Efficacy of Long-Term Ticagrelor in Patients with Coronary Stents in PEGASUS-TIMI 54

Marc P. Bonaca, MD, MPH
on behalf of the PEGASUS-TIMI 54 Executive & Steering Committees and Investigators

NCT00526474
Stable pts with history of MI 1-3 yrs prior + ≥1 additional atherothrombosis risk factor

Randomized Double Blind

Ticagrelor 90 mg bid

Ticagrelor 60 mg bid

Placebo

Follow-up Visits
Q4 mos for 1st yr, then Q6 mos

Planned treatment with ASA 75 – 150 mg/d & Standard background care

Minimum 1 year follow-up Event-driven trial

Bonaca MP et al. NEJM 2015
Background

- PEGASUS-TIMI 54 demonstrated that long-term treatment with ticagrelor (90 mg or 60 mg twice daily) reduced MACE 15-16% in stable patients with history of MI (1-3 years prior)

- Of those randomized, 80% had history of coronary stents and 20% were medically managed only

- The benefit of ticagrelor in stable outpatients with prior MI and coronary stenting has yet to be defined:
  - Overall
  - In terms of major adverse cardiovascular events related & unrelated to the stent

- Other studies have observed that withdrawal of P2Y12 inhibition at 1 year after stenting is associated with increased risk of de-novo ischemic events and stent thrombosis

- The long-term risk of stent thrombosis relative to other MACE events in patients with MI > 1 year prior and coronary stenting is unknown
Hypotheses

Patients with Prior MI 1-3 years prior and history of coronary stenting:

1. **Would be at heightened risk of de-novo MACE events and that this risk would be greater than that of thrombotic stent complications**

2. **Would derive benefit from ticagrelor for reduction of MACE primarily from prevention of de-novo events but also from prevention of coronary stent thrombosis**
Methods

1. Type and date of most recent coronary stent captured at baseline

2. PCI subgroup pre-specified for evaluation of efficacy and safety

3. All potential stent-thrombosis events reviewed and adjudicated by a blinded CEC with angiographic confirmation where available
# Baseline Characteristics by History of PCI

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Coronary Stent N=16,891</th>
<th>No Coronary Stent N=4,271</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>65 (58, 71)</td>
<td>67 (60, 73)</td>
</tr>
<tr>
<td>BMI, median (IQR)</td>
<td>27.8 (25.15, 31.16)</td>
<td>27.8 (25.1, 31.18)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>3603 (21.3%)</td>
<td>1457 (34.1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Coronary Stent N=16,891</th>
<th>No Coronary Stent N=4,271</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (%)</td>
<td>12822 (75.9%)</td>
<td>3585 (84.0%)</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>13255 (78.5%)</td>
<td>2986 (70.0%)</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>2940 (17.4%)</td>
<td>596 (14.0%)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>5186 (30.7%)</td>
<td>1620 (38.0%)</td>
</tr>
<tr>
<td>Multivessel CAD (%)</td>
<td>11302 (66.9%)</td>
<td>1255 (29.4%)</td>
</tr>
<tr>
<td>History of &gt; 1 prior MI (%)</td>
<td>2612 (15.5%)</td>
<td>887 (20.8%)</td>
</tr>
<tr>
<td>Last dose of P2Y12 ≤ 30 days (%)</td>
<td>6431 (39.9%)</td>
<td>750 (28.5%)</td>
</tr>
<tr>
<td>**eGFR at baseline &lt;60 ml/min (%)</td>
<td>3590 (21.5%)</td>
<td>1259 (29.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>Coronary Stent N=16,891</th>
<th>No Coronary Stent N=4,271</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe (%)</td>
<td>5397 (32.0%)</td>
<td>739 (17.3%)</td>
</tr>
<tr>
<td>Eastern Europe (%)</td>
<td>4262 (25.2%)</td>
<td>2028 (47.5%)</td>
</tr>
<tr>
<td>North America (%)</td>
<td>3548 (21.0%)</td>
<td>359 (8.4%)</td>
</tr>
<tr>
<td>South America (%)</td>
<td>1698 (10.1%)</td>
<td>760 (17.8%)</td>
</tr>
<tr>
<td>Asia/Pacific (%)</td>
<td>1986 (11.8%)</td>
<td>383 (9.0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Qualifying Event</th>
<th>Coronary Stent N=16,891</th>
<th>No Coronary Stent N=4,271</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months from MI – median (IQR)</td>
<td>20.4 (14.75, 27.93)</td>
<td>21.2 (15.34, 28.35)</td>
</tr>
<tr>
<td>STEMI</td>
<td>9552 (56.6%)</td>
<td>1777 (41.7%)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>6609 (39.2%)</td>
<td>1972 (46.3%)</td>
</tr>
<tr>
<td>MI type unknown</td>
<td>712 (4.2%)</td>
<td>511 (12.0%)</td>
</tr>
</tbody>
</table>
Timing and Types of Coronary Stents

95% more than 1 year from stenting (i.e., events would be “very late” stent thrombosis)

- **< 1 year:** 825, 5%
- **1-2 years:** 10,299, 59%
- **> 2 years:** 6,431, 36%

- **BMS:** 8,597, 51%
- **DES:** 8,294, 49%
Events at 3 Years by Prior Coronary Stent

21,162

16,891 (80%) With Coronary Stent

4,271 (20%) No Coronary Stent

91% of PEP Events Spontaneous – Unrelated to Coronary Stent

CV Death
Type 1 MI
Stroke
Definite Stent Thrombosis

2.3%
4.1%
1.7%
0.7%

7.7%
4.4%
3.1%
0.0%

Placebo Patients
N=7,067

An Academic Research Organization of Brigham and Women’s Hospital and Harvard Medical School
3 stent thrombosis events occurred in patients who received their first coronary stents after randomization.
MACE in Patients with Prior PCI/Stent

N = 16,891
Median follow-up 33 months

**CVD / MI / Stroke**

Ticagrelor 90 mg
HR 0.86 (0.75 – 0.99)
P = 0.042

Ticagrelor 60 mg
HR 0.84 (0.73 – 0.97)
P = 0.016

Placebo (8.0%)
Ticagrelor 90 (7.1%)
Ticagrelor 60 (6.8%)
# MACE in Patients with & without Prior PCI/Stent

<table>
<thead>
<tr>
<th>Prior PCI/Stent</th>
<th>N = 16,891</th>
<th>3 Year KM Rates</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD / MI / Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticagrelor 60 mg</td>
<td>7.1</td>
<td>0.86 (0.75 – 0.99)</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor 90 mg</td>
<td>6.8</td>
<td>0.84 (0.73 – 0.97)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>7.0</td>
<td>0.85 (0.75 – 0.96)</td>
<td>0.0092</td>
<td></td>
</tr>
<tr>
<td><strong>No Prior PCI/Stent</strong></td>
<td>N = 4,271</td>
<td>3 Year KM Rates</td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>CVD / MI / Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticagrelor 60 mg</td>
<td>10.5</td>
<td>0.80 (0.64 – 1.00)</td>
<td>0.0495</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor 90 mg</td>
<td>11.7</td>
<td>0.85 (0.68 – 1.06)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>11.1</td>
<td>0.82 (0.68 – 0.99)</td>
<td>0.044</td>
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</tbody>
</table>

All p-interaction NS
MACE in Patients with Prior PCI/Stent

$N = 16,891$

<table>
<thead>
<tr>
<th>Event</th>
<th>Ticagrelor Better</th>
<th>Placebo Better</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD / MI / Stroke</td>
<td>7.1</td>
<td>6.8</td>
<td>0.86 (0.75 – 0.99)</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>7.0</td>
<td>7.8</td>
<td>0.85 (0.75 – 0.96)</td>
<td>0.0092</td>
</tr>
<tr>
<td>CV Death</td>
<td>2.2</td>
<td>2.2</td>
<td>0.94 (0.72 – 1.23)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.9</td>
<td>1.9</td>
<td>0.82 (0.62 – 1.08)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.1</td>
<td>2.3</td>
<td>0.88 (0.70 – 1.11)</td>
<td></td>
</tr>
<tr>
<td>Coronary Heart Disease Death</td>
<td>1.1</td>
<td>1.1</td>
<td>0.73 (0.52 – 1.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.0</td>
<td>0.64 (0.45 – 0.91)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.1</td>
<td>1.6</td>
<td>0.68 (0.51 – 0.92)</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>4.3</td>
<td>4.3</td>
<td>0.79 (0.66 – 0.95)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>4.5</td>
<td>0.84 (0.70 – 1.00)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.4</td>
<td>5.2</td>
<td>0.81 (0.70 – 0.95)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.5</td>
<td>1.5</td>
<td>0.88 (0.65 – 1.21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.3</td>
<td>1.3</td>
<td>0.81 (0.59 – 1.12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.4</td>
<td>1.7</td>
<td>0.85 (0.65 – 1.11)</td>
<td></td>
</tr>
</tbody>
</table>
Reduction in MACE with Ticagrelor by Time from P2Y_{12} Inhibitor Withdrawal – Patients with Coronary Stents

Time from P2Y_{12} Inhibitor withdrawal to randomization

- **≤ 30 days**
  - N=6,431
  - **24% RRR**
  - Ticagrelor 60 mg: HR (95% CI) = 0.76 (0.61 – 0.96), P-value = 0.006
  - Ticagrelor 90 mg: HR (95% CI) = 0.76 (0.61 – 0.96)

- **>30 days to 1 year**
  - N=5,458
  - **16% RRR**
  - Ticagrelor 60 mg: HR (95% CI) = 0.89 (0.69 – 1.15)
  - Ticagrelor 90 mg: HR (95% CI) = 0.80 (0.62 – 1.04)
  - P-value = 0.13

- **>1 year**
  - N=4,241
  - **Ø RRR**
  - Ticagrelor 60 mg: HR (95% CI) = 1.04 (0.77 – 1.41)
  - Ticagrelor 90 mg: HR (95% CI) = 1.03 (0.76 – 1.40)
  - P-value = 0.78

P-interaction < 0.01
Primary Endpoint and Stent Thrombosis with Ticagrelor

N = 21,162

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ticagrelor Better</th>
<th>Placebo Better</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD / MI / Stroke</td>
<td>7.9</td>
<td>0.85 (0.75 – 0.96)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Definite Stent Thrombosis*</td>
<td>0.5</td>
<td>0.59 (0.35 – 0.99)</td>
<td>0.046</td>
<td></td>
</tr>
<tr>
<td>Definite/Probable Stent* Thrombosis</td>
<td>0.6</td>
<td>0.65 (0.40 – 1.05)</td>
<td>0.076</td>
<td></td>
</tr>
<tr>
<td>Definite/Probable/Possible Stent Thrombosis*</td>
<td>0.7</td>
<td>0.62 (0.40 – 0.97)</td>
<td>0.038</td>
<td></td>
</tr>
</tbody>
</table>

*Ticagrelor 90 mg
Ticagrelor 60 mg
Pooled

*Includes coronary stent at baseline or during trial
Stent Thrombosis with Ticagrelor
ITT and On-Treatment

**Includes coronary stent at baseline or during trial

*Patients who received at least once dose of study drug with events included through 7 days from their last dose or the common study end date

<table>
<thead>
<tr>
<th>Stent Thrombosis**</th>
<th>3 Year KM Rate</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite Stent Thrombosis**</td>
<td>Ticagrelor: 0.6, Placebo: 0.7</td>
<td>0.74 (0.50 – 1.12)</td>
<td>0.15</td>
</tr>
<tr>
<td>Definite/Probable Stent**</td>
<td>Ticagrelor: 0.4, Placebo: 0.7</td>
<td>0.49 (0.29 – 0.82)</td>
<td>0.0063</td>
</tr>
<tr>
<td>Definite/Probable/Possible Stent Thrombosis**</td>
<td>Ticagrelor: 0.7, Placebo: 1.0</td>
<td>0.72 (0.50 – 1.03)</td>
<td>0.074</td>
</tr>
<tr>
<td>Definite/Probable/Possible Stent Thrombosis**</td>
<td>Ticagrelor: 0.4, Placebo: 0.8</td>
<td>0.46 (0.28 – 0.73)</td>
<td>0.0012</td>
</tr>
</tbody>
</table>
Reduction in Ischemic Outcomes with Ticagrelor

N = 21,162

CV Death
Coronary Heart Disease Death
Myocardial Infarction
Definite Stent Thrombosis*
Stroke

*Ticagrelor 60 mg
Ticagrelor 90 mg
Placebo 60 mg
Placebo 90 mg
Pooled

HR (95% CI) P-value

Ticagrelor Placebo
CV Death
2.9 3.4 0.87 (0.71 – 1.06) 0.15
2.9 0.83 (0.68 – 1.01) 0.068
2.9 0.85 (0.71 – 1.00) 0.057

Coronary Heart Disease Death
1.5 2.1 0.73 (0.56 – 0.95) 0.021
1.7 0.80 (0.62 – 1.04) 0.093
1.6 0.77 (0.62 – 0.96) 0.019

Myocardial Infarction
4.4 5.3 0.81 (0.69 – 0.95) 0.010
4.5 0.84 (0.72 – 0.98) 0.031
4.5 0.83 (0.72 – 0.95) 0.0055

Definite Stent Thrombosis*
0.5 0.7 0.59 (0.35 – 0.99) 0.046
0.6 0.89 (0.57 – 1.41) 0.63
0.6 0.74 (0.50 – 1.12) 0.15

Stroke
1.6 1.9 0.82 (0.63 – 1.07) 0.14
1.5 0.75 (0.57 – 0.98) 0.034
1.5 0.78 (0.62 – 0.98) 0.034

*Includes coronary stent at baseline or during trial

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Safety in Patients with Prior PCI

TIMI Major

TIMI Minor

Fatal bleeding or ICH

Fatal Bleeding

Mortality

P<0.001

P<0.001

P=NS

P=NS

P=NS

Ticagrelor 90 mg
Ticagrelor 60 mg
Placebo

P<0.001
Stable patients with a history of MI and coronary stenting

- Are at heightened risk of *de-novo* atherothrombotic events and at a relatively low risk of coronary stent related complications

- Derive ischemic risk reduction from long-term ticagrelor driven primarily by reduction in *de-novo* events but also by reductions in stent thrombosis

- Very-late stent thrombosis is reduced with long-term P2Y$_{12}$ inhibition with a numerically greater reduction with ticagrelor 90 mg than 60 mg daily
Conclusions

- Patients with prior MI are at heightened risk of ischemic events regardless of whether they have received a coronary stent.

- Long-term ticagrelor broadly reduces ischemic risk including CV death / MI / or stroke, coronary death, and stent thrombosis and increases bleeding.