VOYAGER PAD
Efficacy and Safety of Rivaroxaban in Patients with PAD undergoing Revascularization with and without Coronary Artery Disease


European Society of Cardiology Virtual Scientific Sessions 2020
Late-Breaking Clinical Trial
August 2020
William R Hiatt DOI: Grant support from Bayer, Janssen and Amgen

An Academic Research Organization Affiliated with the University of Colorado School of Medicine
Concomitant CAD Increases MACE Risk in PAD

EUCLID Trial
Adjusted HR 1.50
(1.13 – 1.99)

PEGASUS-TIMI 54 Trial
Adjusted HR 1.60
(1.20 – 2.13)

CV Death, MI or Ischemic Stroke at 3 years

PAD 10.3%
PAD+CAD 17.8%
CAD 8.4%
CAD+PAD 19.3%

Bonaca Vasc Med 2018
Effect of Vorpaxar in Patients in PAD for MACE and Major Adverse Limb Events by CAD Status

- **MACE**
  - PAD with CAD
    - HR 0.82
    - (0.69-0.97)
    - P=0.020
    - Placebo
    - 14.0%
    - ARR -2.3%
    - NNT 43
    - Vorapaxar
    - 11.7%
    - ARR -0.3%
    - NNT 333
  - PAD Alone
    - HR 1.90
    - (0.65-1.46)
    - P=0.98

- **Major Adverse Limb Events**
  - PAD Alone
    - HR 0.50
    - (0.31-0.80)
    - P=0.004
    - ARR -4.0%
    - NNT 25
    - Placebo
    - 8.0%
  - PAD with CAD
    - HR 0.85
    - (0.60-1.19)
    - P=0.33
    - Vorapaxar
    - 4.0%
    - ARR -0.7%
    - NNT 143

Qamar A…Bonaca MP. Vascular Medicine 2019
Rivaroxaban and MACE in Stable CAD

Population selected for PAD or CAD with enrichment

PEP: CV death, MI or stroke

Rivaroxaban + Aspirin vs. Aspirin
HR: 0.72 (0.57-0.90), P=0.005

Concomitant CAD 65%

Lancet 2018;391:219-229
Trial Design

6,564 Patients with Symptomatic Lower Extremity PAD* Undergoing Peripheral Revascularization

Primary Efficacy Endpoint:
Acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke or cardiovascular death

Principal Safety Outcome: TIMI Major Bleeding

*PAD defined as:
- Ischemic symptoms (functional limitation, rest pain or ischemic ulceration) AND
- Imaging evidence of occlusion AND
- Abnormal ABI/TBI

NCT02504216

ASA 100 daily for all Patients
Clopidogrel at Investigator’s Discretion

Randomized 1:1 Double Blind

Stratified by Revascularization Approach
(Surgical or Endovascular with and without clopidogrel)

Rivaroxaban 2.5 mg twice daily

Placebo

Follow up Q6 Months, Event Driven, Median f/u 28 Months

Capell WH, Bonaca MP, Nehler MR...Hiatt WR. AHJ 2018
Bonaca MP...Hiatt WR NEJM 2020
Rivaroxaban Across the Spectrum of PAD

Population selected for lower extremity symptomatic PAD after revascularization with no enrichment for CV risk

PEP: Acute limb ischemia, major amputation of a vascular etiology, MI, ischemic stroke or CV death

**With CAD 32%**

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1.5</td>
<td>65</td>
</tr>
<tr>
<td>1</td>
<td>2.0</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>2.6</td>
<td>39</td>
</tr>
</tbody>
</table>

HR 0.85
95% CI 0.76 – 0.96
P=0.0085

**With CAD 65%**

Rivaroxaban + Aspirin vs. Aspirin
HR: 0.72 (0.57-0.90), P=0.005

Population selected for PAD or CAD with enrichment criteria for CV risk

PEP: CV death, MI or stroke

ARR – absolute risk reduction, NNT number needed to treat

Months from Randomization

Cumulative Incidence (KM%)

6 Months
ARR 1.5%
NNT 65

1 Year
ARR 2.0%
NNT 50

3 Year
ARR 2.6%
NNT 39

Lancet 2018;391:219-229

NEJM 2020;382:1994-2004
Objectives

In PAD patients undergoing LER for ischemic symptoms randomized to rivaroxaban 2.5 mg twice daily plus low dose aspirin versus aspirin alone:

• To evaluate whether CAD is associated with increased risk of MACE and/or major adverse limb events (MALE) compared to no CAD

• To evaluate whether the safety and efficacy of rivaroxaban after lower extremity revascularization is consistent in patients with and without CAD
Methods

• The presence of known coronary artery disease (with CAD) was reported by investigators at baseline and was defined as any known history including prior MI, coronary revascularization, other stable CAD

• Primary outcome is composite of acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke, CV death

• COX model with interaction terms to assess for heterogeneity of efficacy and safety of rivaroxaban by CAD status
# Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>With CAD N=2067</th>
<th>Without CAD N=4496</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR) – yr</td>
<td>68 (62 – 74)</td>
<td>66 (60 – 72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female no. (%)</td>
<td>22</td>
<td>28</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>White Caucasian no. (%)</td>
<td>79</td>
<td>82</td>
<td>0.0168</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>90</td>
<td>77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes Mellitus (type 2) (%)</td>
<td>51</td>
<td>35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>73</td>
<td>54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>27</td>
<td>38</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min.1.73m²</td>
<td>26</td>
<td>18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>100</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Carotid stenosis ≥ 50% (%)</td>
<td>12</td>
<td>6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of heart failure (%)</td>
<td>19</td>
<td>3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

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<th>Baseline Characteristics</th>
<th>With CAD N=2067</th>
<th>Without CAD N=4496</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying revascularization</td>
<td></td>
<td></td>
<td>0.0192</td>
</tr>
<tr>
<td>Surgical (%)</td>
<td>31</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Endovascular (%)</td>
<td>69</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Reason for revascularization</td>
<td></td>
<td></td>
<td>0.0185</td>
</tr>
<tr>
<td>Claudication (%)</td>
<td>96</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Critical limb ischemia (%)</td>
<td>22</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>PAD Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior limb revascularization (%)</td>
<td>43</td>
<td>32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ABI (median, IQR)</td>
<td>0.58 (0.44 – 0.69)</td>
<td>0.54 (0.41 – 0.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior Major Amputation (%)</td>
<td>0.9</td>
<td>1.0</td>
<td>0.5920</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>90</td>
<td>76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>71</td>
<td>60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clopidogrel at randomization</td>
<td>54</td>
<td>49</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Primary Endpoint – Placebo Patients

PAD with CAD
PAD without CAD

Days from Randomization

Cumulative Incidence (%)

0 90 182 274 366 456 547 639 731 821 912 1004 1096

Placebo

PAD with CAD 24.3%
PAD without CAD 17.9% +6.4%
Primary Endpoint with Rivaroxaban with and without CAD

- Placebo
- Rivaroxaban

Cumulative Incidence (%)

Days from Randomization

- CAD
  - HR 0.78
  - (0.64-0.95)
  - ARR 5.4%
  - 24.3%

- PAD with CAD
  - 18.9%
  - 17.9%
  - 16.1%

- No CAD
  - HR 0.89
  - (0.77-1.04)
  - ARR 1.8%

P-Interaction = 0.29
Primary Endpoint Components with and without CAD

**With CAD**

All $p$-interaction > 0.10

- **Placebo**
  - HR 0.78 (0.54 – 1.14)
  - KM (%) at 3 years: 5.4
  - ALI
  - Vasc Amp
  - MI: 8.8
  - IS: 6.6
  - CV Death: 6.5

- **Rivaroxaban**
  - HR 0.96 (0.61 – 1.53)
  - KM (%) at 3 years: 3.7
  - ALI
  - Vasc Amp
  - MI: 7.3
  - IS: 3.9
  - CV Death: 3.9

**Without CAD**

- **Placebo**
  - HR 0.77 (0.55 – 1.08)
  - KM (%) at 3 years: 3.3
  - ALI
  - Vasc Amp
  - MI: 5.2
  - IS: 3.3
  - CV Death: 5.2

- **Rivaroxaban**
  - HR 0.75 (0.44 – 1.26)
  - KM (%) at 3 years: 3.9
  - ALI
  - Vasc Amp
  - MI: 3.9
  - IS: 3.7
  - CV Death: 2.6
MI and ALI with and without CAD

**Placebo**
- MI: HR 0.77 (0.55 – 1.08), ARR 1.5%
- ALI: HR 0.98 (0.70 – 1.35), ARR 0.5%

**Rivaroxaban**
- MI: HR 0.77 (0.55 – 1.08), ARR 1.5%
- ALI: HR 0.98 (0.70 – 1.35), ARR 0.5%

**P-interaction**
- MI: 0.33
- ALI: 0.34

**HR**
- MI: 0.63 (0.49 – 0.81), ARR 3.1%
- ALI: 0.78 (0.54 – 1.14), ARR 1.1%
### Secondary Endpoints With and Without CAD

**All p-interaction > 0.10**

<table>
<thead>
<tr>
<th>Event Description</th>
<th>HR (95% CI)</th>
<th>P-Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, ischemic stroke, CHD, ALI, or major amputation of vascular etiology</td>
<td><strong>With CAD</strong> 0.78 (0.64-0.96)</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td><strong>Without CAD</strong> 0.81 (0.69-0.96)</td>
<td></td>
</tr>
<tr>
<td>Unplanned index limb revascularization for recurrent limb ischemia</td>
<td><strong>With CAD</strong> 1.00 (0.83-1.21)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td><strong>Without CAD</strong> 0.83 (0.72-0.95)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for a coronary or peripheral event (either lower limb) of a thrombotic nature</td>
<td><strong>With CAD</strong> 0.83 (0.63-1.09)</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td><strong>Without CAD</strong> 0.67 (0.55-0.82)</td>
<td></td>
</tr>
<tr>
<td>MI, ischemic stroke, all-cause mortality, ALI, and major amputation of vascular etiology</td>
<td><strong>With CAD</strong> 0.81 (0.68-0.97)</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td><strong>Without CAD</strong> 0.93 (0.81-1.06)</td>
<td></td>
</tr>
<tr>
<td>MI, all-cause stroke, CV death, ALI, and major amputation of vascular etiology</td>
<td><strong>With CAD</strong> 0.77 (0.64-0.94)</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td><strong>Without CAD</strong> 0.90 (0.78-1.05)</td>
<td></td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td><strong>With CAD</strong> 0.92 (0.71-1.20)</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td><strong>Without CAD</strong> 1.18 (0.94-1.44)</td>
<td></td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td><strong>With CAD</strong> 0.88 (0.37-2.08)</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td><strong>Without CAD</strong> 0.51 (0.27-0.94)</td>
<td></td>
</tr>
</tbody>
</table>

**Rivaroxaban Better** vs. **Placebo Better**
Safety of Rivaroxaban With and Without CAD

**With CAD**
N=2067

**Without CAD**
N=4496

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (HR)</th>
<th>Rivaroxaban (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI major with CAD</td>
<td>2.4 (1.10–4.56)</td>
<td>1.15 (0.72–1.84)</td>
</tr>
<tr>
<td>TIMI major without CAD</td>
<td>1.7%</td>
<td>1.5%</td>
</tr>
<tr>
<td>ICH or Fatal with CAD</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>ICH or Fatal without CAD</td>
<td>0.5%</td>
<td>0.6%</td>
</tr>
<tr>
<td>ISTH major with CAD</td>
<td>4.6%</td>
<td>3.2%</td>
</tr>
<tr>
<td>ISTH major without CAD</td>
<td>4.2%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

P-interaction 0.13

P-interaction 0.88

P-interaction 0.81

KM Rate at 3 Years (%)

HR = Hazard Ratio
Summary

• In patients with lower extremity PAD undergoing revascularization for ischemia:
  
  – Patients with PAD and CAD appear to have higher rates of MI and IS relative to those with PAD and no CAD
  
  – Patients with PAD and no CAD have higher rates of major adverse limb events relative to MI and IS
  
  – The efficacy and safety of rivaroxaban in PAD are consistent regardless of CAD with no significant interactions, however, the absolute benefits of rivaroxaban appear greater in those with CAD particularly for MI and IS
Conclusion

- A strategy of rivaroxaban 2.5 mg twice daily plus low dose aspirin versus low dose aspirin alone reduces ischemic events of the limb, brain and heart and increases bleeding with an overall net benefit in patients with lower extremity symptomatic PAD after revascularization.

  - The benefits of this strategy for MI and IS are robust particularly in patients with PAD and CAD and consistent with data from COMPASS (Lancet 2018).

  - In those without known CAD, benefits appear to be driven by reductions in severe limb events.

- These findings suggest heterogeneity of prognostic risk for ischemic events in lower extremity PAD patients and may support shared decision making with patients.