Evolving Challenges in the Evaluation and Treatment of Lower Extremity PAD -- The Peripheral Academic Research Consortium (PARC)

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Disclosures

• Research Grants:
  – Agency for Healthcare Research and Quality
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  – Patient-Centered Outcomes Research Institute

• Honoraria:
  – Mondopoint
2 Major Issues in Peripheral Artery Disease

PAD Management

- Symptom improvement
- Cardiovascular risk reduction*

*In symptomatic patients only?
-- atypical or classic
Consequences of PAD

- Amputation/Tissue Loss
- Myocardial infarction (MI)
- Stroke
- Death

Functional capacity
Quality of Life
### Comparative Effectiveness Review of Antiplatelet Agents in Peripheral Artery Disease

**Figure 8.** Clopidogrel versus aspirin for all outcomes in PAD subgroup of CAPRIE RCT

<table>
<thead>
<tr>
<th>CAPRIE study outcome</th>
<th>Statistics for each study</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV mortality</td>
<td></td>
<td>0.76</td>
<td>0.64</td>
<td>0.91</td>
<td>0.00</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td></td>
<td>0.95</td>
<td>0.68</td>
<td>1.31</td>
<td>0.74</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td></td>
<td>0.62</td>
<td>0.43</td>
<td>0.88</td>
<td>0.01</td>
</tr>
<tr>
<td>Composite CV events</td>
<td></td>
<td>0.78</td>
<td>0.65</td>
<td>0.93</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hazard ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
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</tbody>
</table>

Abbreviations: CV-cardiovascular, MI-myocardial infarction.

### Supervised vs unsupervised exercise for intermittent claudication: A systematic review and meta-analysis

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### Comparative effectiveness of endovascular and surgical revascularization for patients with peripheral artery disease and critical limb ischemia: Systematic review of revascularization in critical limb ischemia

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(Am Heart J 2014; 167:489-498.e7.)
Lipid Lowering Therapy

Critical Limb Ischemia (CLI)

Fate of Patients with CLI after Initial Treatment

Summary of 6-month outcomes from 19 studies


- Dead: 20%
- Alive with amputation: 35%
- Alive without amputation: 45%
The lack of consistent definitions and nomenclature across clinical trials of novel devices, drugs, or biologics poses a significant barrier to accrual of knowledge in and across peripheral artery disease therapies and technologies. Recognizing this problem, the Peripheral Academic Research Consortium, together with the U.S. Food and Drug Administration and the Japanese Pharmaceuticals and Medical Devices Agency, has developed a series of pragmatic consensus definitions for patients being treated for peripheral artery disease affecting the lower extremities. These consensus definitions include the clinical presentation, anatomic depictions, intervention algorithms, surrogate imaging and physiological follow-up, and clinical outcomes of patients with lower-extremity peripheral artery disease. Consistent application of these definitions in clinical trials evaluating novel revascularization technologies should result in more efficient regulatory evaluation and best practice guidelines to inform clinical decisions in patients with lower-extremity peripheral artery disease. (J Am Coll Cardiol 2015;65:931–41) © 2015 by the American College of Cardiology Foundation.
Features

Symptom status

Lesion Stenosis

Lesion Length

Morphology – Calcification, aneurysm, ulceration

Pattern: Discrete / Contiguous / Diffuse

Reference Vessel / Diameter
Diagnostic Testing Options
Atypical Leg Pain

Intermittent Claudication

Critical Limb Ischemia • Ischemic Rest Pain • Tissue Ulceration • Gangrene

Asymptomatic

Medical Therapy & Exercise Training

Endovascular Revascularization

Surgery

Effect of antiplatelet and statin medication use

DECISION REGARDING REVASCULARIZATION

Mortality
MI/stroke
Amputation
Repeat revascularization
Repeat hospitalization
Costs

ANATOMY

90% stenosis
Stent

Factors associated with use

PAD

MEDICATIONS

LESS SEVERE

MORE SEVERE

Pre
Post

DEVICES
27% PTA, 23% Atherectomy, 50% stent
Current State of Antithrombotic and Antiplatelet Usage post-PVI in Medicare

- 85,830 patients
- 1/5th of all patients were not prescribed antithrombotic
- Pts with operators that were radiologists or surgeons had lower odds of P2Y12 use

EUCLID Study Design

Primary Endpoint: cardiovascular death, myocardial infarction, or ischemic stroke

Inclusion Criteria:
Symptomatic PAD AND one of the following:
A. ABI ≤0.80 at Visit 1 ≤0.85 at Visit 2
OR
B. Prior lower extremity revascularization >30 days

Key Exclusion Criteria:
- Poor metabolizer for CYP2C19
- Patients requiring dual anti-platelet therapy

Patients with Symptomatic PAD

Ticagrelor 90 mg bid
Double-blind Double-dummy
1:1
N=13,885

Clopidogrel 75 mg od

Follow-Up Visits 2, 6, 12 Months;
Every 6 months after 1st year
Telephone visits @ a 3 month interval between regular visits

Duration: approximately 18 month recruitment and 18 month follow up

Primary Endpoint: cardiovascular death, myocardial infarction, or ischemic stroke
Global Participation

13,855 patients
811 sites
28 countries

NORTH AMERICA:
3044 patients
US: 2614
Canada: 430

EUROPE:
7499 patients
Bulgaria: 679
Czech Rep: 723
France: 371
Germany: 623
Hungary: 580
Italy: 285
Netherlands: 234
Poland: 609
Romania: 508
Russian Fed: 935
Slovakia: 419
Spain: 323
Sweden: 240
Turkey: 137
Ukraine: 536
UK: 297

ASIA-PACIFIC:
1602 patients
China: 423
Japan: 420
Philippines: 128
S. Korea: 214
Thailand: 122
Vietnam: 295

LATIN AMERICA:
1740 patients
Argentina: 567
Brazil: 643
Chile: 161
Mexico: 369
Primary Efficacy Endpoint (CV Death, MI, or Ischemic Stroke)

Comparing Ticagrelor 90 mg bd (751/6930) vs. Clopidogrel 75 mg od (740/6955)

Ticagrelor vs. clopidogrel:
HR (95% CI): 1.02 (0.92, 1.13)
P value: 0.65

Months from randomization

Frequencies of events:

- Ticagrelor: 6930, 6792, 6679, 6583, 6474, 6360, 6248, 6143, 6036, 5802, 3830, 2089, 865
- Clopidogrel: 6955, 6830, 6744, 6639, 6538, 6455, 6353, 6237, 6111, 5835, 3834, 2055, 852
So What Is the Problem?

- Few ongoing clinical trials
- Current data sources are inadequate
- Heterogeneity complicates our understanding of PAD treatment
  - Anatomy and disease severity varies
  - Multiple specialties with different training, experience, bias
  - Multiple devices available for treating similar lesions:
- Lack of clinical outcomes in electronic health records
- Many single-center studies, very few large heterogeneous datasets
- Need data about real-world treatment from multiple sources
Registry Assessment of Peripheral Interventional Devices (RAPID)

• Phase 1
  – Standardize core data elements that could serve as a global case report form for both pre- and post-market assessment of peripheral interventional devices including clinical research, quality improvement, and device surveillance

• Phase 2
  – Implement the variables in the RAPID core data set in at least 2 major existing registries (SVS VQI and ACC NCDR) & extract core variables from 2-4 unique electronic sources (e.g., professional society registries & hospital EHR systems) to populate a patient-level database

• Phase 3
  – Use the RAPID core data set and structured data extraction to perform device evaluation projects (e.g., complete a prospective clinical trial of peripheral revascularization) from a common, patient-level multi-source database
**Computable Phenotype**
- History of PAD
- History of Endovascular Revascularization
- History of Surgical Revascularization

**via clinical information or administrative claims data**

**Data Extraction using**
Retrieve Form for Data Capture (RFD)

**Source Document Review and Data Abstraction by Clinical Experts**

**REDCAP Database**

**Medicare Outcomes Dataset**
All Patients with ICD-9 and/or ICD-10 codes for PAD in North Carolina

Outcomes of interest include: Death, Myocardial Infarction, Stroke, Lower Extremity Amputation

**ICD-10 Diagnosis Codes for PAD:**
- I70.2x Atherosclerosis of native arteries
- I70.3x - I70.7x Atherosclerosis of bypass graft(s)
- I73.9 PVD, unspecified

**ICD-9 Procedure Codes:**
- Angioplasty: 00.40-00.44, 39.50
- Atherectomy: 39.50
- Stenting: 00.45-00.48, 39.90

**CPT Codes:**
- Angioplasty: 35450, 35470, 35473, 35474
- Atherectomy: 35492, 35493, 35495
- Stenting: 37205-37208

**Combined Analytic File**

*** linkage of REDCAP and Medicare datasets**
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