Disclosures

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- Research Grants to Institution: AHRQ, American Heart Association, AstraZeneca, Bristol Myers Squibb, Boston Scientific Corporation
- Consultant/Honoraria: American College of Physicians, American College of Radiology
- Professional Society Roles: Member, American Heart Association Joint Vascular Imaging and Intervention Committee of the Council on Cardiovascular Radiology & Intervention (CVRI) and the Council on Peripheral Vascular Disease (PVD)

Manesh R. Patel, MD
- Research Grants to Institution: NHLBI, AHRQ, AstraZeneca, Maquet, Jansen, CSI
- Advisory Board: Jansen, Merck, Bayer
- Professional Society Roles: Chair ACC/AHA Appropriate Use Criteria Task Force, AHA Diagnostic and Interventional Cath Committee
Disclosures

Sreekanth Vemulapalli, MD

– Research Grants to Institution: AHRQ, Boston Scientific, American College of Cardiology; Duke O’Brien Center for Kidney Research supported by the National Institute of Diabetes, Digestive and Kidney Diseases of the National Institutes of Health under Award Number P30-DK096493

– Consultant/Honoraria: Premiere: significant

Other co-authors

No conflicts of interest to disclose

Note:

– Key Informants (TEP, Peer reviewers) must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained.

– The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.
Peripheral Artery Disease (PAD)

- Chronic narrowing or blockage of the arteries of the *lower* extremities.
Symptomatology of PAD

• Asymptomatic

• Intermittent claudication
  – Exercise-induced ischemic leg pain while walking and/or weakness, relieved by rest
  – Mortality rate from stroke and MI two to three times greater than in age-matched controls¹

• Critical limb ischemia
  – Pain at rest, eventually resulting in gangrene and amputation²

Clinical Classifications

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Fontaine Stage</th>
<th>Rutherford Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Stage I</td>
<td>Stage 0</td>
</tr>
<tr>
<td>Intermittent Claudication or Atypical Limb Symptoms</td>
<td>Stage IIa, Stage IIb</td>
<td>Stage 1, Stage 2, Stage 3</td>
</tr>
<tr>
<td>CLI</td>
<td>Stage III, Stage IV</td>
<td>Stage 4, Stage 5, Stage 6</td>
</tr>
</tbody>
</table>

Table II. Society for Vascular Surgery Lower Extremity Threatened Limb (SVS WiFi) classification system

1. Wound
2. Ischemia
3. Foot Infection
4. Wound/clinical category

SVS grades for rest pain and wounds/tissue loss (ulcers and gangrene):
0 (ischemic rest pain, ischemia grade 3; no ulcer) 1 (mild) 2 (moderate) 3 (severe)

(J Vasc Surg 2014;59:220-34.)
Focusing on Classic Symptoms Misses Majority of Patients

- ≥50% Atypical limb symptoms (functionally limited)
- ~33% Typical claudication
- ≤5%–10% Critical limb ischemia

Using Ankle Brachial Index (ABI)

- Mild to moderate PAD = ABI of 0.41 to 0.90
- Severe PAD = ABI ≤ 0.40
- Requires further testing = ABI ≥ 1.30

Fowkes FGR et al. Ankle Brachial Index Combined With Framingham Risk Score to Predict Cardiovascular Events and Mortality: A Meta-analysis
JAMA. 2008;300(2):197-208
Prevalence of PAD

Taken from: Hirsch A. Atlas of Heart Diseases: Vascular Disease. Edited by Eugene Braunwald (series editor), Mark A. Creager. ©2002 Current Medicine, Inc.
Risk Factors for PAD

- Male
- Age
- Diabetes
- Smoking
- Hypertension
- Renal Insufficiency
- High Cholesterol
Consequences of PAD

Amputation/Tissue Loss
Myocardial infarction (MI)
Stroke
Death

Functional capacity
Quality of Life
Goals of Therapies for PAD

All PAD patients
- Reduce cardiovascular morbidity & mortality

Patients with IC
- Improve functional status
- Reduce morbidity & mortality

Patients with CLI
- Prevent leg amputation
- Restore mobility
- Reduce mortality
Reducing Cardiovascular Morbidity & Mortality

- Prevention includes:
  - Antiplatelet agents
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Management of other risk factors:
    - Tobacco use
    - Diabetes
    - Dyslipidemia
    - Hypertension
Medical Therapy & Functional Capacity

Cilostazol

- Prevents blood clots (antiplatelet effect)
- Widens blood vessels (vasodilator effect)
- Side effects: headache and diarrhea
- Contraindicated in patients with congestive heart failure

Pentoxifylline

- Prevents blood clots (antiplatelet effect)
- Widens blood vessels (vasodilator effect)
- Side effects: nausea and diarrhea
Exercise Training & Functional Capacity

- Exercise therapy
  - Improved endothelial function
  - Reduced systemic inflammation
  - Improved mitochondrial function and skeletal muscle metabolism
Revascularization

- Goals of revascularization
  - Restore blood flow
  - Improve wound healing
  - Prevent amputation

- Revascularization depends on:
  - Patient-specific characteristics
  - Anatomic characteristics
  - Severity of symptoms
  - Need for possible repeat procedure
  - Patient and physician preference
Revascularization: Strategies

• Surgery
  – Lower extremity bypass (native vein conduit, PTFE graft), endarterectomy

• Angioplasty
  – Cryoplasty, drug-coated, cutting, and standard angioplasty balloons

• Stenting
  – Self-expanding and balloon-expandable; drug-eluting stents are now available

• Atherectomy
  – Laser, directional, orbital, and rotational atherectomy
Revascularization: Endpoints

• Cardiovascular:
  – Death (all-cause and cardiovascular), MI, stroke

• Quality of Life

• Limb-specific:
  – Functional capacity
  – Major amputation, amputation-free survival, wound healing, analog pain scale
  – Target limb revascularization, target lesion revascularization, acute limb ischemia

• Surrogate-other:
  – Primary and secondary patency
Treatment Strategies for Patients With Peripheral Artery Disease

Background
Peripheral artery disease (PAD) refers to chronic narrowing or occlusion of the lower extremities and represents a spectrum of disease severity from asymptomatic disease to intermittent claudication (IC), to critical limb ischemia (CLI). PAD has a similar atherosclerotic process to coronary artery disease and shares similar risk factors: male gender, age, diabetes, smoking, hyperlipidemia, high cholesterol, and renal insufficiency. PAD is known to be associated with a reduction in functional capacity and quality of life as well as an increased risk for myocardial infarction (MI), stroke, and death; it is also a major cause of limb amputation. Therefore, the general goals of treatment for PAD are cardiovascular protection, relief of symptoms, preservation of walking and functional status, and prevention of amputation. The optimal treatment for PAD—with specific emphasis on the comparative effectiveness of treatment options—is not known.

The backbone of treatment for PAD is smoking cessation, risk factor modification, dietary modifications, and increased physical activity. There are three main treatment options for improving functional status and other clinical outcomes in patients with PAD:

1. Medical therapy
2. Exercise training
3. Revascularization

The treatment options offered to PAD patients depend on whether the patient is asymptomatic or symptomatic (with either IC or CLI).
Analytical Framework

Adults with PAD

Asymptomatic (KQ 1)

Symptomatic PAD (atypical leg symptoms, intermittent claudication) (KQs 1, 2)

Critical limb ischemia (KQs 1, 3)

Interventions

- KQ 1a: Antiplatelets
- KQ 2a: Exercise training, medications, endovascular interventions, surgical revascularization
- KQ 3a: Endovascular interventions, surgical revascularization

Safety concerns

- Adverse drug reactions,
- Bleeding, contrast nephropathy, radiation,
- Infection, exercise-related harms, periprocedural complications

Outcomes

- Cardiovascular events:
  - All-cause mortality
  - Myocardial infarction
  - Stroke
  - Cardiovascular death
- Amputation
- Quality of life
- Wound healing
- Analog pain score
- Functional capacity
- Repeat revascularization
- Vessel patency

Individual characteristics

- Age
- Race/ethnicity
- Sex
- Body weight
- Risk factors (e.g. smoking)
- Comorbidities (e.g. diabetes, renal insufficiency)
- PAD classification
- Burden of disease
- Anatomic location of disease
- Sequence of therapies

KQs 1b, 2b, 3b

KQs 1c, 2c, 3c
Key Question 1

- In adults with peripheral artery disease (PAD), including asymptomatic patients and symptomatic patients with atypical leg symptoms, intermittent claudication (IC), or critical limb ischemia (CLI):
  a) What is the comparative effectiveness of aspirin and other antiplatelet agents in reducing the risk of adverse cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), functional capacity, and quality of life?
  b) Does the effectiveness of treatments vary according to the patient's PAD classification or by subgroup (age, sex, race, risk factors, or comorbidities)?
  c) What are the significant safety concerns associated with each treatment strategy (e.g., adverse drug reactions, bleeding)? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, or PAD classification)?
Key Question 2

In adults with symptomatic PAD (atypical leg symptoms or IC):

a) What is the comparative effectiveness of exercise training, medications (cilostazol, pentoxifylline), endovascular intervention (percutaneous transluminal angioplasty, atherectomy, or stents), and/or surgical revascularization (endarterectomy, bypass surgery) on outcomes including cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, quality of life, wound healing, analog pain scale score, functional capacity, repeat revascularization, and vessel patency?

b) Does the effectiveness of treatments vary by use of exercise and medical therapy prior to invasive management or by subgroup (age, sex, race, risk factors, comorbidities, or anatomic location of disease)?

c) What are the significant safety concerns associated with each treatment strategy (e.g., adverse drug reactions, bleeding, contrast nephropathy, radiation, infection, exercise-related harms, and periprocedural complications causing acute limb ischemia)? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, anatomic location of disease)?
Key Question 3

In adults with CLI due to PAD:

a) What is the comparative effectiveness of endovascular intervention (percutaneous transluminal angioplasty, atherectomy, or stents) and surgical revascularization (endarterectomy, bypass surgery) for outcomes including cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, quality of life, wound healing, analog pain scale score, functional capacity, repeat revascularization, and vessel patency?

b) Does the effectiveness of treatments vary by subgroup (age, sex, race, risk factors, comorbidities, or anatomic location of disease)?

c) What are the significant safety concerns associated with each treatment strategy (e.g., adverse drug reactions, bleeding, contrast nephropathy, radiation, infection, and periprocedural complications causing acute limb ischemia)? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, or anatomic location of disease)?
Strength of the Evidence

**High**
- Further research is very unlikely to change the confidence in the estimate of effect.

**Moderate**
- Further research may change the confidence in the estimate of effect and may change the estimate.

**Low**
- Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.

**Insufficient**
- Evidence either is unavailable or does not permit estimation of an effect.
Studies Addressing the Key Questions

Literature Search: January 1995 – August 2012
5,908 citations identified (1,035 duplicate articles)
4,873 abstracts reviewed

- Antiplatelet question in asymptomatic or symptomatic patients with PAD: 11
- Symptomatic patients with IC or atypical leg symptoms: 35
- Patients with CLI due to PAD: 37
Antiplatelet Therapy in Adults with PAD
1) Aspirin vs. placebo/no antiplatelet
2) Clopidogrel vs. aspirin
3) Clopidogrel + aspirin vs. aspirin
Aspirin vs. Placebo

No difference: all-cause mortality, nonfatal MI, composite vascular events
Strength of Evidence: High (asymptomatic), Low (intermittent claudication)

0 studies: functional outcomes, quality of life, safety concerns among subgroups
Strength of Evidence: Insufficient
Clopidogrel vs. Aspirin

N=6,452
Clopidogrel more effective for reducing nonfatal MI, cardiovascular mortality, and composite vascular events.
Strength of Evidence: Moderate
0 studies: all-cause mortality, functional outcomes, quality of life, modifiers of effectiveness, general safety or among subgroups
Strength of Evidence: Insufficient
Clopidogrel + Aspirin vs. Aspirin

4 total studies:
1. CHARISMA (N=3,096)—PAD subpopulation; 92% intermittent claudication
2. CASPAR (N=851)—IC/CLI mixed population undergoing bypass surgery
3. MIRROR (N=80)—IC population undergoing peripheral vascular intervention
4. Cassar et al (N=103)—safety evaluation; platelet inhibition study

1. No difference: all-cause mortality, composite cardiovascular events
   A. Strength of Evidence: Moderate
2. Dual therapy may reduce nonfatal MI
3. No difference: nonfatal stroke, cardiovascular mortality
   A. Strength of Evidence: Low
4. Minor bleeding significantly higher (34.4%) with dual therapy vs. aspirin (20.8%)
   A. Strength of Evidence: Insufficient
Exercise, Medications, and Endovascular and Surgical Revascularization for Claudication
Prior reports have investigated effectiveness and safety of endovascular and surgical revascularization technology.

Same treatment strategy comparisons were not included in the scope of Duke’s CER for KQ2 (claudication) or KQ3 (critical limb ischemia).
## Exercise, Medications, and Revascularization: Adults with IC

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Number of Studies</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cilostazol vs. placebo</td>
<td>10</td>
<td>4,103</td>
</tr>
<tr>
<td>Exercise training vs. usual care</td>
<td>12</td>
<td>754</td>
</tr>
<tr>
<td>Endovascular intervention vs. usual care</td>
<td>9</td>
<td>1,593</td>
</tr>
<tr>
<td>Surgical revascularization vs. usual care</td>
<td>1</td>
<td>427</td>
</tr>
<tr>
<td>Endovascular intervention vs. exercise training</td>
<td>9</td>
<td>1,005</td>
</tr>
<tr>
<td>Surgical revascularization vs. exercise + medical therapy</td>
<td>1</td>
<td>127</td>
</tr>
<tr>
<td>Endovascular vs. surgical revascularization</td>
<td>3</td>
<td>836</td>
</tr>
</tbody>
</table>
 Supervised Exercise Training and the combination of Endovascular Revascularization + Exercise Training resulted in Large improvements in Maximal Walking Distance (when compared with usual care). Strength of Evidence: Moderate

- Cilostazol and Endovascular Revascularization resulted in Moderate improvements in Maximal Walking Distance (when compared with usual care). Strength of Evidence: Low

- When network meta-analysis was performed, no individual treatment was found to have statistically significant effect when compared to the others.
Initial Claudication Distance or Pain-Free Walking Distance

- Exercise Training and Endovascular Revascularization were found to have **moderate to large** effects on ICD/PFWD. **Strength of Evidence: Low**
- Cilostazol was found to have **no** statistically significant effect on ICD/PFWD. **Strength of Evidence: Low**
- When network meta-analysis was performed, no individual treatment was found to have statistically significant effect when compared to the others.
Cilostazol, Exercise Training, Endovascular Revascularization, and Surgical Revascularization were all found to have moderate to large effects on QOL (when compared with usual care). Strength of Evidence: Low

When network meta-analysis was performed, no individual treatment was found to have statistically significant effect when compared to the others.
When compared to each other, no specific treatment was found to have a significant effect on mortality in patients with intermittent claudication.
• Inconclusive evidence: nonfatal MI, nonfatal stroke, amputation, modifiers of effectiveness, general safety

Strength of Evidence: Insufficient

• 0 studies: composite cardiovascular events, wound healing, pain, safety (subgroups)

Strength of Evidence: Insufficient
Supervised vs. Home Exercise

Peripheral Vascular Disease

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

Sreekanth Vemulapalli, MD, a Rowena J. Dolor, MD, MHS, b,c,d Vic Hasselblad, PhD, e Kristine Schmit, MD, MPH, f Adam Banks, MD, c Brooke Heidenfelder, PhD, d Manesh R. Patel, MD, a,b and W. Schuyler Jones, MD a,b Durham, NC

• 6,029 initial abstracts
• 4,994 abstracts screened
• 27 studies included in final report

* Not part of AHRQ original report
** No external funding
Panel A = 6 month outcome
Panel B = 12 month outcome

Maximal Walking Distance

Panel B = 12 month outcome

Initial Claudication Distance

SE is more effective at improving MWD and ICD than HE
**Quality of Life**

**General QOL (SF-36)**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Std diff in means</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patterson, 1997</td>
<td>-0.13</td>
<td>-0.66</td>
<td>0.40</td>
<td>0.63</td>
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<tr>
<td>Regensteiner, 1997</td>
<td>0.41</td>
<td>-0.47</td>
<td>1.30</td>
<td>0.36</td>
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<tr>
<td>Pinto, 1997</td>
<td>-0.16</td>
<td>-0.69</td>
<td>0.37</td>
<td>0.55</td>
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<tr>
<td>Savage, 2001</td>
<td>-0.22</td>
<td>-1.08</td>
<td>0.64</td>
<td>0.61</td>
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<tr>
<td>Gardner, 2011</td>
<td>0.06</td>
<td>-0.43</td>
<td>0.56</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>-0.04</td>
<td>-0.31</td>
<td>0.23</td>
<td>0.77</td>
</tr>
</tbody>
</table>

**Walking Impairment Questionnaire**

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<thead>
<tr>
<th>Study name</th>
<th>Std diff in means</th>
<th>Standard error</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regensteiner, 1997</td>
<td>0.34</td>
<td>0.45</td>
<td>-0.54</td>
<td>1.22</td>
<td>0.45</td>
</tr>
<tr>
<td>Gardner, 2011</td>
<td>0.11</td>
<td>0.25</td>
<td>-0.38</td>
<td>0.61</td>
<td>0.66</td>
</tr>
<tr>
<td>Gardner, 2012</td>
<td>0.21</td>
<td>0.19</td>
<td>-0.17</td>
<td>0.69</td>
<td>0.27</td>
</tr>
<tr>
<td>Guidon, 2013</td>
<td>0.55</td>
<td>0.38</td>
<td>-0.20</td>
<td>1.30</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>0.24</td>
<td>0.14</td>
<td>-0.63</td>
<td>0.50</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Panel A = 3 month outcome

Panel B = 6 month outcome

No difference in QOL between SE and HE
Endovascular and Surgical Revascularization in Adults with CLI due to PAD
Endovascular and Surgical Revascularization for CLI

Endovascular vs. Usual Care
- Population: CLI only or IC-CLI mixed
- 4 Studies

Endovascular vs. Surgical
- Population: CLI only
- 23 studies
- 12,779 patients
Endovascular vs. Surgical Revascularization: CLI

All-Cause Mortality at 2-3 years

<table>
<thead>
<tr>
<th>Group by Population</th>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
<th>Death / Total</th>
<th>Odds ratio and 95% CI</th>
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</thead>
<tbody>
<tr>
<td>CLJ - Obs</td>
<td>Wolfe, 2000</td>
<td></td>
<td>0.10</td>
<td>0.05</td>
<td>0.20</td>
<td>0.00</td>
<td>21 / 84</td>
<td>95 / 125</td>
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<tr>
<td>CLJ - Obs</td>
<td>Taylor, 2006</td>
<td></td>
<td>2.75</td>
<td>1.28</td>
<td>5.89</td>
<td>0.01</td>
<td>33 / 65</td>
<td>15 / 57</td>
</tr>
<tr>
<td>CLJ - Obs</td>
<td>Kudo, 2006</td>
<td></td>
<td>0.92</td>
<td>0.54</td>
<td>1.57</td>
<td>0.77</td>
<td>80 / 153</td>
<td>45 / 84</td>
</tr>
<tr>
<td>CLJ - Obs</td>
<td>Ah Chong, 2009</td>
<td></td>
<td>3.92</td>
<td>2.32</td>
<td>6.61</td>
<td>0.00</td>
<td>79 / 100</td>
<td>178 / 364</td>
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<tr>
<td>CLJ - Obs</td>
<td>Sultan, 2009</td>
<td></td>
<td>1.10</td>
<td>0.62</td>
<td>1.93</td>
<td>0.75</td>
<td>41 / 190</td>
<td>24 / 119</td>
</tr>
<tr>
<td>CLJ - Obs</td>
<td>Soderstrom, 2010</td>
<td></td>
<td>0.91</td>
<td>0.69</td>
<td>1.21</td>
<td>0.54</td>
<td>143 / 262</td>
<td>431 / 761</td>
</tr>
<tr>
<td>CLJ - Obs</td>
<td>Korthonen, 2011</td>
<td></td>
<td>1.37</td>
<td>0.96</td>
<td>1.97</td>
<td>0.08</td>
<td>122 / 241</td>
<td>103 / 241</td>
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<td>CLJ - Obs</td>
<td>Adam, 2005 (BASIL)</td>
<td></td>
<td>1.05</td>
<td>0.54</td>
<td>2.06</td>
<td>0.88</td>
<td>84 / 224</td>
<td>82 / 228</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.07</td>
<td>0.73</td>
<td>1.56</td>
<td>0.74</td>
<td></td>
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</table>

Amputation-Free Survival at 2-3 years

<table>
<thead>
<tr>
<th>Group by Population</th>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
<th>Amputation / Total</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLJ - Obs</td>
<td>Soderstrom, 2010</td>
<td></td>
<td>0.80</td>
<td>0.59</td>
<td>1.09</td>
<td>0.16</td>
<td>114 / 262</td>
<td>212 / 431</td>
</tr>
<tr>
<td>CLJ - Obs</td>
<td>Varela, 2011</td>
<td></td>
<td>1.34</td>
<td>0.58</td>
<td>3.11</td>
<td>0.50</td>
<td>26 / 42</td>
<td>27 / 49</td>
</tr>
<tr>
<td>CLJ - Obs</td>
<td>Korthonen, 2011</td>
<td></td>
<td>0.57</td>
<td>0.39</td>
<td>0.84</td>
<td>0.00</td>
<td>145 / 241</td>
<td>175 / 241</td>
</tr>
<tr>
<td>CLJ - Obs</td>
<td>Adam, 2005 (BASIL)</td>
<td></td>
<td>1.22</td>
<td>0.84</td>
<td>1.77</td>
<td>0.29</td>
<td>128 / 224</td>
<td>119 / 228</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.96</td>
<td>0.74</td>
<td>1.24</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Graphs showing odds ratio and 95% CI for both all-cause mortality and amputation-free survival.
Endovascular vs. Surgical Revascularization: CLI

- At 1 year, no difference in primary patency
  Strength of Evidence: Moderate
- Endovascular revasc may reduce all-cause mortality (≤ 6 mos), improve secondary patency at > 1 yr
- No difference: all-cause mortality (> 1 yr); amputation (all timepoints); amputation-free survival (>1 yr) Strength of Evidence: Low
- Inconclusive evidence: nonfatal MI, wound healing, primary patency (> 2 yrs), length of stay, modifiers of effectiveness
Published Data since AHRQ Review

- Updated literature search dates:
  - August 2012 – March 2015
- 1700+ citations included after literature search for abstract review
- 61 abstracts were included for full text review
- 25 individual, full-text articles were available for qualitative review
KQ1 – Antiplatelet question
Published Data since AHRQ Review

7 total studies
Only 4 are good quality studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Type of study</th>
<th>Comparison</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonaca et al, 2013</td>
<td>Claudication, abnormal ABI, or prior revascularization</td>
<td>RCT</td>
<td>Vorapaxar vs. placebo</td>
<td>3,787</td>
<td>No difference in CV death, MI, stroke Reduction in limb events</td>
</tr>
<tr>
<td>Platel et al, 2014</td>
<td>Subgroup analysis of PAD patients with ACS</td>
<td>RCT</td>
<td>Ticagrelor vs. clopidogrel in addition to aspirin</td>
<td>1,144</td>
<td>Consistent results in PAD subgroup when compared with overall trial</td>
</tr>
<tr>
<td>Shigematsu et al, 2012</td>
<td>History of claudication &amp; abnormal ABI, or prior revascularization</td>
<td>RCT</td>
<td>Clopidogrel vs. ticlopidine</td>
<td>431</td>
<td>Clopidogrel &gt;&gt; ticlopidine for cumulative incidence of safety endpoints</td>
</tr>
<tr>
<td>Strobl et al, 2013</td>
<td>Symptomatic patients undergoing PVI</td>
<td>RCT</td>
<td>ASA + Clopidogrel vs. ASA + Placebo</td>
<td>80</td>
<td>Improved TLR rates at 6 months; no improvement at 12 months</td>
</tr>
</tbody>
</table>
## Published Data since AHRQ Review

**KQ2 (intermittent claudication):** 13 studies; 1 good quality study

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Comparison</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy et al, 2014</td>
<td>Intermittent claudication in patients with aorto-iliac stenosis</td>
<td>Endovascular revascular vs. supervised exercise training vs. optimal medical therapy</td>
<td>79</td>
<td>PWT improved with ER and SET vs medical therapy QOL improved with ER and SET vs OMT</td>
</tr>
</tbody>
</table>

**KQ3 (critical limb ischemia):** 8 studies; 0 good quality studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Comparison</th>
<th>N</th>
<th>Results</th>
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<td>Critical Limb Ischemia</td>
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</table>

*3 included studies had mixed IC/CLI population

Limited impact of updated evidence for KQ2 and KQ3 results
Conclusions for KQ1

Aspirin vs. placebo

• No benefit for preventing vascular events in asymptomatic PAD (SOE: High)
• Aspirin favored for reducing nonfatal MI and combined vascular events in IC patients (SOE: Low)

Clopidogrel monotherapy vs. aspirin monotherapy

• Clopidogrel favored for reducing adverse cardiovascular outcomes in PAD subgroups (SOE: Moderate)

Dual antiplatelet therapy vs. aspirin monotherapy

• No difference in reducing stroke or cardiovascular mortality in PAD subgroup, IC or CLI patients (SOE: Moderate)
• Dual therapy favored for reducing nonfatal MI (SOE: Moderate)
Conclusions for KQ2 and KQ3

Exercise or Endovascular Revasc vs. usual care (intermittent claudication)

- Favors exercise training for improving walking distance (Large effect; SOE=Moderate)
- Favors endovascular revasc for improving walking distance (Moderate effect; SOE=Low)

Supervised exercise vs. Home exercise (intermittent claudication)

- Favors endovascular intervention for functional improvement but not quality of life (Moderate effect; SOE=High)

Endovascular + exercise vs. exercise or endovascular intervention alone (intermittent claudication)

- Endovascular intervention + exercise improved both maximal walking distance (Large effect; SOE=Moderate) and initial claudication distance (Moderate effect; SOE=Low)
Conclusions for KQ3

- Limited evidence for the effectiveness of surgical vs. endovascular revascularization
- No difference in all-cause death (> 1yr), amputation (all time points), and amputation-free survival (>1 yr); SOE: Low
Limitations of the Evidence-base

• Few published large-scale RCTs comparing antiplatelets in PAD
• Few direct comparisons of treatment strategies in patients with IC.
• Same-treatment strategy comparisons studied previously and excluded from Duke’s CER.
• No studies comparing a majority of treatment strategies in patients with atypical leg pain.
• Unable to stratify analysis by disease severity, risk, or symptoms.
Challenges in Evaluating the Existing Literature in PAD patients

- Population differences
- Endpoint differences
- Length of follow-up
- Evolution of revascularization
- Crossover between surgical and endovascular therapies
Recent Data

Temporal Trends and Geographic Variation of Lower-Extremity Amputation in Patients With Peripheral Artery Disease

Results From U.S. Medicare 2000–2008

W. Schuyler Jones, MD,† Manesh R. Patel, MD,† David Dai, PhTD, Sumeet Subherwal, MD, MBA,† Judith Stafford, MS, Sarah Calhoun, BS, Eric D. Peterson, MD, MPH†

Durham, North Carolina

Trends in Settings for Peripheral Vascular Intervention and the Effect of Changes in the Outpatient Prospective Payment System

W. Schuyler Jones, MD,† Xiaojuan Mi, PhD, Laura G. Qualls, MS, Sreekanth Vemulapalli, MD,† Eric D. Peterson, MD, MPH,† Manesh R. Patel, MD,† Lesley H. Curtis, PhD†
Evaluation and Treatment of Patients With Lower Extremity Peripheral Artery Disease

Consensus Definitions From Peripheral Academic Research Consortium (PARC)

Manesh R. Patel, MD,* Michael S. Conte, MD,† Donald E. Cutlip, MD,‡‡‡ Nabil Dib, MD,§ Patrick Geraghty, MD,¶ William Gray, MD,## William R. Hiatt, MD,††,‡ Mami Ho, MD, PhD,**, Koji Ikeda, PhD,†† Fumiaki Ikeno, MD,§§ Michael R. Jaff, DO,¶¶ W. Schuyler Jones, MD,* Masayuki Kawahara, MD,|| Robert A. Lookstein, MD,### Roxana Mehran, MD,#### Sanjay Misra, MD,**** Lars Norgren, MD,***** Jeffrey W. Olin, MD,#### Thomas J. Povsic, MD, PhD,* Kenneth Rosenfield, MD,#### John Rundback, MD,§§§ Fadi Shamoun, MD,|||| James Tcheng, MD,* Thomas T. Tsai, MD,¶¶¶ Yuka Suzuki, PhD,#### Pascal Vranckx, MD,**** Bret N. Wiechmann, MD,***** Christopher J. White, MD,****** Hiroyoshi Yokoi, MD,***** Mitchell W. Krucoff, MD*

Abstract

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 depiction, interventional outcomes, 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.
UPCOMING/ONGOING STUDIES

Clinical Trials in Peripheral Vascular Disease
Pipeline and Trial Designs: An Evaluation of the ClinicalTrials.gov Database

Sumeet Subherwal, MD, MBA; Manesh R. Patel, MD; Karen Chiswell, PhD; Beth A. Tidemann-Miller, MS; W. Schuyler Jones, MD; Michael S. Conte, MD; Christopher J. White, MD; Deepak L. Bhatt, MD, MPH; John R. Laird, MD; William R. Hiatt, MD; Asba Tasneem, PhD; Robert M. Califf, MD

Conclusions—PVD studies represent a small group of trials registered in ClinicalTrials.gov, despite the high prevalence of vascular disease in the general population. This low number, compounded by the decreasing number of PVD trials in the United States, is concerning and may limit the ability to inform current clinical practice of patients with PVD. (Circulation. 2014;130:00-00.)

**Updated Search Results:
Only 2 between-treatment comparison studies planning to enroll > 500 patients
EUCLID (Examining Use of Ticagrelor in PAD)

- Double-blind randomized controlled comparison of ticagrelor vs. clopidogrel in symptomatic PAD (ABI < 0.80 or prior revascularization)
- Primary endpoint: CV death, MI, ischemic stroke
- ClinicalTrials.gov Identifier: NCT01732822

BEST-CLI (Best Endovascular vs. Best Surgical Therapy in Patients With Critical Limb Ischemia)

- Open label, randomized controlled trial of endovascular and surgical revascular in patients with CLI
- Primary endpoint: Time to major adverse limb event or death
- ClinicalTrials.gov Identifier: NCT02060630