Risk of Limb Events and Effect of Ticagrelor in Patients with and without Peripheral Artery Disease: Insights from the THEMIS Trial

Presented by Marc P. Bonaca MD MPH


*co-Chairs and co-Principal Investigators of THEMIS
Disclosures

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• Marc P. Bonaca reports grant support to CPC Clinical Research from Amgen, AstraZeneca, Bayer, Janssen, Merck
Ticagrelor with Aspirin Reduces MACE in Diabetes and CAD

**Primary Composite Endpoint**
Cardiovascular death/MI/stroke

**No heterogeneity for the primary efficacy outcome on the basis of PAD**
Ticagrelor with Aspirin Increases Bleeding in Diabetes and CAD

No heterogeneity for the principal safety outcome on the basis of PAD

**Bleeding Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (N=9562)</th>
<th>Placebo (N=9531)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TIMI major bleeding</strong></td>
<td>206 (2.2%)</td>
<td>100 (1.0%)</td>
<td>2.32 (1.82–2.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>TIMI major or minor bleeding</strong></td>
<td>285 (3.0%)</td>
<td>129 (1.4%)</td>
<td>2.49 (2.02–3.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>TIMI major, minor, or requiring medical attention</strong></td>
<td>1072 (11.2%)</td>
<td>485 (5.1%)</td>
<td>2.51 (2.26–2.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PLATO major bleeding</strong></td>
<td>310 (3.2%)</td>
<td>145 (1.5%)</td>
<td>2.41 (1.98–2.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>BARC bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (fatal bleeding)</td>
<td>17 (0.2%)</td>
<td>10 (0.1%)</td>
<td>1.90 (0.87–4.15)</td>
<td>0.11</td>
</tr>
<tr>
<td>5 or 4</td>
<td>17 (0.2%)</td>
<td>11 (0.1%)</td>
<td>1.73 (0.81–3.69)</td>
<td>0.16</td>
</tr>
<tr>
<td>5, 4, or 3</td>
<td>341 (3.6%)</td>
<td>163 (1.7%)</td>
<td>2.36 (1.96–2.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Intracranial hemorrhage</strong></td>
<td>70 (0.7%)</td>
<td>46 (0.5%)</td>
<td>1.71 (1.18–2.48)</td>
<td>0.005</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>28 (0.3%)</td>
<td>27 (0.3%)</td>
<td>1.17 (0.69–1.98)</td>
<td>0.57</td>
</tr>
<tr>
<td>Procedural</td>
<td>1 (0.0%)</td>
<td>3 (0.0%)</td>
<td>1.00 (0.49–2.20)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Traumatic</strong></td>
<td>41 (0.4%)</td>
<td>16 (0.2%)</td>
<td>2.87 (1.61–5.12)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Includes events with onset from randomization up to 7 days after last dose. BARC bleeding was defined according to a score of 3 to 5 as follows: type 3, bleeding with a decrease in the hemoglobin of more than 3 g per deciliter, any transfusion, cardiac tamponade, or intracranial or ocular involvement; type 4, CABG-related bleeding; and type 5, fatal bleeding. Traumatic (ICH: 27 (6%) on ticagrelor and 6 (3%) on placebo) reported as subdural bleeding by investigators.

BARC=Bleeding Academic Research Consortium; CABG=coronary artery bypass grafting; CI=confidence interval; N=number of patients; PLATO=PLATElet inhibition and patient outcomes; TIMI=Thrombolysis in Myocardial Infarction

NCT01991795

Steg PG, Bhatt DL et al. NEJM 2019
Diabetes Associated with Increased Risk of Adverse Limb Events

Presence or Absence of Polyvascular Disease (PVD) or Diabetes Mellitus (DM)

*Adjusted for: age, weight, sex, region, ABI, GFR, statin use, ARB use, tobacco use

Behan S...Bonaca MP et al ACC 2020
Diabetes Increases the Risk of Major Adverse Limb Events

- **Limb hospitalization**
  - **PAD with Diabetes**: 12.41%
  - **PAD without Diabetes**: 8.56%
  - OR 1.67 (1.64, 1.70)

- **MALE**
  - **PAD with Diabetes**: 12.13%
  - **PAD without Diabetes**: 3.38%
  - OR 3.03 (2.92, 3.14)

- **ALI**
  - **PAD with Diabetes**: 1.96%
  - **PAD without Diabetes**: 1.91%
  - OR 1.75 (1.68, 1.82)

One-year outcomes
In 374,776 real world outpatients after lower extremity revascularization (~39% with T2DM)

Hess C….Bonaca MP et al ACC 2020
Objectives

• To characterize the spectrum of limb ischemic events in patients with Type 2 diabetes mellitus (T2DM) and CAD overall and based on the presence of concomitant peripheral artery disease (PAD):
  • Acute limb ischemia (ALI)
  • Major amputation of vascular etiology
  • Peripheral revascularization (urgent and elective)
  • Overall limb ischemic outcomes defined as composite of ALI, major amputation of vascular etiology, and peripheral revascularization

• To evaluate the efficacy of ticagrelor + ASA vs. ASA alone for reducing limb ischemic events in patients with T2DM and CAD

• To evaluate whether the effect of ticagrelor on limb events was consistent in those with and without concomitant PAD
Methods

• THEMIS was a large, multi-center, international trial randomizing patients to ticagrelor vs. placebo on a background of low dose aspirin
  • Patients with DM with CAD (incl. prior PCI) without history of MI or Stroke
  • Patients at high risk of bleeding or requiring anticoagulation excluded

• Sites prospectively reported limb ischemic events in an electronic data capture system

• Major adverse limb events (MALE) prospectively adjudicated including:
  • Acute limb ischemia – acute thrombotic occlusion of a lower extremity artery threatening or resulting in tissue loss
  • Major amputation of a vascular etiology – amputation above the foot with impaired perfusion as a primary etiology, including chronic critical limb threatening ischemia

• The need for peripheral revascularization was investigator reported and categorized as urgent or elective
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PAD (N=1687)</th>
<th>No PAD (N=17533)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – median (IQR), yrs</td>
<td>68 (62 – 73)</td>
<td>66 (61 – 72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female (%)</td>
<td>27</td>
<td>32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>83</td>
<td>70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>95</td>
<td>92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>92</td>
<td>87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current Smoking (%)</td>
<td>15</td>
<td>11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of T2DM – median (IQR), yrs</td>
<td>12 (6 – 19)</td>
<td>10 (5 – 16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes complication (%)</td>
<td>41</td>
<td>24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1C – median (IQR), %</td>
<td>7.1 (6.4 – 8.1)</td>
<td>7.1 (6.4 – 8.1)</td>
<td>0.65</td>
</tr>
<tr>
<td>eGFR – median (IQR), mL/min/1.73m²</td>
<td>71 (56 – 86)</td>
<td>75 (61 – 90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary revascularization (%)</td>
<td>83</td>
<td>80</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Outcomes in Placebo Patients with PAD versus no PAD

- **PAD + CAD + DM**
  - \( N = 860 \)
  - MACE Mortality: HR 1.48, 95% CI (1.20 – 1.81), \( p < 0.001 \)

- **CAD + DM and no PAD**
  - \( N = 8741 \)
  - MACE Mortality: HR 1.73, 95% CI (1.38 – 2.17), \( p < 0.001 \)

Chart shows the Kaplan-Meier (KM) survival analysis at 3 years.
Outcomes in Placebo Patients with PAD versus no PAD

- **Limb ischemic events**
  - HR 10.67 (7.90 – 14.40) p<0.001
  - N=860

- **Peripheral Revascularization**
  - HR 10.54 (7.72 – 14.38) p<0.001
  - N=8741

- **Major amputation of vascular etiology**
  - HR 9.96 (3.74 – 26.55) p<0.001

- **Acute limb ischemia**
  - HR 5.61 (2.08 – 15.18) p<0.001

### Outcomes

- 85 86 79 80
- 0.80 0.80
- 8 8 6 11
- N=860
- N=8741
Overall Limb Ischemic Outcomes with Ticagrelor versus Placebo

HR 0.77
(0.61 – 0.96)
P=0.022

Ticagrelor
Placebo

N=19,220

<table>
<thead>
<tr>
<th>Event</th>
<th>Ticagrelor</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limb Ischemic</td>
<td>171</td>
<td>131</td>
</tr>
<tr>
<td>KM (%) at 3 yrs</td>
<td>1.59%</td>
<td>1.30%</td>
</tr>
</tbody>
</table>

P=0.022
Limb Outcomes by Type with Ticagrelor versus Placebo

- **KM (%) at 3 years**
  - **Limb Ischemic Event**
    - Ticagrelor: 1.59%
    - Placebo: 1.51%
    - HR 0.77 (0.61 – 0.96)
    - P=0.022
  - **Peripheral Revascularization**
    - Ticagrelor: 1.30%
    - Placebo: 1.23%
    - HR 0.79 (0.62 – 0.99)
  - **Acute Limb Ischemia**
    - Ticagrelor: 0.16%
    - Placebo: 0.12%
    - HR 0.63 (0.28 – 1.38)
  - **Major Amputation**
    - Ticagrelor: 0.04%
    - Placebo: 0.10%
    - HR 0.24 (0.08 – 0.70)

N=19,220
Peripheral Revascularization with Ticagrelor versus Placebo

HR 0.79 (0.62 – 0.99)  
P=0.044

N=19,220

KM (%) at 3 years

- **Peripheral Revascularization**
  - Placebo: 1.50%
  - Ticagrelor: 1.20%
  - HR 0.79 (0.62 – 0.99)
  - P=0.044

- **Elective**
  - Placebo: 1.30%
  - Ticagrelor: 1.10%
  - HR 0.80 (0.62 – 1.02)

- **Non-elective**
  - Placebo: 0.30%
  - Ticagrelor: 0.20%
  - HR 0.57 (0.31 – 1.05)

Procedure Type

KM (%) at 3 years

- **Peripheral Revascularization**
  - Placebo: 159
  - Ticagrelor: 126

- **Elective**
  - Placebo: 141
  - Ticagrelor: 113

- **Non-elective**
  - Placebo: 28
  - Ticagrelor: 16
Limb Events with Ticagrelor versus Placebo in PAD vs. no PAD

**All Patients**

- **Ticagrelor**
  - 1.59%
  - 171 cases

- **Placebo**
  - 1.30%
  - 131 cases

- **HR 0.77**
  - (0.61 – 0.96)
  - P=0.022

**PAD Status at Baseline**

- **PAD**
  - 9.50%
  - 7.60%
  - 9.50%

- **no PAD**
  - 0.80%
  - 0.70%

- **HR 0.80**
  - (0.58 – 1.11)
- **HR 0.76**
  - (0.55 – 1.05)

- **P-interaction 0.81**
Summary

• Among patients with T2DM and CAD, those with known PAD were at very high risk of limb events with a ~10-fold risk relative those with no known PAD

• In patients enrolled in THEMIS, ticagrelor reduced limb ischemic events including:
  • ~50% reduction in major adverse limb events (ALI, amputation of vascular etiology)
  • ~20% reduction in peripheral revascularization, including elective

• These benefits were consistent regardless of PAD status, however, due to their higher risk profile, patients with PAD enjoyed a greater absolute benefit
Conclusion

• These findings suggest that patients with T2DM, CAD, and concomitant PAD may derive particular benefit from long-term ticagrelor when considering both adverse cardiovascular and limb outcomes.

• Coupled with observations from PEGASUS-TIMI 54, these data further support the benefit of ticagrelor for limb ischemic events.

• Future studies are needed to establish whether such a strategy is beneficial in patients selected for PAD and the safety after peripheral revascularization.