Reductions in Total Ischemic Events with Rivaroxaban in Patients with Symptomatic PAD after Revascularization: The VOYAGER PAD Trial

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on behalf of the VOYAGER PAD Investigators

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17634
Disclosures

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• Other research grants to CPC Clinical Research from Arca, Amgen, AstraZeneca, Bayer, Janssen, Merck, Novo Nordisk
After Lower Extremity Revascularization there is a 4-Fold Risk of Acute Limb Ischemia

After Acute Limb Ischemia Outcomes are poor and Repeat Revascularizations are frequently required

<table>
<thead>
<tr>
<th>Study</th>
<th>HR for ALI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRA2P-TIMI 50 PAD</td>
<td>HR 3.60 (2.10 – 6.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bonaca et al. Circulation 2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEGASUS-TIMI 54 PAD</td>
<td>Adjusted HR 3.76 (2.26 – 6.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bonaca et al. JACC 2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EUCLID</td>
<td>Adjusted HR 4.23 (2.86 – 6.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Jones et al. Circulation 2016</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Most Frequent Outcomes after an ALI Event are Limb Related

<table>
<thead>
<tr>
<th>Event</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>11.7%</td>
</tr>
<tr>
<td>Death</td>
<td>12.1%</td>
</tr>
<tr>
<td>Recurrent ALI</td>
<td>24.0%</td>
</tr>
<tr>
<td>Amputation</td>
<td>27.0%</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>54.0%</td>
</tr>
<tr>
<td>Peripheral Revascularization</td>
<td>63.2%</td>
</tr>
</tbody>
</table>

Bonaca et al. Circulation 2016
VOYAGER PAD 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 2.5 years

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

Principal Safety Outcome: TIMI Major Bleeding

Capell WH, Bonaca MP, Nehler MR...Hiatt WR. AHJ 2018
Bonaca MP...Hiatt WR NEJM 2020
VOYAGER PAD Primary Results

**Primary Endpoint**

ITT - HR 0.85
(0.76 – 0.96)
P=0.0085
ARR 2.6%, NNT 39

**Secondary Vascular Outcomes**

TIMI Major Bleeding
On Treatment - HR 1.43
(0.97 – 2.10)
P=0.0695
ARI 0.8%, NNH 125

Unplanned Limb Revascularization for Ischemia

HR 0.88
(0.79 – 0.99)
P=0.028
ARR 2.48

VTE

HR 0.61
(0.37 – 1.00)
P=0.0469

Days from Randomization

*Composite of acute limb ischemia, major amputation of a vascular cause, myocardial infarction, ischemic stroke, cardiovascular death*
Objectives

- In a pre-specified analysis to investigate the number of first and total events in PAD patients undergoing LER.
- To evaluate the composition of events including all limb and cardiovascular events.
- To evaluate the efficacy of rivaroxaban on first and total events.

1 in 5 patients undergoing LER experienced a first adverse limb or cardiovascular event inspite of aspirin in all patients, statins in 80% and clopidogrel in half of the patients.

The addition of rivaroxaban 2.5 mg twice daily reduced first events by app. 15% (NNT of 39 to prevent a first event at 3 years).

The rate of total (first and potentially subsequent) events after LER and the effect of rivaroxaban on reduction of total events is unknown.
Methods

• Patients:
  • Qualifying patients had symptomatic PAD defined by abnormal ankle-brachial index (ABI) ≤ 0.80 or toe-brachial index (TBI) ≤ 0.60 (in those without a prior history of LER) with an anatomy of occlusive disease distal to the external iliac artery

• Efficacy:
  • Primary composite (ITT) of acute limb ischemia, major amputation of a vascular etiology, myocardial infarction, ischemic stroke or CV death
  • Prespecified categories of Vascular events included subsequent LER and venous thromboembolic events

• Outcomes adjudicated by a blinded CEC*

• Marginal proportional hazards model
  • allowing for the possibility of multiple vascular events within a given participant
  • non-vascular death as a competing terminal event

* Peripheral revascularizations and venous thromboembolism were reported by investigators blinded to treatment assignment
## Baseline Characteristics of Participants by Number of Vascular Events

<table>
<thead>
<tr>
<th></th>
<th>(A) No Events (n=4263; 65%)</th>
<th>(B) One Event (n=1209; 18%)</th>
<th>(C) Multiple Events (n=1092; 17%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(A) vs. (B) + (C)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>29.3</td>
<td>35.2</td>
<td>35.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37.3</td>
<td>45.2</td>
<td>45.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR&lt;60 ml/min/1.73m²</td>
<td>19.2</td>
<td>22.2</td>
<td>21.8</td>
<td>0.008</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>30.2</td>
<td>40.8</td>
<td>50.7</td>
<td></td>
</tr>
<tr>
<td>Qualifying revascularization</td>
<td></td>
<td></td>
<td></td>
<td>0.0007</td>
</tr>
<tr>
<td>Endovascular</td>
<td>65.3</td>
<td>68.4</td>
<td>70.5</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>34.7</td>
<td>31.6</td>
<td>29.5</td>
<td></td>
</tr>
<tr>
<td>≥15 cm target lesion</td>
<td>30.8</td>
<td>36.3</td>
<td>45.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atherectomy</td>
<td>3.4</td>
<td>5.5</td>
<td>9.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Randomized to rivaroxaban</td>
<td>50.8</td>
<td>51.4</td>
<td>45.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>78.7</td>
<td>82.4</td>
<td>82.2</td>
<td>0.0005</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>49.5</td>
<td>51.0</td>
<td>53.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Symptomatic PAD after LER - First and Total Vascular Events

PAD patients over a median of 28 months after LER

Patients Randomized: 6564
Vascular Events:
- Total Vascular Events: 4714
- First Primary Endpoint events: 1092
- Total Primary Endpoint events: 1614

Total Vascular Events
### Categories of Total Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Rivaroxaban (n = 3286)</th>
<th>Placebo (n = 3278)</th>
<th>Total (n = 6564)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Vascular</td>
<td>2186</td>
<td>2528</td>
<td>4714</td>
</tr>
<tr>
<td>Primary endpoint events</td>
<td>745</td>
<td>869</td>
<td>1614</td>
</tr>
<tr>
<td>Other Vascular events</td>
<td>1441</td>
<td>1659</td>
<td>3100</td>
</tr>
<tr>
<td>Non-vascular death</td>
<td>122</td>
<td>123</td>
<td>245</td>
</tr>
</tbody>
</table>

* Investigator-reported; not subject to adjudication by independent committee
## Categories of Total Events

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<td></td>
</tr>
<tr>
<td>Primary endpoint events</td>
<td>745</td>
<td>869</td>
<td>1614</td>
</tr>
<tr>
<td><em>Acute limb ischemia</em></td>
<td>202</td>
<td>306</td>
<td>508</td>
</tr>
<tr>
<td><em>Major amputation for vascular causes</em></td>
<td>117</td>
<td>133</td>
<td>250</td>
</tr>
<tr>
<td><em>Non-fatal myocardial infarction</em></td>
<td>152</td>
<td>170</td>
<td>322</td>
</tr>
<tr>
<td><em>Non-fatal ischemic stroke</em></td>
<td>75</td>
<td>86</td>
<td>161</td>
</tr>
<tr>
<td><em>Cardiovascular Death</em></td>
<td>199</td>
<td>174</td>
<td>373</td>
</tr>
<tr>
<td><strong>Other Vascular events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Peripheral revascularization</em></td>
<td>1416</td>
<td>1618</td>
<td>3034</td>
</tr>
<tr>
<td><em>Venous thromboembolic event</em></td>
<td>25</td>
<td>41</td>
<td>66</td>
</tr>
<tr>
<td>Non-vascular death</td>
<td>122</td>
<td>123</td>
<td>245</td>
</tr>
</tbody>
</table>

* Investigator-reported; not subject to adjudication by independent committee
Second Vascular Event by Type of First Non-fatal Vascular Event

60% of second events were in patients who had a first peripheral revascularization.

MACE = major adverse cardiovascular event; MALE = major adverse limb event.
First and Subsequent Vascular Events

MACE = major adverse cardiovascular event; MALE = major adverse limb event.
First and Subsequent Vascular Events

MACE = major adverse cardiovascular event; MALE = major adverse limb event.

**Placbo Rivaroxaban Placebo Rivaroxaban Placebo Rivaroxaban Placebo Rivaroxaban**

300
600
900
1200

Events

-61 Events

-94 Events

-44 Events

-143 Events

MACE
First and Subsequent Vascular Events

MACE = major adverse cardiovascular event; MALE = major adverse limb event.
First and Subsequent Vascular Events

There were 342 fewer total vascular events with rivaroxaban versus 61 fewer first vascular events (Δ 18%).

MACE = major adverse cardiovascular event; MALE = major adverse limb event.
Accrual of Events per 100 Patients

Total Primary: HR (95% CI) 0.86 (0.75, 0.98), p=0.02
Accrual of Events per 100 Patients

Total Vascular: HR (95% CI) 0.86 (0.79, 0.95), p=0.003
Total Primary: HR (95% CI) 0.86 (0.75, 0.98), p=0.02
ITT vs. “On-Treatment”

Total Primary Endpoint Events
- Intention-to-Treat: HR (95% CI) = 0.86 (0.75, 0.98)

Total Vascular Events
- Intention-to-Treat: HR (95% CI) = 0.86 (0.79, 0.95)

Treatment

- Rivaroxaban Better
- Placebo Better
ITT vs. “On-Treatment”

903 of 2186 vascular events in rivaroxaban group occurred after given patient’s last dose

<table>
<thead>
<tr>
<th>Total Primary Endpoint Events</th>
<th>Treatment HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-Treat</td>
<td>0.86 (0.75, 0.98)</td>
</tr>
<tr>
<td>Time-Varying Rivaroxaban Exposure</td>
<td>0.42 (0.37, 0.49)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Vascular Events</th>
<th>Treatment HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-Treat</td>
<td>0.86 (0.79, 0.95)</td>
</tr>
<tr>
<td>Time-Varying Rivaroxaban Exposure</td>
<td>0.63 (0.57, 0.69)</td>
</tr>
</tbody>
</table>
# Treatment Effects on Total Vascular Events

<table>
<thead>
<tr>
<th>Total Events per 100 Patients*</th>
<th>Rivaroxaban (n=3286)</th>
<th>Placebo (n=3278)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint events</strong></td>
<td>25.9</td>
<td>30.3</td>
<td>0.86 (0.75, 0.98)</td>
</tr>
<tr>
<td>Acute limb ischemia</td>
<td>6.6</td>
<td>10.2</td>
<td>0.66 (0.52, 0.83)</td>
</tr>
<tr>
<td>Major amputation</td>
<td>3.8</td>
<td>4.3</td>
<td>0.88 (0.66, 1.16)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>5.3</td>
<td>5.7</td>
<td>0.89 (0.69, 1.15)</td>
</tr>
<tr>
<td>Non-fatal ischemic stroke</td>
<td>2.6</td>
<td>3.0</td>
<td>0.87 (0.63, 1.20)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>7.1</td>
<td>6.5</td>
<td>1.14 (0.93, 1.40)</td>
</tr>
<tr>
<td><strong>Other vascular events</strong></td>
<td>48.5</td>
<td>56.5</td>
<td>0.87 (0.78, 0.97)</td>
</tr>
<tr>
<td>Peripheral revascularization</td>
<td>47.8</td>
<td>55.0</td>
<td>0.87 (0.78, 0.97)</td>
</tr>
<tr>
<td>Venous thromboembolic event</td>
<td>0.7</td>
<td>1.5</td>
<td>0.61 (0.37, 1.00)</td>
</tr>
<tr>
<td><strong>All vascular events</strong></td>
<td>75.9</td>
<td>88.4</td>
<td>0.86 (0.79, 0.95)</td>
</tr>
</tbody>
</table>

* 3 years after randomization

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*HR (95% CI)*

- **Rivaroxaban** Better
- **Placebo** Better

---

* 3 years after randomization
• In VOYAGER PAD, among 6,564 randomized there were
  • 4714 total first and subsequent vascular events including
    • 1614 primary endpoint events and 3100 other vascular events

• Rivaroxaban reduced
  • total primary endpoint events (HR 0.86, 95% CI 0.75-0.98; p=0.02)
  • total vascular events (HR 0.86, 95% CI 0.79-0.95; p=0.003)

• An estimated 4.4 primary and 12.5 vascular events /100 participants were avoided with rivaroxaban over three years.
Conclusions

- PAD Patients undergoing LER are at high risk of adverse limb and cardiovascular events, with particularly high burden when considering total events inspite of standard available medical therapy.
- The risk profile in patients with symptomatic PAD is dominantly driven by adverse limb outcomes, particularly after LER, including acute limb ischemia, major vascular amputation and recurrent revascularization.
- Rivaroxaban 2.5 mg twice daily with aspirin versus aspirin alone reduces first and subsequent adverse limb and cardiovascular events with an even greater total benefit when considering all events.
- Rivaroxaban 2.5 mg twice daily with aspirin should be considered as adjunctive therapy after LER to reduce first and subsequent adverse outcomes.
Thank you very much for your attention!

Results accepted for Publication at JACC