation in those that tolerated 1 year of therapy

- The efficacy and safety compared evaluating events that occurred through the last dose plus 7 days
Drug discontinuation by Treatment Arm

First Year

- Placebo: Total=908
  - AE/SAE: 25
  - Patient Decision: 52
  - Administrative: 376
  - Other: 455

- Ticagrelor 90 mg: Total=1669
  - AE/SAE: 50
  - Patient Decision: 489
  - Administrative: 1104
  - Other: 51

- Ticagrelor 60 mg: Total=1367
  - AE/SAE: 20
  - Patient Decision: 421
  - Administrative: 875
  - Other: 51

Years 2 + 3

- Placebo: Total=6,996
  - Placebo: N=6,996
  - Randomized Treatment Arm: N=6,988

- Ticagrelor 90 mg: Total=588
  - Placebo: N=6,088
  - Ticagrelor 90 mg: N=5,319
  - Randomized Treatment Arm: N=5,591

- Ticagrelor 60 mg: Total=632
  - Placebo: N=6,088
  - Ticagrelor 60 mg: N=5,591
  - Randomized Treatment Arm: N=5,591

HR 1.91
95% CI (1.77 – 2.07)

HR 1.57
95% CI (1.44 – 1.70)

HR 1.12
95% CI (0.99 – 1.26)

HR 1.18
95% CI (1.06 – 1.32)
Drug discontinuation for AE by Treatment

First Year

P-value for each dose vs. placebo < 0.01

Years 2 + 3

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Annualized Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor 90</td>
<td>3.3%</td>
</tr>
<tr>
<td>Ticagrelor 60</td>
<td>3.0%</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Days from Randomization
Adverse Events Leading to Discontinuation

3 Year KM Rate (%) – p-value for each dose vs. placebo <0.001

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Any AE</th>
<th>Bleeding</th>
<th>Dyspnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor 90</td>
<td>19.0%</td>
<td>7.8%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Ticagrelor 60</td>
<td>16.4%</td>
<td>6.2%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.9%</td>
<td>1.5%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

P=NS each for D/C for arrhythmia or other

Number of Patients

Placebo: 388
- Arrhythmia: 96
- Dyspnea: 51
- Bleeding: 86

Ticagrelor 90 mg BID: 453
- Arrhythmia: 78
- Dyspnea: 430
- Bleeding: 354

Ticagrelor 60 mg BID: 385
- Arrhythmia: 103
- Dyspnea: 297
- Bleeding: 354

P=NS each for D/C for arrhythmia or other
Discontinuation over time for Dyspnea by Randomization Group

Number of Patients Discontinued for Dyspnea

- **Placebo**
- **Ticagrelor 60 mg twice daily**
- **Ticagrelor 90 mg twice daily**

P<0.01 for each dose vs. placebo

Median Days to Discontinuation:
- Ticagrelor 90 mg twice daily: 53 days
- Ticagrelor 60 mg twice daily: 11 days
- Placebo: 8 days
Discontinuation over time for Bleeding by Randomization Group

Number of Patients Discontinued for Bleeding

- Placebo
- Ticagrelor 60 mg twice daily
- Ticagrelor 90 mg twice daily

P<0.01 for each dose vs. placebo
Dyspnea and Bleeding

**Dyspnea**

- **Non-serious (AE)**
- **Serious (SAE)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Ticagrelor 90 mg BID</th>
<th>Ticagrelor 60 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>82%</td>
<td>85%</td>
<td>88%</td>
</tr>
<tr>
<td>82% mild or moderate</td>
<td>49</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>85% mild or moderate</td>
<td>422</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>88% mild or moderate</td>
<td>286</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

**Bleeding**

- **TIMI Major**
- **TIMI Minor**
- **Med Attention**
- **Minimal**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Ticagrelor 90 mg BID</th>
<th>Ticagrelor 60 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>66</td>
<td>221</td>
<td>52</td>
</tr>
<tr>
<td>TIMI Major</td>
<td>14</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>TIMI Minor</td>
<td>43</td>
<td>59</td>
<td>52</td>
</tr>
<tr>
<td>Med Attention</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cardiovascular Death, Myocardial Infarction or Stroke at 3 Years by Randomization Group in Patients On Treatment

KM Rate (%) at 3 Years

Placebo

Ticagrelor 60 mg BID

HR 0.79
(95% CI 0.68 – 0.91)
P<0.001

Ticagrelor 90 mg BID

HR 0.78
(95% CI 0.68 – 0.90)
P<0.001

Days from Randomization

0% 1% 2% 3% 4% 5% 6% 7% 8%

0 90 180 270 360 450 540 630 720 810 900 990 1080
Efficacy of Ticagrelor – On Treatment*

*CVD / MI / Stroke

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Year KM Rate (%)</td>
<td>6.6</td>
<td>8.4</td>
<td>0.79 (0.68 – 0.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>6.8</td>
<td>8.0</td>
<td>0.78 (0.68 – 0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.7</td>
<td>8.8</td>
<td>0.78 (0.70 – 0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td>1.9</td>
<td>2.4</td>
<td>0.78 (0.60 – 1.03)</td>
<td>0.076</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>1.8</td>
<td>2.2</td>
<td>0.74 (0.57 – 0.97)</td>
<td>0.031</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.9</td>
<td>2.1</td>
<td>0.76 (0.61 – 0.96)</td>
<td>0.019</td>
</tr>
<tr>
<td>Coronary Heart Disease Death</td>
<td>1.3</td>
<td>1.6</td>
<td>0.75 (0.54 – 1.04)</td>
<td>0.087</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>1.2</td>
<td>1.5</td>
<td>0.72 (0.52 – 1.00)</td>
<td>0.052</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.3</td>
<td>1.6</td>
<td>0.74 (0.56 – 0.97)</td>
<td>0.029</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>3.8</td>
<td>4.9</td>
<td>0.78 (0.65 – 0.94)</td>
<td>0.0080</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>4.1</td>
<td>4.9</td>
<td>0.81 (0.68 – 0.97)</td>
<td>0.0236</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.0</td>
<td>4.7</td>
<td>0.80 (0.68 – 0.93)</td>
<td>0.0036</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.4</td>
<td>1.8</td>
<td>0.77 (0.56 – 1.05)</td>
<td>0.094</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>1.4</td>
<td>1.5</td>
<td>0.73 (0.53 – 1.00)</td>
<td>0.048</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.4</td>
<td>1.6</td>
<td>0.75 (0.58 – 0.97)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

* N=20,942 patients who received at least one dose of study drug including events through 7 days from the last dose of study drug. Results consistent after propensity score adjustment.
Summary

• Discontinuation of newly started ticagrelor among stable outpatients with prior MI was driven by adverse events of bleeding and dyspnea

• Although significant enough to prompt discontinuation, the majority of:
  – Dyspnea was non-serious (>95%) and only mild-mod. in intensity (> 80%)
  – Bleeds were minimal or medical attention

• Among patients who remained on therapy
  – Discontinuation for an AE after one year of exposure was low (~3%/y)
  – Ischemic risk was robustly reduced, particularly in those continuing P2Y_{12} inhibition or restarting after a brief interruption (≤ 30 days)
Conclusions

• “Non-serious” bleeding and other AEs still have important consequences including discontinuation of therapy

• These data underscore the need for patient counseling when initiating anti-thrombotic therapies in order to maximize adherence and improve outcomes