Efficacy and Safety of Rivaroxaban in Patients with PAD Undergoing Lower Extremity Revascularization for Critical Limb Ischemia


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Late Breaking Science
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Disclosures

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Critical Limb Ischemia (CLI) represents the most severe manifestation of late stage peripheral artery disease.

Traditionally defined by rest pain or tissue loss with evidence of ischemia, the most recent definition of *Chronic Limb Threatening Ischemia (CLTI)* and WIFI recognize its multifactorial nature including infection and wound characteristics.

Revascularization is recommended (Class I) to prevent/minimize tissue loss.

Outcomes after CLI are poor with high risk of ischemic complications, amputation and mortality.

**Optimal adjunctive medical therapy to improve outcomes in CLI/CLTI patients undergoing intervention has not been defined.**
Selected Cardiovascular Trials Enrolling Patients with PAD

Medical Therapy Trials including PAD patients generally:

- In stable/chronic setting
- Therefore, few patients with CLI
Selected Cardiovascular Trials Enrolling Patients with PAD

- **TRA2P-TIMI 50**
  - CLI: 165, 2%
  - No CLI: 7806, 98%
  - Bonaca et al. AHA 2018

- **EUCLID**
  - CLI: 643, 5%
  - No CLI: 13242, 95%
  - Norgren et al. EJVS 2017

- **FOURIER**
  - CLI: 126, 3%
  - No CLI: 3516, 97%
  - Bonaca et al. Circ 2018

- **COMPASS PAD**
  - CLI: 206, 5%
  - No CLI: 3923, 95%
  - Anand et al. Lancet 2017

**Medical Therapy Trials including PAD patients generally:**

- In stable/chronic setting
- Therefore, few patients with CLI

**Total = 1,140**
VOYAGER PAD 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

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

NCT02504216

*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
VOYAGER PAD Primary Results

**Primary Endpoint**

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

**TIMI Major Bleeding**

- **On Treatment - HR 1.43**
  - (0.97 – 2.10)
  - \( P = 0.0695 \)
  - **ARI 0.8\%, NNH 125**

*Composite of acute limb ischemia, major amputation of a vascular cause, myocardial infarction, ischemic stroke, cardiovascular death*
Trials with PAD Subgroups

**TRAP2P-TIMI 50**
- 165 patients (2%)
- 7806 patients (98%)
- Norgren et al. EJVS 2017

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- 643 patients (5%)
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**COMPASS PAD**
- 206 patients (5%)
- 3923 patients (95%)
- Anand et al. Lancet 2017

**VOYAGER PAD**
- 1533 patients (23%)
- 5031 patients (77%)
- Bonaca et al. NEJM 2020

**Total** = 1,140

VOYAGER PAD Patients with CLI at Baseline = 1,533
Objectives

• To evaluate the risk profile of patients undergoing lower extremity revascularization (LER) based on CLI vs no CLI at randomization

• To evaluate whether the efficacy and safety of rivaroxaban 2.5 mg twice daily with aspirin vs. aspirin alone is consistent in those with and without CLI at randomization:
  • **Primary efficacy endpoint and principal safety outcome**
  • **Key secondary outcome of unplanned index limb revascularization due to the high risk of recurrent procedures in this population**
  • **Prespecified net clinical outcome including the primary outcome, ICH, fatal bleeding and all cause mortality due to the high mortality rate in this population**
Objectives and Methods

**Methods**

- Patients assigned Rutherford (2-3 claudication, 4-6 CLI) classification *at the time of qualifying revascularization* by trained vascular investigators

- **Efficacy**:
  - Primary composite (ITT) of acute limb ischemia, major amputation of a vascular etiology, myocardial infarction, ischemic stroke or CV death
  - Secondary outcome for efficacy of unplanned index limb revascularization

- **Safety**
  - Principal safety outcome (on-treatment) of TIMI major bleeding
  - Secondary outcome for safety of ISTH major bleeding

- Prespecified net outcome (safety) including irreversible harm bleeding events (ICH or fatal bleeding) and all-cause mortality

- Outcomes adjudicated by a blinded CEC

- COX model used to test for effect modification on the basis of CLI
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics at Randomization</th>
<th>CLI N=1533</th>
<th>Claudication (no CLI) N=5031</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Yrs Median</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td>Female</td>
<td>29%</td>
<td>25%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>79%</td>
<td>81%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>47%</td>
<td>38%</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>30%</td>
<td>36%</td>
</tr>
<tr>
<td>COPD</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min/1.73m²</td>
<td>23%</td>
<td>19%</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>29%</td>
<td>32%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Known Carotid Stenosis</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Statin</td>
<td>81%</td>
<td>80%</td>
</tr>
<tr>
<td>ACEi or ARB</td>
<td>60%</td>
<td>64%</td>
</tr>
</tbody>
</table>

*CLI = Rutherford 4-6, No CLI = Rutherford 2-3/Claudication*
# PAD & Procedural Characteristics

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<thead>
<tr>
<th>Characteristics at Randomization</th>
<th>CLI N=1533</th>
<th>Claudication (no CLI) N=5031</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>Prior Peripheral Artery Disease History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of Claudication</td>
<td>82</td>
<td>99</td>
</tr>
<tr>
<td>History of Revascularization</td>
<td>27</td>
<td>38</td>
</tr>
<tr>
<td>History of Amputation</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Ankle Brachial Index, Median (IQR)</td>
<td>0.46 (0.32 – 0.60)</td>
<td>0.58 (0.45 – 0.69)</td>
</tr>
<tr>
<td><strong>Type of Revascularization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>44</td>
<td>30</td>
</tr>
<tr>
<td>Endovascular or Hybrid</td>
<td>56</td>
<td>70</td>
</tr>
<tr>
<td>Days from Procedure to Rando, Median (IQR)</td>
<td>6 (3 – 8)</td>
<td>4 (2 – 7)</td>
</tr>
<tr>
<td><strong>Target Lesion Length</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short (&lt; 5cm)</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>Intermediate (5cm to &lt; 15cm)</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>Long (≥ 15cm)</td>
<td>43</td>
<td>32</td>
</tr>
</tbody>
</table>

CLI = Rutherford 4-6, No CLI = Rutherford 2-3/Claudication
Primary Endpoint in Placebo Arm with and without CLI at Randomization

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

Cumulative Incidence (KM%)

Days from Randomization

Without CLI

N=5031

16.7%

4.9%
Primary Endpoint in Placebo Arm with and without CLI at Randomization

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

With CLI
N=1533
26.9%

+10.2%

Without CLI
N=5031
16.7%

10.7%

+5.8%

4.9%
Primary Endpoint

Acute limb ischemia, major amputation of a vascular etiology, myocardial infarction, ischemic stroke, CV death

With CLI
N=1533
HR 0.85
95% CI 0.69 – 1.05
3 Year ARR 4.5%
NNT 23

Without CLI
N=5031
HR 0.86
95% CI 0.74 – 0.99
3 Year ARR 2.2%
NNT 47

ARR – absolute risk reduction, NNT number needed to treat
Primary Endpoint Components in Patients with CLI

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Rivaroxaban</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Limb Ischemia</td>
<td>6.9%</td>
<td>9.3%</td>
<td>0.70</td>
<td>(0.48 – 1.03)</td>
</tr>
<tr>
<td>Major Amputation</td>
<td>7.6%</td>
<td>8.7%</td>
<td>0.90</td>
<td>(0.62 – 1.32)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>5.9%</td>
<td>7.4%</td>
<td>0.86</td>
<td>(0.56 – 1.31)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>3.2%</td>
<td>4.1%</td>
<td>0.83</td>
<td>(0.47 – 1.48)</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>8.6%</td>
<td>9.9%</td>
<td>0.93</td>
<td>(0.66 – 1.32)</td>
</tr>
</tbody>
</table>

ARR – absolute risk reduction, NNT number needed to treat
Safety of Rivaroxaban by CLI at Randomization

**With CLI**
- N=1533

**Without CLI**
- N=5031

### KM Rate at 3 Years (%)

#### Placebo
- With CLI: 4.0%
- Without CLI: 2%

#### Rivaroxaban
- With CLI: 1.7%
- Without CLI: 4%

#### P-interaction 0.84
- HR 1.37 (0.64 – 2.94) p=0.41
- HR 1.47 (0.94 – 2.30) P=0.091

#### P-interaction 0.82
- HR 1.08 (0.22 – 5.35) p=0.93
- HR 0.88 (0.43 – 1.80) P=0.73

#### P-interaction 0.86
- HR 1.38 (0.84 – 2.26) P=0.20
- HR 1.45 (1.07 – 1.96) P=0.015

#### With CLI
- TIMI major with CLI: 15
- TIMI major without CLI: 47
- ICH or Fatal with CLI: 0.6%
- ICH or Fatal without CLI: 0.5%
- ISTH major with CLI: 36
- ISTH major without CLI: 104
Primary Endpoint CLI Patients by Concomitant Clopidogrel Use

**Primary Endpoint**

- Placebo
  - With Clopidogrel: 17.8% (n=661)
  - Without Clopidogrel: 23.2% (n=870)
  - HR 0.71 (0.51 – 1.00) *P*-interaction 0.21

- Rivaroxaban
  - With Clopidogrel: 24.2% (n=661)
  - Without Clopidogrel: 24.7% (n=870)
  - HR 0.93 (0.71 – 1.22) *P*-interaction 0.53

**TIMI major bleeding**

- Placebo
  - With Clopidogrel: 2.8% (n=658)
  - Without Clopidogrel: 1.8% (n=861)
  - HR 1.65 (0.58 – 4.68) *P*-interaction 0.53

- Rivaroxaban
  - With Clopidogrel: 1.4% (n=658)
  - Without Clopidogrel: 1.4% (n=861)
  - HR 1.08 (0.35 – 3.36)
Primary Endpoint in CLI Patients by Concomitant Diabetes Mellitus

**Primary Endpoint**

- With Diabetes
  - Placebo: HR 0.80 (0.60 – 1.07)
  - Rivaroxaban: HR 0.89 (0.65 – 1.21)
  - n/N (%): 23.3%/716, 18.6%/817

- Without Diabetes
  - Placebo: HR 2.51 (0.77 – 8.26)
  - Rivaroxaban: HR 0.80 (0.28 – 2.31)
  - n/N (%): 2.5%/709, 1.2%/812

**TIMI major bleeding**

- Placebo: HR 0.80 (0.28 – 2.31)
- Rivaroxaban: HR 2.51 (0.77 – 8.26)

**P-interaction**

- 0.62
- 0.16
Primary Endpoint CLI Patients by *Prior Limb Revascularization*

**Primary Endpoint**

- HR 0.81 (0.56 – 1.17)
- HR 0.88 (0.68 – 1.13)

**TIMI major bleeding**

- HR 1.49 (0.53 – 4.15)
- HR 1.41 (0.44 – 4.45)

**With Prior Revascularization**
- Placebo: 25.1%
- Rivaroxaban: 19.4%

**First Revascularization**
- Placebo: 30.0%
- Rivaroxaban: 22.2%

**Placebo**
- N=415
- N=1117

**Rivaroxaban**
- N=416
- N=1106

P-interaction 0.73

P-interaction 0.90
Unplanned Index Limb Revascularization

With CLI

N=1533

HR 0.78
95% CI 0.62 – 0.99
P=0.0376

ARR – absolute risk reduction, NNT number needed to treat
Unplanned Index Limb Revascularization

**With CLI**
- N=1533
- HR 0.78
- 95% CI 0.62 – 0.99
- P=0.0376

30 Day ARR=1.02%

Days from Randomization

Cumulative Incidence (KM%)

ARR – absolute risk reduction, NNT number needed to treat
Net Clinical Benefit

Acute limb ischemia, major amputation of a vascular etiology, myocardial infarction, ischemic stroke, all cause mortality, ICH or fatal bleeding

**With CLI**
- N=1,521*
- HR 0.78
- 95% CI 0.61 – 1.00
- p=0.0457

**Without CLI**
- N=4,983*
- HR 0.74
- 95% CI 0.63 – 0.88
- p=0.0003

**P-interaction 0.77**
- 3 Year
- ARR 5.7%
  - 24.9%
  - 19.2%
- NNT 18

**3 Year**
- ARR 3.9%
  - 17.5%
  - 13.6%
- NNT 26

*Safety Population, On-Treatment Scope
Summary

• In VOYAGER PAD, patients with PAD presenting for LER for CLI were at very high risk of irreversible harm events of the heart, limb and brain with:
  • ~1 in 10 having a first event within 6 months of intervention
  • > 1 in 4 having a first event within 3 years of intervention

• Rivaroxaban 2.5 mg twice daily with aspirin versus aspirin alone significantly reduces this risk with benefits apparent early and continued over time and with consistency in those with and without CLI

• The benefits of rivaroxaban 2.5 mg twice daily with aspirin versus aspirin alone extend to reductions in the need for unplanned index limb revascularization with benefits apparent at 1 month after LER
Conclusions

• Patients with CLI (now CLTI), one of the most severe manifestations of PAD, represent an extreme risk population characterized by high rates of recurrent procedures and adverse events of the limb, heart and brain.

• Lower extremity revascularization is recommended in CLI to minimize/prevent tissue loss; however, the risk of complications appears particularly high in the post intervention setting.

• Despite this extreme risk profile, there are few adjunctive medical therapies that have demonstrated benefit in CLI patients overall and particularly after intervention.

• **Rivaroxaban 2.5 mg twice daily with aspirin should be considered as adjunctive therapy after LER for CLI to reduce adverse events of the heart, limb and brain as well as the need for repeat revascularizations.**