VOYAGER PAD
Efficacy and Safety of Rivaroxaban in Patients with PAD undergoing Recurrent Lower Extremity Revascularization

CIRSE
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Marc P. Bonaca on behalf of the VOYAGER PAD Investigators, Executive and Steering Committees
Disclosures

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• Grant support from: Amgen, AstraZeneca, Bayer, Medtronic, Merck, Novo Nordisk, Pfizer
### TRA2P-TIMI 50 PAD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted HR for ALI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Peripheral</td>
<td>3.60 (2.10 – 6.18) P&lt;0.001</td>
</tr>
<tr>
<td>Revascularization</td>
<td></td>
</tr>
<tr>
<td>ABI ≤ 0.5</td>
<td>2.86 (1.81 – 4.51)</td>
</tr>
<tr>
<td>ABI ≥ 1.3</td>
<td>2.71 (1.09 – 6.72)</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>2.17 (1.01 – 4.67) P=0.046</td>
</tr>
</tbody>
</table>

Bonaca et al. Circulation 2016

### PEGASUS-TIMI 54 PAD

**Prior revascularization**

Adjusted HR for ALI 3.76 (2.26 – 6.25) p<0.001

Bonaca et al. JACC 2016

### EUCLID

**Prior revascularization**

Adjusted HR for ALI 4.23 (2.86 – 6.25) p<0.001

Jones et al. Circulation 2016
Heterogeneity in Risk of Major Adverse Limb Events by Severity of Limb Disease

- Prior Revascularization or Amputation: 3.80% (N=2264, 36% of Population)
- Claudication but no History of Revascularization or Amputation: 1.37% (N=2705, 42% of Population)
- Asymptomatic, low ABI (<=0.90): 0.50% (N=1422, 22% of Population)

Bonaca MP, Creager MA. JACC 2018
Trial Design

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

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

Randomized 1:1 Double Blind

Rivaroxaban 2.5 mg twice daily

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

Placebo

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

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

Capell WH, Bonaca MP, Nehler MR...Hiatt WR. AHJ 2018
Bonaca MP...Hiatt WR NEJM 2020

NCT02504216
Primary Endpoint

Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death

Bonaca MP…Hiatt WR et al. NEJM 2020;382:1994–2004

ARR – absolute risk reduction,
NNT number needed to treat

ARR – absolute risk reduction,
NNT number needed to treat

3 Year
ARR 2.6%
NNT 39

19.9%

17.3%

6 Months
ARR 1.5%
NNT 65

1 Year
ARR 2.0%
NNT 50

HR 0.85
95% CI 0.76 – 0.96
P=0.009

Bonaca MP…Hiatt WR et al. NEJM 2020;382:1994–2004

ARR – absolute risk reduction,
NNT number needed to treat

ARR – absolute risk reduction,
NNT number needed to treat
Hypotheses

Symptomatic PAD patients undergoing *recurrent* lower extremity revascularization (prior LER) versus those undergoing *first* LER:

- Will have a higher rate of acute limb ischemia
- Will derive even greater benefits with a rivaroxaban plus aspirin strategy versus aspirin alone, particularly for acute limb ischemia
Methods

• The presence of known prior LER was reported by investigators at baseline and was defined as any history of endovascular, hybrid or surgical LER

• 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 prior LER status
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>No Prior LER N=4226</th>
<th>Prior LER N=2336</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, median (IQR) – yr</td>
<td>67 (61 – 73)</td>
<td>67 (61 – 73)</td>
<td>0.74</td>
</tr>
<tr>
<td>Female no. (%)</td>
<td>26</td>
<td>25</td>
<td>0.46</td>
</tr>
<tr>
<td>White Caucasian no. (%)</td>
<td>81</td>
<td>80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>79</td>
<td>86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>35</td>
<td>51</td>
<td>0.066</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>54</td>
<td>71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>35</td>
<td>33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min.1.73m²</td>
<td>19</td>
<td>22</td>
<td>0.0259</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>28</td>
<td>38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid stenosis ≥ 50% (%)</td>
<td>6</td>
<td>11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of heart failure (%)</td>
<td>8</td>
<td>8</td>
<td>0.42</td>
</tr>
</tbody>
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## Baseline Characteristics

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Qualifying revascularization</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgical (%)</td>
<td>36</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Endovascular (%)</td>
<td>64</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td><strong>Reason for revascularization</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Critical limb ischemia (%)</td>
<td>26</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td><strong>PAD Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior major amputation (%)</td>
<td>0.7</td>
<td>1.5</td>
<td>0.0026</td>
</tr>
<tr>
<td>Prior amputation (%)</td>
<td>5</td>
<td>7</td>
<td>0.0054</td>
</tr>
<tr>
<td>Prior bypass (%)</td>
<td>0</td>
<td>28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior endovascular (%)</td>
<td>0</td>
<td>82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABI (median, IWR)</td>
<td>0.53 (0.40 – 0.65)</td>
<td>0.58 (0.45 – 0.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>77</td>
<td>85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>61</td>
<td>68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clopidogrel at randomization</td>
<td>47</td>
<td>56</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Primary Endpoint – Placebo Patients

Placebo

Days from Randomization

Cumulative Incidence (%)

No Prior LER 17.7%
Primary Endpoint – Placebo Patients

- Prior LER: 23.8%
- No Prior LER: 17.7%

Cumulative Incidence (%) vs. Days from Randomization
Primary Endpoint by Prior LER

No Prior LER

HR 0.94
(0.81 – 1.10)

HR 0.73
(0.60 – 0.88)

P-interaction 0.0360
Limb Outcomes with Rivaroxaban with and without Prior LER

**No Prior LER**

- **Placebo**: HR 0.74 (0.56 – 0.98)
- **Rivaroxaban**: HR 0.91 (0.65 – 1.27)

**Prior LER**

- **Placebo**: HR 0.91 (0.65 – 1.27)
- **Rivaroxaban**: HR 0.59 (0.44 – 0.80)

All p-interaction > 0.05

**KM (%) at 3 years**

- **ALI**
  - Placebo: 4.5%
  - Rivaroxaban: 6.0%
- **Vasc Amp**
  - Placebo: 3.3%
  - Rivaroxaban: 3.4%

- **ALI**
  - Placebo: 6.6%
  - Rivaroxaban: 10.8%
- **Vasc Amp**
  - Placebo: 3.7%
  - Rivaroxaban: 4.5%
Safety of Rivaroxaban With and Without CAD

No Prior LER
N=4,187

Prior LER
N=2,316

P-interaction 0.16

HR 1.88
(1.09 – 3.25)

HR 1.08
(0.62 – 1.89)

P-interaction 0.38

HR 1.19
(0.50 – 2.80)

HR 0.66
(0.23 – 1.84)

P-interaction 0.93

HR 1.44
(1.02 – 2.05)

HR 1.41
(0.97 – 2.06)

KM Rate at 3 Years (%)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Placebo</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI major no prior LER</td>
<td>2.3%</td>
<td>3.1%</td>
</tr>
<tr>
<td>ICH or Fatal no prior LER</td>
<td>0.9%</td>
<td>0.7%</td>
</tr>
<tr>
<td>ISTH major no prior LER</td>
<td>1.4%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

P-values:
- P-interaction 0.16
- P-interaction 0.38
- P-interaction 0.93

Notes:
- HR: Hazard Ratio
- N: Number of participants
- KM: Kaplan-Meier
Summary

Symptomatic PAD patients undergoing *recurrent* lower extremity revascularization (prior LER) versus those undergoing *first* LER:

- Have higher rates of ischemic events, particularly acute limb ischemia

- Derive even greater benefit of a rivaroxaban plus aspirin versus aspirin alone for the composite of acute limb ischemia, major amputation of a vascular etiology, myocardial infarction, ischemic stroke or cardiovascular death with the greatest absolute benefit for acute limb ischemia

• The safety of rivaroxaban plus aspirin versus aspirin alone is consistent regardless of prior LER
Conclusion

• Prior analyses in stable PAD demonstrate that prior LER is an independent predictor of ALI even late after intervention

• The current analysis demonstrates that within this population, those with a multiple revascularizations are at higher risk than those who have undergone a first revascularization only and may derive particularly robust benefit from rivaroxaban plus aspirin versus aspirin alone

• These observations further demonstrate the heterogeneity of risk in the PAD population and may assist in clinical risk stratification and therapeutic decision making