VOYAGER-PAD Angiographic Core Lab:  
*Design and Initial Results*

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Vascular Medicine and Intervention  
CPC Clinical Research  
University of Colorado
PAD affects 230 million people worldwide and 10% suffer adverse cardiovascular events

PAD patients are heterogeneous
PAD Patients with Prior Revascularization have High Major Adverse Limb Events

Of 1813 CLTI patients, 888 (49%) experienced primary events (death, MALE)

BEST-CLI

Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia

VOYAGER-PAD

Rivaroxaban in Peripheral Artery Disease after Revascularization

Of 6564 symptomatic PAD patients, 1092 (17%) experienced primary outcome (limb and CV events)

Farber . . . Rosenfield, et al. NEJM Nov 2022
PAD Patients with Prior Revascularization have High Major Adverse Limb Events

**BEST-CLI**

Sparse data exists regarding PAD anatomy and clinical outcomes

Of 1813 CLTI patients, 888 (49%) experienced primary events (death, MALE)

**VOYAGER-PAD**

Of 6564 symptomatic PAD patients, 1092 (17%) experienced primary outcome (limb and CV events)

Farber . . Rosenfield, et al. NEJM Nov 2022  
  
PAD Anatomic Classification Systems

**BOLLINGER**

Earliest, 1981
Case-based

Angiographic anatomy of 417 CLTI patients with diabetes was characterized

**GRAZIANI**

Angiogram reports of 908 patients were reviewed

Association with traditional CV outcomes

**ANATOMIC RUNOFF SCORE**

Calculation of Anatomic Runoff Score (ARS)

**TASC**

Expert consensus to guide revascularization strategies for all PAD

**GLASS**

Created by expert consensus and systematic literature review to predict endovascular outcomes based on anatomy
Current anatomic scores are based on expert opinion or are from datasets without associations with limb-specific outcomes.
SYNTAX Score in CAD

SYNTAX score correlates with anatomic complexity of CAD and is associated with adverse cardiovascular outcomes.

Figure 1. Long-term survival free from cardiac mortality (A) or major adverse cardiac events (B) according to SXscore tertiles.

Capodanno et al. JACC Int Vol 2, No 8 2009
VOYAGER-PAD 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
  - Stratified by Revascularization Approach (Surgical or Endovascular) and Use of Clopidogrel
  - 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 Outcome: TIMI Major Bleeding

Capell WH, Bonaca MP, Nehler MR...Hiatt WR. AHJ 2018
VOYAGER-PAD Trial Design

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- Principal Safety Outcome: TIMI Major Bleeding

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

Angiographic studies obtained for a core lab
VOYAGER-PAD Trial Design

Independent adjudication of limb-specific events available for analysis

Angiographic studies obtained for a core lab
VOYAGER-PAD Trial Design

Panel of experts in PAD convened to plan data collection and objectives of an angiographic core lab.

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

Capell WH, Bonaca MP, Nehler MR...Hiatt WR. AHJ 2018
Anatomic and Flow Characteristics Across 16 Anatomic Segments from 2646 Angiograms in Core Lab Database

1. Infra-renal abdominal aorta
2. Common iliac
3. External iliac
4. Common femoral
5. Profunda femoral
6. Superficial femoral
7. Popliteal 1
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9. Popliteal 3
10. Anterior tibial
11. Tibioperoneal trunk
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14. Lateral plantar
15. Dorsalis pedis
16. Pedal arch

Severity of stenosis
Length of Disease
Calcification
Prior stenting or bypass
Thrombus
Aneurysm
Revascularization

Adjudicated MACE and MALE outcomes and PROs (association with anatomy)

28-month median followup

Cross-sectional Analyses

PAD characteristics (Rutherford Category, ABI, CLTI) associations with anatomic features

Clinical characteristics (age, sex, diabetes, smoking, CKD) association with anatomic features
Eligible reviewer trained in Vascular Surgery, Interventional Radiology, or Interventional Cardiology with experience in angiographic peripheral vascular imaging

Reviewer undergoes standardization phase. >5 angiographic studies are reviewed. Results are compared among reviewers. Feedback provided to reviewers to promote inter-rater agreement.

Formal angiographic interpretations are performed
VOYAGER PAD
6564 randomized subjects

Angiographic substudy
1667 participants

Compare:
baseline characteristics & outcomes

Angiographic substudy
4897 non-participants

Concordance Analysis

2 independent reviewers
165 subjects (9.9%)

1 reviewer
1502 subjects (90.1%)

Subgroups of interest:
- Age
- Sex
- Diabetes
- Renal disease
- Rutherford category
- WIQ
- ABI
- Prior revascularization

Initial Analysis Scheme
Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Included in Angiographic Core Lab (N=1667)</th>
<th>Non-Angiographic Core Lab (N=4897)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics and General Descriptors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (SD), years</td>
<td>67.2 (8.4)</td>
<td>67.0 (8.5)</td>
<td>0.4527</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>463 (27.8%)</td>
<td>1241 (25.3%)</td>
<td>0.0504</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1448 (86.9%)</td>
<td>3855 (78.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Black or African American</td>
<td>66 (4.0%)</td>
<td>89 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>107 (6.4%)</td>
<td>859 (17.5%)</td>
<td></td>
</tr>
<tr>
<td>American Indian Alaska Native</td>
<td>3 (0.2%)</td>
<td>2 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>26.9</td>
<td>26.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>329 (19.7%)</td>
<td>365 (7.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Western Europe</td>
<td>618 (37.1%)</td>
<td>1208 (24.7%)</td>
<td></td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>519 (31.1%)</td>
<td>2080 (42.5%)</td>
<td></td>
</tr>
<tr>
<td>Asia Pacific</td>
<td>100 (6.0%)</td>
<td>861 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>South America</td>
<td>101 (6.1%)</td>
<td>383 (7.8%)</td>
<td></td>
</tr>
</tbody>
</table>
### Demographics and Baseline Characteristics

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<th>Non-Angiographic Core Lab (N=4897)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of qualifying revascularization procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endovascular</td>
<td>1273 (76.4%)</td>
<td>2818 (57.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hybrid</td>
<td>47 (2.8%)</td>
<td>241 (4.9%)</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>347 (20.8%)</td>
<td>1838 (37.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR group 2 (ml/min/1.73m²)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>10 (0.6%)</td>
<td>33 (0.7%)</td>
<td></td>
</tr>
<tr>
<td>≥30 to &lt; 60</td>
<td>369 (22.1%)</td>
<td>915 (18.7%)</td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>1183 (71.0%)</td>
<td>3809 (77.8%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, no. (%)</td>
<td>697 (41.8%)</td>
<td>1932 (39.5%)</td>
<td>0.1717</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>302 (18.1%)</td>
<td>1049 (21.4%)</td>
<td>0.0152</td>
</tr>
<tr>
<td>Former</td>
<td>752 (45.1%)</td>
<td>2179 (44.5%)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>613 (36.8%)</td>
<td>1666 (34.0%)</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel used at baseline, no. (%)</td>
<td>1150 (69.0%)</td>
<td>2769 (56.5%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Efficacy Outcomes: Core Lab versus Non-core lab

<table>
<thead>
<tr>
<th></th>
<th>Angio Core Lab</th>
<th>Non-core Lab</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite</strong></td>
<td>0.84 (0.67-1.06)</td>
<td>0.85 (0.74-0.98)</td>
<td>0.934</td>
</tr>
<tr>
<td><strong>MACE</strong></td>
<td>0.89 (0.67-1.18)</td>
<td>1 (0.83-1.19)</td>
<td>0.508</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>0.78 (0.52-1.17)</td>
<td>0.9 (0.67-1.21)</td>
<td>0.567</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>0.86 (0.47-1.58)</td>
<td>0.86 (0.59-1.25)</td>
<td>0.996</td>
</tr>
<tr>
<td><strong>CV death</strong></td>
<td>1.09 (0.72-1.65)</td>
<td>1.16 (0.92-1.47)</td>
<td>0.797</td>
</tr>
<tr>
<td><strong>MALE</strong></td>
<td>0.8 (0.56-1.14)</td>
<td>0.73 (0.59-0.89)</td>
<td>0.651</td>
</tr>
<tr>
<td><strong>ALI</strong></td>
<td>0.7 (0.46-1.05)</td>
<td>0.67 (0.53-0.85)</td>
<td>0.869</td>
</tr>
<tr>
<td><strong>Major Amputation</strong></td>
<td>1.03 (0.59-1.79)</td>
<td>0.87 (0.64-1.18)</td>
<td>0.588</td>
</tr>
</tbody>
</table>

Rivaroxaban better | Hazard Ratio | Placebo better
Safety Outcomes: Core Lab versus Non-core lab

TIMI Major Bleeding
- Angio Core Lab: 1.65 (0.81-3.36)
- Non-core Lab: 1.37 (0.86-2.19)

Fatal Bleed
- Angio Core Lab: 2.82 (0.29-27.07)
- Non-core Lab: 0.62 (0.15-2.60)

ICH
- Angio Core Lab: 0.79 (0.24-2.58)
- Non-core Lab: 0.76 (0.30-1.88)

ICH and Fatal Bleed
- Angio Core Lab: 1.1 (0.37-3.27)
- Non-core Lab: 0.8 (0.35-1.82)

P value for interaction:
- TIMI Major Bleeding: 0.671
- Fatal Bleed: 0.267
- ICH: 0.956
- ICH and Fatal Bleed: 0.642

Rivaroxaban better → Placebo better
VOYAGER PAD Angiographic Core Lab

Anatomic and Flow Characteristics Across 16 Anatomic Segments from 2646 Angiograms in Core Lab Database

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Severity of stenosis
Length of Disease
Calcification
Prior stenting or bypass
Thrombus
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Revascularization

Adjudicated MACE and MALE outcomes and PROs (association with anatomy)

28-month median followup

Cross-sectional Analyses

PAD characteristics (Rutherford Category, ABI, CLTI) associations with anatomic features

Clinical characteristics (age, sex, diabetes, smoking, CKD) association with anatomic features
Generation of Stenosis-Length Severity Score

<table>
<thead>
<tr>
<th>Stenosis severity of segment</th>
<th>Stenosis-severity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50%</td>
<td>0</td>
</tr>
<tr>
<td>50-69%</td>
<td>1</td>
</tr>
<tr>
<td>70-99%</td>
<td>2</td>
</tr>
<tr>
<td>100%</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Length severity of segment</th>
<th>Length-severity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1/3</td>
<td>1</td>
</tr>
<tr>
<td>1/3-2/3</td>
<td>2</td>
</tr>
<tr>
<td>&gt;2/3</td>
<td>3</td>
</tr>
</tbody>
</table>

For each segment:

\[
\text{Stenosis-severity score} \times \text{Length-severity score}
\]

For Index Limb:

Stenosis-Length score products per segment are summed

Stenosis-Length Severity Score
Concordance for Components of SLS Score

**Concordance for Stenosis Severity**

- Inflow: 82%
- SFA-popliteal: 78%
- Tibioperoneal: 72%
- Pedal: 80%

N=165

- <50%, 50-99%, vs. 100% stenosis severity per segment

**Concordance for Lesion Length**

- Inflow: 93%
- SFA-popliteal: 76%
- Tibioperoneal: 81%

N=165

- <1/3, 1/3-2/3, vs. >2/3 length of lesion per segment
Distribution of Stenosis-Length Severity Score Terciles

- **Low tercile**
  - $n=519$
  - (1-7 points)
  - Median Stenosis-Length Severity Score: 4

- **Mid tercile**
  - $n=512$
  - (7-16 points)
  - Median Stenosis-Length Severity Score: 10

- **High tercile**
  - $n=515$
  - (16-57 points)
  - Median Stenosis-Length Severity Score: 24
# Baseline Characteristics by Stenosis-Length Severity Score Terciles

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Tertile n=519</th>
<th>Mid Tertile n=496</th>
<th>High Tertile n=522</th>
<th>P value tertile 1 vs. 2</th>
<th>P value tertile 2 vs. 3</th>
<th>P value tertile 1 vs. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean, SD)</td>
<td>66.6 (8.3)</td>
<td>67 (8.3)</td>
<td>68 (8.5)</td>
<td>0.49</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex, female (n, %)</td>
<td>154 (29.7%)</td>
<td>148 (29.8%)</td>
<td>129 (24.7%)</td>
<td>0.95</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>Black (n, %)</td>
<td>17 (3.3%)</td>
<td>21 (4.2%)</td>
<td>24 (4.6%)</td>
<td>0.28</td>
<td>0.07</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI (mean, Kg/m2)</td>
<td>27.6</td>
<td>26.8</td>
<td>26.3</td>
<td>&lt;0.01</td>
<td>0.07</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CKD, yes (n, %)</td>
<td>62 (11.9%)</td>
<td>56 (11.3%)</td>
<td>60 (11.5%)</td>
<td>0.74</td>
<td>0.92</td>
<td>0.82</td>
</tr>
<tr>
<td>Diabetes, yes (n, %)</td>
<td>208 (40.1%)</td>
<td>197 (39.7%)</td>
<td>248 (47.5%)</td>
<td>0.91</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking, never (n, %)</td>
<td>67 (12.9%)</td>
<td>83 (16.7%)</td>
<td>115 (22.0%)</td>
<td>0.14</td>
<td>0.09</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Index leg ABI at screen (mean, SD)</td>
<td>0.6 (0.16)</td>
<td>0.6 (0.18)</td>
<td>0.5 (0.20)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Cubic Spline of Stenosis-Length Severity Score and MALE*

*MALE=ALI, vascular amputation
Survival Plot of MALE* by Stenosis-Length Severity Score Terciles

*MALE=ALI, vascular amputation
Survival Plot of MALE* by Stenosis-Length Severity Score Terciles

Claudication

Chronic Limb-Threatening Ischemia

*MALE=ALI, vascular amputation
ROC Analysis for SLS Severity Score, ABI, and Rutherford for MALE*

***MALE=ALI, vascular amputation***
Conclusions

PAD is prevalent and confers increased risk of limb events

Understanding how PAD anatomy contributes to risk may improve outcomes (as in CAD)

VOYAGER-PAD Angiographic Core lab offers an opportunity to better understand the relationships with anatomy, outcomes, and PAD subgroups

The stenosis-length severity score seems to add incremental predictive value for major adverse limb events to ABI and Rutherford category
Thank you!

Questions?
Concordance for Stenosis Severity

N=165

<50%, 50-99%, vs. 100% stenosis severity per segment

<table>
<thead>
<tr>
<th>Percent Concordance</th>
<th>Inflow</th>
<th>SFA-popliteal</th>
<th>Tibioperoneal</th>
<th>Pedal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordance for Stenosis Severity</td>
<td>82%</td>
<td>78%</td>
<td>72%</td>
<td>80%</td>
</tr>
</tbody>
</table>
Concordance for Lesion Length

N=165

<1/3, 1/3-2/3, vs. >2/3 length of lesion per segment

<table>
<thead>
<tr>
<th>Segment</th>
<th>Percent Concordance for Lesion Length</th>
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<tbody>
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<td>Inflow</td>
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<td>SFA-popliteal</td>
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