Outcomes in Peripheral Artery Disease

CPC Clinical Research
PAD Outcomes

• Outcomes can be grouped into

• Cardiovascular (Major Adverse Cardiovascular Events – MACE)
  – Myocardial infarction
  – Stroke
  – Death

• Limb (Major Adverse Limb Events – MALE)
  – Revascularization
  – Major amputation
  – Acute limb ischemia
Ankle Brachial Index

- Used to diagnose and Stratify PAD
- The highest systolic pressure at the ankle (posterior tibial and dorsalis pedis arteries)
- Brachial pressure (typically same on each side but if not the highest)
- Divide the Highest ankle pressure/highest brachial pressure
- Values below 0.9 diagnostic of PAD (above 1.2 indicate calcified arteries and could be PAD)

- Example – patient has:
  - Posterior tibial pressure of 70.
  - Dorsalis pedis pressure of 80
  - Brachial pressure of 120
- ABI equals 80/120 or 0.67
How to Perform and Calculate the ABI

PARTNERS Program ABI Interpretation

Above 0.90 — Normal
0.71-0.90 — Mild Obstruction
0.41-0.70 — Moderate Obstruction
0.00-0.40 — Severe Obstruction

Right ABI
\[
\frac{\text{Higher Right Ankle Pressure}}{\text{Higher Arm Pressure}} = \frac{\text{mm Hg}}{\text{mm Hg}} = \text{Higher Left Ankle Pressure} / \text{Higher Arm Pressure} = \frac{\text{mm Hg}}{\text{mm Hg}} = \_
\]

Example
\[
\frac{92}{164} \text{ mm Hg} = 0.56 \text{ See ABI Chart}
\]
PAD Outcomes

• PAD Mortality can be stratified by presenting PAD severity

• Severity is determined by the ankle brachial index (ABI)
  – Lower values more severe
  – Values beyond 1.2 also consider severe due to calcification

• This creates a mortality risk curve with elevations at both ends of the spectrum

Fowkes FG et al. JAMA 2008;300:197-208
Total Mortality Hazard Ratios

Figure 2. Hazard Ratios for Total Mortality in Men and Women by Ankle Brachial Index at Baseline for All Studies Combined in the ABI Collaboration

Hazard ratios are not adjusted for age or cardiovascular risk factors.

Fowkes FG et al. JAMA 2008;300:197-208
PAD Outcomes

- PAD Mortality can also be stratified by presenting PAD severity based on PAD history
- Stratified by least to greatest:
  - Asymptomatic
  - Claudication
  - Prior lower extremity revascularization
  - Prior lower extremity amputation
Almost one in ten individuals with PAD will die over 2 years of follow-up.

### Event Rate

- **Asymptomatic (ABI < 0.90)**
  - (n=670)
  - Event rate: 5.35*

- **Claudication**
  - (n=5,558)
  - Event rate: 7.98*

- **Prior lower extremity revascularization**
  - (n=4,252)
  - Event rate: 8.70

- **Prior lower extremity amputation**
  - (n=1,153)
  - Event rate: 14.88**

* P < 0.05
** P < 0.0001

---

Hirsch A et al, on behalf of the REACH Registry Investigators. Poster presented at ESC (Vienna, Austria), 2007
### Spectrum of Outcomes in PAD
Limb Ischemic Events Occur in a Spectrum Similar to Cardiac Ischemic Events

<table>
<thead>
<tr>
<th>CARDIAC</th>
<th>Stable Angina</th>
<th>Elective Coronary Revasc.</th>
<th>Severe Stable Angina</th>
<th>Unstable Angina</th>
<th>Urgent Coronary Revasc.</th>
<th>Myocardial Infarction</th>
<th>Cardiovascular Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIMB</td>
<td>Claudication</td>
<td>Elective Peripheral Revasc.</td>
<td>Chronic Limb Ischemia Rest Pain</td>
<td>Chronic Limb Ischemia Tissue loss</td>
<td>Urgent Peripheral Revasc.</td>
<td>Acute Limb Ischemia</td>
<td>Cardiovascular Death</td>
</tr>
</tbody>
</table>

### Definition
- **Subjective**
- **Objective**

### Reason for Intervention
- **Symptom Relief**
- **Prevent Irreversible Tissue Loss**

### Etiology
- **Multifactorial/Atherosclerotic**
- **Thrombosis** (artery, stent, graft)
PAD Outcomes

- Contributions of MACE and MALE outside of CV Death
- Examining events over time in:
  - PAD subgroup of large cardiovascular registry (Reduction in Atherosclerosis for Continued Health – REACH)
  - PAD subgroup of large cardiovascular clinical trial of antiplatelet therapy (Vorapaxar) TRA2³P-TIMI 50

Kumbhani et al. Eur Heart Journal 2014;35:2864-72
Burden of Risk in PAD is Driven by MALE more than MACE

Events in PAD Patients at 4 Years
REACH Registry

<table>
<thead>
<tr>
<th>Event</th>
<th>REACH Registry</th>
<th>TRA2P-TIMI 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Stroke</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Any Perip. Revasc</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Amputation</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

Events in PAD Patients at 3 Years
TRA2P-TIMI 50

<table>
<thead>
<tr>
<th>Event</th>
<th>TRA2P-TIMI 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>6</td>
</tr>
<tr>
<td>Stroke</td>
<td>3</td>
</tr>
<tr>
<td>Any Perip. Revasc</td>
<td>22</td>
</tr>
<tr>
<td>Acute Limb Ischemia</td>
<td>4</td>
</tr>
</tbody>
</table>

Kumbhani et al. Eur Heart Journal 2014;35:2864-72
PAD MALE Risk – Prior Revascularization

- Prior Revascularization increases MALE risk in PAD
- Two large cardiovascular Trials
  - COMPASS
    - Randomized trial of low dose Rivaroxaban and aspirin in cardiovascular population (with PAD subgroup)
  - EUCLID
    - Randomized trial of Ticagrelor vs clopidogrel in PAD population

Hiatt WR et al. NEJM 2017:376:32-40
Prior Limb Revascularization Associated with Greater Limb Risk – COMPASS Trial

- **3.80%** Incidence of MALE in Prior Revascularization or Amputation (N=2264, 36% of Population)
- **1.37%** Incidence of MALE in Claudication but no History of Revascularization or Amputation (N=2705, 42% of Population)
- **0.50%** Incidence of MALE in Asymptomatic low ABI (<=0.30) (N=1422, 22% of Population)

Prior Revascularization is also a major risk factor for ALI in EUCLID

<table>
<thead>
<tr>
<th>Table 3. Baseline Factors Associated With ALI Hospitalization Among the Overall Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age, per 10 y</td>
</tr>
<tr>
<td>BMI, per unit increase, kg/m²</td>
</tr>
<tr>
<td>Region (South America as the reference)</td>
</tr>
<tr>
<td>Asia</td>
</tr>
<tr>
<td>Europe</td>
</tr>
<tr>
<td>North America</td>
</tr>
<tr>
<td>Previous lower extremity revascularization</td>
</tr>
<tr>
<td>Previous atrial fibrillation</td>
</tr>
<tr>
<td>Baseline ABI</td>
</tr>
<tr>
<td>Per 0.1 ABI decrease in patients with baseline ABI ≤0.60</td>
</tr>
<tr>
<td>Per 0.1 ABI decrease in patients with baseline ABI &gt;0.60</td>
</tr>
<tr>
<td>Baseline statin use</td>
</tr>
<tr>
<td>Baseline angiotensin receptor blocker use</td>
</tr>
<tr>
<td>Randomized treatment: ticagrelor (clopidogrel as reference)</td>
</tr>
</tbody>
</table>

ABI indicates ankle-brachial index; BMI, body mass index; CI, confidence interval; and HR, hazard ratio.
PAD increases MACE in high-risk populations

- Pegasus – A large multicenter cardiovascular trial of ticagrelor and aspirin vs aspirin after myocardial infarction

- A population at higher risk for additional MACE

- Examining MACE in patients with and without baseline PAD is instructive

Bonaca MP et al.  NEJM 2015;372:791-800
Bonaca MP et al JACC 2016;67(23):2719-2728
PAD Increases Risk of MACE After MI

The risk of major cardiovascular (CV) events and major adverse limb events in patients with PAD and a prior MI in PEGASUS
PAD Increases Risk of MACE/MALE After MI

The risk of major cardiovascular (CV) events and major adverse limb events in patients with PAD and a prior MI in PEGASUS

<table>
<thead>
<tr>
<th>Event</th>
<th>no PAD N=6663</th>
<th>PAD N=404</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular Death</strong></td>
<td>3.32 (2.30–4.79, p&lt;0.001)</td>
<td>3.16 (2.35–4.27, p&lt;0.001)</td>
</tr>
<tr>
<td><strong>Myocardial Infarction</strong></td>
<td>1.93 (1.35–2.75, p&lt;0.001)</td>
<td>1.47 (0.53–4.07, p=0.46)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>2.80 (1.68–4.67, p&lt;0.001)</td>
<td>1.67 (0.72–3.85, p=0.23)</td>
</tr>
<tr>
<td><strong>Acute Limb Ischemia</strong></td>
<td>13.70 (3.67–50.90, p&lt;0.001)</td>
<td>3.16 (2.35–4.27, p&lt;0.001)</td>
</tr>
<tr>
<td><strong>Coronary Revascularization</strong></td>
<td>1.78 (1.31–2.43, p&lt;0.001)</td>
<td>1.78 (1.31–2.43, p&lt;0.001)</td>
</tr>
<tr>
<td><strong>Peripheral Revascularization</strong></td>
<td>19.04 (11.47–31.59, p&lt;0.001)</td>
<td>19.04 (11.47–31.59, p&lt;0.001)</td>
</tr>
<tr>
<td><strong>All-Cause Mortality</strong></td>
<td>3.16 (2.35–4.27, p&lt;0.001)</td>
<td>3.16 (2.35–4.27, p&lt;0.001)</td>
</tr>
</tbody>
</table>

**KM Rate at 3 Years (%)**

- **CVD**: 9.6% (3.0%), 9.5% (1.8%)
- **Myocardial Infarction**: 5.0%, 4.0%
- **Stroke**: 0.1%, 0.1%
- **Acute Limb Ischemia**: 12.5%, 7.0%
- **Coronary Revascularization**: 9.2%, 4.6%
- **Peripheral Revascularization**: 14.0%, 5.0%
- **TIMI Major Bleeding**: 1.0%, 1.6%
- **TIMI Major/Minor Bleeding**: 1.4%, 2.2%
- **ICH or Fatal Bleeding**: 0.6%, 1.3%

*Bonnaca, MP. JACC 2016; 67(23):2719-2728*
Polyvascular Disease increases MACE risk in PAD

- Polyvascular is symptomatic atherosclerotic disease in more than one vascular bed
- Coronary
- Peripheral
- Cerebral
A large proportion of atherothrombosis patients have polyvascular disease in REACH registry

Approximately 1/6 of the 55,499 patients with symptomatic atherothrombosis suffered the disease in multiple arterial territories.

Patients with CAD = 59.3% of the REACH Registry population

Patients with PAD = 12.2% of the total REACH Registry population

Patients with CVD = 27.8% of the REACH Registry population

Multiple risk factors only population

CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease.

Bhatt DL et al, on behalf of the REACH Registry Investigators. JAMA 2006;295:180-189.
Polyvascular Disease in PAD is Associated with Increased MACE Risk

EUCLID Trial
Adjusted HR 1.50
(1.13 – 1.99)

PEGASUS-TIMI 54 Trial
Adjusted HR 1.60
(1.20 – 2.13)

Bonaca MP Vasc Med 2018;23:531-33.
Outcomes in PAD Summary

- Increased Mortality
- Increased events
- MALE greater than MACE in overall PAD populations
- MALE further enhanced by
  - Lower ABI
  - Prior Revascularization
- MACE further enhanced by
  - Prior MACE
  - Polyvascular disease