Reduction in Venous Thromboembolism with Rivaroxaban versus Placebo in Peripheral Artery Disease after Lower Extremity Revascularization: Insights from VOYAGER PAD


Scientific Sessions of the American Heart Association 2020
November 13, 2020
Disclosures

- Research grants to CPC Clinical Research from Bayer, Janssen, Amgen, Merck, and Arca Biopharma
Peripheral Artery Disease (PAD) and Risk of Arterial Thrombosis

393,017 PAD patients treated with lower extremity revascularization

4 Year Events in REACH Registry
3 Year Events in TRA2P-TIMI 50

CV Events | Limb Events
---|---
MI | 5 | 6
Stroke | 6 | 3
Any Perip. Revasc | 6 |
Amputation | 22 |
Acute Limb Ischemia | 4 |

Cumulative Incidence

Major Amputation or Peripheral Revascularization
4x Risk of ALI
Long-term vs. No Revascularization

MI/stroke

Years from Index Revascularization

An affiliate of:
Kumbhani et al. EHJ 2014
Bonaca MP et al. Circulation 2013
Hess CN et al. JACC 2020
Bonaca MP et al. Circulation 2016
Risk for Venous Thromboembolism (VTE) in Atherosclerosis and Polyvascular Disease

47,611 patients followed for 3 years

An affiliate of:

Cavallari I et al. Circulation 2018
More Intense Antithrombotic Therapy Reduces VTE Risk in Stable Vascular Disease

More intensive antiplatelet therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPASS</td>
<td>0.61 (0.37-1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Rivaroxaban + ASA vs. ASA alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban alone vs. ASA alone</td>
<td>0.88 (0.56-1.38)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

- Risk of VTE and effect of vascular dose rivaroxaban in symptomatic PAD undergoing revascularization has not been described
- Whether effect of vascular dose rivaroxaban on VTE is modified by background dual antiplatelet therapy is unknown
**Trail 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
    - 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 Endpoint:** TIMI Major Bleeding

**Primary Endpoint**

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

- **Cumulative Incidence (KM%)**
  - Placebo: 19.9%
  - Rivaroxaban: 17.3%

- **HR 0.85**
  - 95% CI 0.76 – 0.96
  - P=0.0085

- **ARR**
  - 6 Months: ARR 1.5%, NNT 65
  - 1 Year: ARR 2.0%, NNT 50
  - 3 Year: ARR 2.6%, NNT 39

- **ARR, absolute risk reduction; NNT, number needed to treat**

Bonaca MP, et al. NEJM 2020
Objectives

In symptomatic PAD patients undergoing lower extremity revascularization (LER):

• To characterize the pattern of risk for VTE

• To evaluate the effect of rivaroxaban 2.5 mg twice daily plus low dose aspirin versus low dose aspirin alone on VTE as well as the spectrum of acute arterial and venous thrombotic events
Methods

• Prespecified secondary analysis of VOYAGER PAD
• Primary outcome symptomatic VTE
• VTE prospectively ascertained and a prespecified secondary endpoint
• Exploratory outcome composite of acute venous or arterial thrombotic events (VTE, acute limb ischemia, major amputation of vascular etiology, myocardial infarction, or ischemic stroke)
• Effect of rivaroxaban estimated with Cox proportional hazards model
## Baseline Characteristics

66 patients with VTE by efficacy cut-off date
Incidence of 0.42 per 100 patient-years

<table>
<thead>
<tr>
<th>Characteristic at Randomization</th>
<th>With VTE</th>
<th>Without VTE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=66 %</td>
<td>N=6498 %</td>
<td></td>
</tr>
<tr>
<td>Age, years median (IQR)</td>
<td>68 (64-75)</td>
<td>67 (61-73)</td>
<td>0.14</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>29</td>
<td>20</td>
<td>0.09</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>26</td>
<td>0.89</td>
</tr>
<tr>
<td>Caucasian</td>
<td>89</td>
<td>81</td>
<td>0.14</td>
</tr>
<tr>
<td>Weight ≤60 kg</td>
<td>8</td>
<td>17</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>91</td>
<td>81</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>39</td>
<td>40</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>55</td>
<td>60</td>
<td>0.37</td>
</tr>
<tr>
<td>Current smoking</td>
<td>29</td>
<td>35</td>
<td>0.41</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min/1.73m²</td>
<td>26</td>
<td>20</td>
<td>0.28</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>32</td>
<td>31</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Baseline clopidogrel use</td>
<td>52</td>
<td>60</td>
<td>0.24</td>
</tr>
<tr>
<td>Baseline statin use</td>
<td>77</td>
<td>80</td>
<td>0.54</td>
</tr>
</tbody>
</table>
## PAD & Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>With VTE N=66</th>
<th>Without VTE N=6498</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral Artery Disease History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior endovascular revascularization</td>
<td>38%</td>
<td>29%</td>
<td>0.13</td>
</tr>
<tr>
<td>Prior surgical revascularization</td>
<td>15%</td>
<td>10%</td>
<td>0.21</td>
</tr>
<tr>
<td>Prior amputation</td>
<td>11%</td>
<td>6%</td>
<td>0.11</td>
</tr>
<tr>
<td>ABI at screening, median (IQR)</td>
<td>0.5 (0.4-0.7)</td>
<td>0.6 (0.4-0.7)</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Indication for Revascularization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical limb ischemia</td>
<td>26%</td>
<td>23%</td>
<td>0.66</td>
</tr>
<tr>
<td>Claudication</td>
<td>74%</td>
<td>77%</td>
<td></td>
</tr>
<tr>
<td><strong>Qualifying Revascularization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>38%</td>
<td>33%</td>
<td>0.43</td>
</tr>
<tr>
<td>Endovascular or hybrid</td>
<td>62%</td>
<td>67%</td>
<td></td>
</tr>
</tbody>
</table>
Effect of Rivaroxaban 2.5 mg on VTE

Cumulative Incidence (%) vs. Months from Randomization

- Placebo
- Rivaroxaban

1.7% at 36 months
Effect of Rivaroxaban 2.5 mg on VTE

40% hospitalized and 21% died after VTE

Cumulative Incidence (%)

Placebo
Rivaroxaban

HR 0.61
95% CI 0.37 – 1.00
P=0.047*

*nominal p-value
Effect of Rivaroxaban 2.5 mg on VTE in Selected Subgroups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>HR (95% CI)</th>
<th>P-interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>0.8</td>
<td>1.3</td>
<td>0.61 (0.37, 1.00)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 years</td>
<td>0.7</td>
<td>1.1</td>
<td>0.63 (0.35, 1.13)</td>
<td>0.89</td>
</tr>
<tr>
<td>≥75 years</td>
<td>1.0</td>
<td>1.8</td>
<td>0.63 (0.25, 1.59)</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60 kg</td>
<td>0.2</td>
<td>0.7</td>
<td>0.26 (0.03, 2.33)</td>
<td>0.42</td>
</tr>
<tr>
<td>&gt;60 kg</td>
<td>0.9</td>
<td>1.4</td>
<td>0.64 (0.39, 1.08)</td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 ml/min/1.73m²</td>
<td>1.1</td>
<td>1.5</td>
<td>0.73 (0.28, 1.92)</td>
<td>0.65</td>
</tr>
<tr>
<td>≥60 ml/min/1.73m²</td>
<td>0.7</td>
<td>1.2</td>
<td>0.56 (0.31, 1.02)</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.0</td>
<td>1.1</td>
<td>0.88 (0.37, 2.08)</td>
<td>0.31</td>
</tr>
<tr>
<td>No</td>
<td>0.7</td>
<td>1.3</td>
<td>0.51 (0.27, 0.94)</td>
<td></td>
</tr>
<tr>
<td>Baseline clopidogrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.7</td>
<td>1.0</td>
<td>0.69 (0.32, 1.48)</td>
<td>0.67</td>
</tr>
<tr>
<td>No</td>
<td>0.9</td>
<td>1.6</td>
<td>0.55 (0.29, 1.07)</td>
<td></td>
</tr>
<tr>
<td>Baseline statin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.8</td>
<td>1.2</td>
<td>0.65 (0.37, 1.14)</td>
<td>0.62</td>
</tr>
<tr>
<td>No</td>
<td>0.7</td>
<td>1.6</td>
<td>0.47 (0.16, 1.38)</td>
<td></td>
</tr>
</tbody>
</table>
Effect of Rivaroxaban 2.5 mg on Acute Venous and Arterial Thrombotic Events

VTE, acute limb ischemia, major amputation of vascular etiology, myocardial infarction, or ischemic stroke

Cumulative Incidence (%)

- Placebo
- Rivaroxaban

16.2%
Effect of Rivaroxaban 2.5 mg on Acute Venous and Arterial Thrombotic Events

VTE, acute limb ischemia, major amputation of vascular etiology, myocardial infarction, or ischemic stroke

Cumulative Incidence (%)

Months from Randomization

Placebo
Rivaroxaban

HR 0.75
95% CI 0.65 – 0.86
P<0.0001

16.2%
12.2%
Effect of Rivaroxaban 2.5 mg on Acute Venous and Arterial Thrombotic Events

VTE, acute limb ischemia, major amputation of vascular etiology, myocardial infarction, or ischemic stroke

- Cumulative Incidence (%)
- Months from Randomization
- HR 0.75
- 95% CI 0.65 – 0.86
- P<0.0001

- ARR 4.0%
- NNT 25

- 3 Years

0 3 6 9 12 15 18 21 24 27 30 33 36

Cumulative Incidence (%)
Summary

• VTE risk is linear after revascularization for PAD and occurs at a rate ~2x that observed in stable vascular disease populations

• Risk of VTE is lower with Rivaroxaban 2.5 mg twice daily with aspirin compared to aspirin alone

• This benefit appears early, persists over time, and is consistent in major subgroups, including:
  – Age, body weight, renal dysfunction, polyvascular disease, statin use
  – Background clopidogrel/DAPT use

• Rivaroxaban 2.5 mg twice daily with aspirin compared to aspirin alone reduces risk of acute venous and arterial thrombotic events
Conclusions

• Atherosclerosis severity is a risk factor for VTE, and patients with symptomatic PAD undergoing revascularization are at high risk

• Outcomes after VTE are poor

• Rivaroxaban plus aspirin provides protection against the full spectrum of acute venous and arterial thrombotic events after LER regardless of background therapy and should be considered early to reduce this risk
Thank You