State of the Art Therapy for Peripheral Artery Disease

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Disclosures

Consulting
Amgen
Antidote Therapeutics
Astra Zeneca
Boehringer Ingelheim
Merck
Novo Nordisk
Sanofi

DSMB
Bayer
Novartis
The Impact of Prior Lower Extremity Revascularization on MACE and Limb Outcomes in PAD

EUCLID randomized 13,885 patients with PAD to treatment with ticagrelor 90 mg BID or clopidogrel 75 mg QD with a median follow up of 30 months.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Adjusted Analyses</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Revascularization (n=7875)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABI ≤ 0.8 (n = 6010)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>894 (11.4%)</td>
<td>597 (9.9%)</td>
<td>1.10 (0.98, 1.23)</td>
</tr>
<tr>
<td>CV Death</td>
<td>372 (4.7%)</td>
<td>334 (5.6%)</td>
<td>0.97 (0.82, 1.14)</td>
</tr>
<tr>
<td>MI</td>
<td>466 (5.9%)</td>
<td>217 (3.6%)</td>
<td>1.29 (1.08, 1.55)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>176 (2.2%)</td>
<td>124 (2.1%)</td>
<td>0.93 (0.72, 1.20)</td>
</tr>
<tr>
<td>Acute Limb Ischemia</td>
<td>196 (2.5%)</td>
<td>36 (0.6%)</td>
<td>4.23 (2.86, 6.25)</td>
</tr>
</tbody>
</table>


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What Is Guideline-Based Care?

- 4 major medical therapy recommendations to reduce CV events:
  - Statins (Class I)
  - Smoking cessation (Class I)
  - Antiplatelet therapy (Class I)
  - ACE inhibitors (Class IIa)
  - Supervised exercise

- Performance measures include statins, smoking cessation, antiplatelet therapy, and supervised exercise.
### Heart Protection Study: Vascular Event by Prior Disease

**Incidence of events**

<table>
<thead>
<tr>
<th>Existing disease</th>
<th>Statin (n=10,269)</th>
<th>Control (n=10,267)</th>
<th>Risk vs Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI</td>
<td>23.5</td>
<td>29.4</td>
<td>Statin favored</td>
</tr>
<tr>
<td>Other CHD</td>
<td>18.9</td>
<td>24.2</td>
<td>Placebo</td>
</tr>
<tr>
<td>No prior CHD or CBV disease</td>
<td>18.7</td>
<td>23.6</td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>24.7</td>
<td>30.5</td>
<td>24% Reduction</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13.8</td>
<td>16.6</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>19.8</td>
<td>25.2</td>
<td></td>
</tr>
</tbody>
</table>


### Statins Improve Outcomes in CLI

380 CLI patients who underwent diagnostic angiography or therapeutic endovascular intervention from 2006 through 2012

Westin, G. JACC 2014;63(7):682
LDL Lowering With Evolocumab and Outcomes in Patients With PAD

3642 patients (13.2%) had PAD (1505) with no prior MI or stroke

MACE or MALE in Patients with and without PAD

Bonaca, M. Circulation. 2017;137:338–350
Smoking Cessation and Incident PAD

Bonaca and Creager Circ Res. 2015;116:1579-1598

Smoking cessation decreases mortality and improves amputation-free survival

739 patients with claudication or CLI. Assessed relationship between smoking cessation within 1 year and outcomes.

ACE inhibitors are a Class IIa recommendation among patients with PAD.

Event rate 17.8% vs. 13.8%
P<0.001


ACEI/ARB in Critical Limb Ischemia

464 patients with critical limb ischemia followed for 3 years. 269 (58%) prescribed ACEI or ARB.

Armstrong. Vasc Med. 2015;20:237-244
Guideline-Recommended Treatment and Outcomes

1357 patients undergoing endovascular intervention for stable claudication. 85% taking aspirin. 76% taking statin. 65% abstained from smoking.

**Supervised Exercise Therapy (Now Covered by CMS!)**

- **Frequency**
  - Three times per week, supervised
  - Build up walking time in a 50 minute period

- **Type of exercise**
  - Treadmill walking

- **Duration**
  - 12 to 24 weeks
Aspirin for the Prevention of Cardiovascular Events in Patients With PAD: A Meta-analysis of Randomized Trials

Berger, JS JAMA. 2009;301(18):1909-1919.

CAPRIE Subgroup: Benefit of Clopidogrel in PAD

3.7% vs. 4.9% per year (p=0.0026)
RRR = 23.8%
EUCLID Primary Efficacy Endpoint 
(CV Death, MI, or Ischemic Stroke)

Hiatt, WR. NEJM 2017; 376(1):32-40

CHARISMA PAD Subgroup

Post hoc analysis of the 3096 patients with symptomatic (2838) or asymptomatic (258) PAD from the CHARISMA trial.

Cacoub, P. Eur Heart J. 2009;30(2):192-201
The Addition of Vorapaxar to ASA and/or Clopidogrel in Symptomatic PAD

Risk Differences for 1000 Patients per 3 years - Vora vs. PBO

CVD/MI CVD MI Ischemic Stroke ALI Peripheral Revasc

-18 -10 -7 -8 -13 -13 -39

GUSTO Severe ICH Fatal Bleeds

Events/1000 Patient/3 Years

Bonaca et al. Circulation 2016

Vorapaxar and Limb Vascular Efficacy

Hospitalization for Acute Limb Ischemia Pre-specified, adjudicated

N = 3767

Hazard Ratio 0.58
95% CI 0.39 to 0.86
p = 0.006

Vorapaxar

Peripheral Revascularization Prespecified, Investigator

Placebo 22.2%
18.4%

Vorapaxar

Hazard Ratio 0.84:
95% CI 0.73 to 0.97
p = 0.017

Bonaca et al. Circulation 2012
Rivaroxaban With or Without ASA in Stable PAD: CV Death/MI/Stroke

7470 patients with PAD randomized to ASA 100 mg, Rivaroxaban 5 mg BID, or ASA 100 mg & Riva 2.5 mg BID.


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Rivaroxaban With or Without ASA in Stable PAD: CV Death/MI/Stroke/MALE

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**Rivaroxaban With or Without ASA in Stable PAD: MALE**


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**Rivaroxaban With or Without ASA in Stable PAD: MALE**

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**Table:**

<table>
<thead>
<tr>
<th>Rivaroxaban + aspirin group</th>
<th>Rivaroxaban alone group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose rivaroxaban + aspirin</td>
<td>Rivaroxaban alone group</td>
<td>Placebo group</td>
</tr>
<tr>
<td>Number at risk</td>
<td>Number at risk</td>
<td>Number at risk</td>
</tr>
<tr>
<td>Rivaroxaban + aspirin</td>
<td>2492</td>
<td>2099</td>
</tr>
<tr>
<td>Rivaroxaban alone</td>
<td>2474</td>
<td>2071</td>
</tr>
<tr>
<td>Placebo</td>
<td>2504</td>
<td>2072</td>
</tr>
</tbody>
</table>

**Graph:**

- Low-dose rivaroxaban + aspirin group
- Rivaroxaban alone group
- Aspirin alone group

**Legend:**

- Risk ratio (RR) 0.74 (0.5-1.0) p=0.043
- Risk ratio 0.67 (0.5-0.9) p=0.05

**Notes:**

### COMPASS: Limb outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>R + A</th>
<th>R</th>
<th>A</th>
<th>Riva + aspirin vs. aspirin</th>
<th>Riva vs. aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>MALE</td>
<td>30 (1.2)</td>
<td>35 (1.4)</td>
<td>56 (2.2)</td>
<td>0.54 (0.35-0.84)</td>
<td>0.63 (0.41-0.96)</td>
</tr>
<tr>
<td>Major amputation</td>
<td>5 (0.2)</td>
<td>8 (0.3)</td>
<td>17 (0.7)</td>
<td>0.30 (0.11-0.80)</td>
<td>0.46 (0.20-1.08)</td>
</tr>
</tbody>
</table>

*Anand, SS. Lancet 2017; in press*

### GLP-1 Agonism and Diabetic Foot Amputation

Randomly assigned 9340 patients with T2DM and high CV risk to receive liraglutide or placebo.

*Dhatariya, K. Diabetes Care 2018;41:2229–2235*
Amputation Outcomes By Location in the Integrated CANVAS Program

10,142 participants with T2DM and high CV risk randomly assigned to canagliflozin or placebo and were followed for a mean of 188.2 weeks.

<table>
<thead>
<tr>
<th>Location</th>
<th>Canagliflozin Event rate per 1000 patient-years</th>
<th>Placebo Event rate per 1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All amputation</td>
<td>6.30</td>
<td>3.37</td>
<td>1.97 (1.41–2.75)</td>
</tr>
<tr>
<td>Minor amputation</td>
<td>4.48</td>
<td>2.44</td>
<td>1.94 (1.31–2.84)</td>
</tr>
<tr>
<td>Toe</td>
<td>3.44</td>
<td>2.16</td>
<td>1.61 (1.11–2.32)</td>
</tr>
<tr>
<td>Transmetatarsal</td>
<td>1.03</td>
<td>0.29</td>
<td>5.87 (2.43–14.2)</td>
</tr>
<tr>
<td>Major amputation</td>
<td>1.62</td>
<td>0.93</td>
<td>1.80 (1.05–3.07)</td>
</tr>
<tr>
<td>Ankle</td>
<td>0.04</td>
<td>0.07</td>
<td>1.30 (0.45–3.78)</td>
</tr>
<tr>
<td>Below-knee</td>
<td>1.16</td>
<td>0.64</td>
<td>1.85 (1.11–3.07)</td>
</tr>
<tr>
<td>Above-knee</td>
<td>0.62</td>
<td>0.21</td>
<td>3.03 (1.32–6.96)</td>
</tr>
</tbody>
</table>

Amputation Outcomes By PAD History in the Integrated CANVAS Program

10,142 participants with T2DM and high CV risk randomly assigned to canagliflozin or placebo and were followed for a mean of 188.2 weeks.

<table>
<thead>
<tr>
<th>History of amputation</th>
<th>Canagliflozin Per 1000 patient-years</th>
<th>Placebo Per 1000 patient-years</th>
<th>Hazard ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>96.30</td>
<td>59.16</td>
<td>2.15 (1.11–4.19)</td>
</tr>
<tr>
<td>No</td>
<td>4.68</td>
<td>2.48</td>
<td>1.88 (1.27–2.78)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of peripheral vascular disease</th>
<th>Canagliflozin Per 1000 patient-years</th>
<th>Placebo Per 1000 patient-years</th>
<th>Hazard ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>12.09</td>
<td>8.16</td>
<td>1.39 (0.80–2.40)</td>
</tr>
<tr>
<td>No</td>
<td>5.20</td>
<td>2.41</td>
<td>2.34 (1.53–3.58)</td>
</tr>
</tbody>
</table>
The Impact of HIV on PAD and Survival

91,953 participants in the Veterans Aging Cohort Study from April 1, 2003 through December 31, 2014...
30-Day Readmissions After Endovascular or Surgical Therapy for CLI

Incidence, reasons, and costs of 30-day unplanned readmissions were determined 2013 to 2014 Nationwide Readmissions Databases for patients with CLI Admission

Incidence, reasons, and costs of 30-day unplanned readmissions were determined 2013 to 2014 Nationwide Readmissions Databases for patients with CLI Admission.
Summary

- The presence of PAD increases MACE risk in every situation.
- The risk of limb adverse events is markedly increased by the presence of a prior revascularization.
- There are three therapies that have evidence of modifying the limb risk.
- All interventionists should get comfortable with using low-dose rivaroxaban or vorapaxar and see what story VOYAGER tells.