Rutherford Chronic Limb Ischemia Classification System Stratifies Risk in Patients Undergoing Lower Extremity Revascularization: Insights from VOYAGER PAD

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• Risk stratification for patients with PAD is important for both medical and surgical care

• Novel medical therapies such as aggressive lipid lowering therapy, antiplatelets, anti-thrombotics, are being used to mitigate progression of disease and adverse limb events (amputation, acute limb ischemia)
Rutherford Chronic Limb Ischemia Classification

- Designed in 1986 to grade severity of peripheral artery disease
- Widely accepted for risk stratification in trials and registries

<table>
<thead>
<tr>
<th>Rutherford Stage</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>1</td>
<td>Mild claudication</td>
</tr>
<tr>
<td>2</td>
<td>Moderate claudication</td>
</tr>
<tr>
<td>3</td>
<td>Severe claudication</td>
</tr>
<tr>
<td>4</td>
<td>Rest pain</td>
</tr>
<tr>
<td>5</td>
<td>Ischemic ulcers of digits</td>
</tr>
<tr>
<td>6</td>
<td>Severe ischemic ulcers or gangrene</td>
</tr>
</tbody>
</table>
Objective

• Primary Objective: examine the risk of amputation post lower extremity revascularization (LER) stratified by baseline Rutherford Chronic Limb Ischemia Stage

• Determine the risk of other limb events based on Rutherford Stage

• Examine utility of low dose rivaroxaban in each Rutherford Stage
Methods

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)
and Use of 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

*Ankle Brachial Index < 0.90 and Imaging Evidence of Occlusive Disease

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

• VOYAGER PAD patients were categorized by baseline Rutherford Chronic Limb Ischemia Stage
  • Rutherford 1 and 2 are combined due to trial protocol
• Amputation incidence (major, minor and major) at one year and three years were determined
• Incidence of the composite of Major amputation + Acute Limb Ischemia at each baseline Rutherford Stage were determined; comparisons between Rivaroxaban and placebo were made
Rutherford Chronic Limb Ischemia Stage Determined

Baseline Rutherford

Revascularization

Open/Endo

Randomization

Rivaroxaban  Placebo

Follow up

Median 28 months
Results - Amputation Events

Panel A: Major Amputation Rate Post LER at Year 1 and Year 3
(p < 0.0001)

Panel B: Major and Minor Amputation Rate Post LER at Year 1 and Year 3
(p < 0.0001)
Results - Composite of Major Amputation and ALI: Rivaroxaban vs. Placebo

3 Year Incidence of Amputation/ALI
Rivaroxaban vs. Placebo

HR [95% CI]

- Rutherford 5 and 6: 0.72 [0.46-1.11]
- Rutherford 4: 0.86 [0.57-1.29]
- Rutherford 3: 0.79 [0.61-1.01]
- Rutherford 1 and 2: 0.59 [0.38-0.91]
- Overall: 0.75 [0.63-0.89]

p_interaction = 0.46
Conclusion

- Baseline pre LER Rutherford Chronic Limb Ischemia Stage provides risk stratification for amputation events.
- There is a significant association between Rutherford Stage and outcomes, even after successful LER suggesting other drivers of limb events.
- These data are useful when risk stratifying patients or predicting limb event rates in PAD post LER clinical trials.
- Rutherford remains relevant in the modern era of PAD.