Treatment Strategies For Patients with Peripheral Artery Disease

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Duke University Medical Center & Duke Clinical Research Institute
AHRQ Comparative Effectiveness Review Process

- Topic Nomination
- Systematic Review
  - Public Comment
  - Expert Input
  - Peer Review
Treatment Strategies for Patients With Peripheral Artery Disease

Executive Summary

Background
Peripheral artery disease (PAD) refers to chronic narrowing or occlusion of the lower extremity vessels 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, hypertension, 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 modification, 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, and (3) revascularization. The treatment options offered to PAD patients depend on whether the patient is asymptomatic or symptomatic (with IC or CLI).
Learning Objectives

• Compare the effectiveness of exercise, medications, and revascularization.

• Discuss key evidence regarding the effectiveness of treatments within subgroups.

• Identify important safety concerns related to each treatment strategy.
What to Expect

- Definitions, diagnosis of, and prevalence of peripheral artery disease (PAD)
- Grading the strength of a body of evidence
- Clinical questions addressed
- What was found
- What was learned about treatment strategies for PAD
- How to use these findings
What is PAD?

How prevalent is PAD?

How is PAD diagnosed?

What are the consequences of PAD?
Peripheral Artery Disease (PAD)

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

- PAD
  - Asymptomatic
  - Symptomatic
    - Classic intermittent claudication (IC)
    - Atypical claudication
    - Critical limb ischemia (CLI)
Intermittent Claudication (IC)

- **IC**: Leg muscle discomfort provoked by exertion; relieved by rest.

- *Atypical claudication*: Lower extremity discomfort provoked by exertion; does not consistently resolve with rest (AKA *atypical leg discomfort*).
Prevalence of IC

~ 33% Classic claudication

> 50% Atypical claudication

5%-10% Critical limb ischemia
Critical Limb Ischemia (CLI)

- **CLI:**
  - Defined as:
    - Ischemic rest pain for > 14 days
    - Ulceration
    - Tissue loss or gangrene
  - Occurs in 5%-10% of patients with PAD
  - Initial presentation in ~1% to 2% of patients with PAD
  - 25% mortality at 1 year
Prevalence of PAD

![Graph showing the prevalence of PAD by age and gender.](image-url)

- **Men with PAD**
- **Women with PAD**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>55 – 59</td>
<td></td>
</tr>
<tr>
<td>60 – 64</td>
<td></td>
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<tr>
<td>65 – 69</td>
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<td>70 – 74</td>
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<td>75 – 79</td>
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<tr>
<td>80 – 84</td>
<td></td>
</tr>
<tr>
<td>≥ 85 yrs</td>
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</table>
Risk Factors for PAD

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

Myocardial infarction (MI)
Stroke
Death

Functional capacity
Quality of life
Diagnosing PAD

Using Ankle Brachial Index (ABI):

• Mild to moderate PAD: $\text{ABI} = 0.41-0.90$

• Severe PAD: $\text{ABI} \leq 0.40$

• Requires further testing: $\text{ABI} \geq 1.30$
Decrease in ABI

Risk of ischemic events
## Classifying Clinical Severity

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Fontaine Stage</th>
<th>Rutherford Stage</th>
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</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Stage I</td>
<td>Stage 0</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Stage IIa</td>
<td>Stage 1</td>
</tr>
<tr>
<td></td>
<td>Stage IIb</td>
<td>Stage 2</td>
</tr>
<tr>
<td>CLI</td>
<td>Stage III</td>
<td>Stage 4</td>
</tr>
<tr>
<td></td>
<td>Stage IV</td>
<td>Stage 5</td>
</tr>
<tr>
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<td>Stage 6</td>
</tr>
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</table>
Goals of Therapies for PAD

All PAD patients
Reduce cardiovascular morbidity & mortality

Patients with IC
- Improve functional status
- Improve quality of life
- Reduce morbidity & mortality

Patients with CLI
- Prevent leg amputation
- Restore mobility
- Improve quality of life
- Reduce mortality

Reduce morbidity & mortality
Improve functional status
Improve quality of life
Reduce morbidity & mortality
Reducing Cardiovascular Morbidity & Mortality

• Prevention includes:
  ► Antiplatelet agents
  ► Angiotensin-converting enzyme (ACE) inhibitors
  ► Management of other risk factors:
    o Tobacco use
    o Diabetes
    o Dyslipidemia
    o Hypertension
Cilostazol
• Increases blood flow to limb
• Prevents blood clots
• Widens blood vessels
• Side effects: headache and diarrhea
• Contraindicated in patients with congestive heart failure

Pentoxifylline
• Increases blood flow to limb
• Prevents blood clots
• Widens blood vessels
• Side effects: nausea and diarrhea
• Not as effective
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
- Angioplasty
  - Cryoplasty, drug-coated, cutting, and standard angioplasty balloons
- Stenting
  - Self-expanding, balloon-expandable, drug-eluting
- Atherectomy
  - Laser, directional, orbital, and rotational atherectomy
Interlude

SCOPE OF THE REVIEW
# Scope of the Review

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults (≥ 18 years) with lower extremity PAD</th>
</tr>
</thead>
</table>
| Interventions    | a) Antiplatelet agents  
                    | b) Exercise training  
                    | c) Endovascular intervention  
                    | d) Surgical revascularization |
| Comparators      | a) Medications  
                    | b) Exercise training  
                    | c) Endovascular intervention  
                    | d) Surgical revascularization  
                    | e) Usual care |
| Outcomes         | a) Functional capacity  
                    | b) Quality of life  
                    | c) Vessel patency  
                    | d) Amputation  
                    | e) Wound healing  
                    | f) Pain  
<pre><code>                | g) Cardiovascular events |
</code></pre>
<table>
<thead>
<tr>
<th>Strength of the Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change the confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research may change the confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Evidence either is unavailable or does not permit estimation of an effect.</td>
</tr>
</tbody>
</table>
**Key Questions**

**KQ 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? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, or PAD classification)?

**KQ 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? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, anatomic location of disease)?

**KQ 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, 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? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, or anatomic location of disease)?
Key Questions in Relation to Each Other

**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

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

**Individual characteristics**
- Age
- Race/ethnicity
- Sex
- Body weight
- Risk factors
- Comorbidities
- PAD classification
- Burden of disease
- Anatomic location of disease
- Sequence of therapies

**Safety concerns**
Adverse drug reactions, bleeding, contrast nephropathy, radiation, infection, exercise-related harms, periprocedural complications

**Asymptomatic (KQ 1)**

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

**Critical limb ischemia (KQs 1, 3)**

**KQs 1b, 2b, 3b**

**KQs 1c, 2c, 3c**

Adults with PAD
Studies Addressing the Key Questions

Asymptomatic or symptomatic PAD

11

Symptomatic PAD

35

CLI due to PAD

37
Antiplatelet Therapy in Adults with PAD
1) Aspirin vs. placebo or no antiplatelet

2) Clopidogrel + aspirin vs. aspirin; clopidogrel vs. aspirin

3) Aspirin or iloprost vs. no antiplatelet; high-dose aspirin vs. low-dose aspirin
Aspirin vs. placebo:

- No difference: all-cause mortality, nonfatal MI, composite vascular events
  
  *Strength of Evidence: High*

- No difference: cardiovascular mortality
  
  *Strength of Evidence: Moderate*

- 0 studies: functional outcomes, quality of life, safety concerns among subgroups

- Inconclusive evidence: subgroups, general safety
  
  *Strength of Evidence: Insufficient*
Aspirin: Adults with IC

- Aspirin vs. placebo:
  - Aspirin may reduce fatal and nonfatal MI and composite vascular events (MI, stroke, and pulmonary embolus)
  
    **Strength of Evidence: Low**

  - 0 studies: functional outcomes, quality of life, or safety concerns among subgroups

  - Inconclusive evidence: nonfatal stroke, cardiovascular mortality, subgroups, safety related to aspirin use

    **Strength of Evidence: Insufficient**
Aspirin: Adults with CLI

- Aspirin vs. placebo:
  - 0 studies: functional outcomes, quality of life, modifiers of effectiveness, safety among subgroups, general safety
  - Inconclusive evidence: nonfatal MI, nonfatal stroke, cardiovascular mortality

**Strength of Evidence: Insufficient**
Clopidogrel vs. Aspirin: Adults with IC

- Clopidogrel vs. aspirin:
  - Clopidogrel more effective for reducing nonfatal MI, cardiovascular mortality, and composite vascular events
    Strength of Evidence: Moderate
  - No difference: nonfatal stroke
    Strength of Evidence: Low
  - 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:
  ► No difference: all-cause mortality, composite cardiovascular events
    Strength of Evidence: Moderate
  ► Dual therapy may reduce nonfatal MI
  ► No difference: nonfatal stroke, cardiovascular mortality
    Strength of Evidence: Low
  ► 0 studies: functional outcomes, quality of life, safety among subgroups, or modifiers of effectiveness
  ► Inconclusive evidence: general safety
  ► Minor bleeding significantly higher (34.4%) with dual therapy vs. aspirin (20.8%)
    Strength of Evidence: Insufficient
Clopidogrel + Aspirin: Adults with IC or CLI

• Clopidogrel + Aspirin vs. aspirin:
  ► No difference: nonfatal stroke, composite cardiovascular events
    Strength of Evidence: Low
  ► Dual therapy may reduce nonfatal MI
  ► No difference: nonfatal stroke, cardiovascular mortality
    Strength of Evidence: Low
  ► 0 studies: functional outcomes, quality of life, safety among subgroups
  ► Inconclusive evidence: all-cause mortality, nonfatal MI, cardiovascular mortality, subgroups, and overall safety
    Strength of Evidence: Insufficient
Exercise, Medications, and Endovascular and Surgical Revascularization for Claudication
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Number of Studies</th>
<th>Number of patients</th>
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</thead>
<tbody>
<tr>
<td>Medical therapy vs. placebo</td>
<td>10</td>
<td>4,103</td>
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<tr>
<td>Exercise training vs. usual care</td>
<td>12</td>
<td>754</td>
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<tr>
<td>Endovascular intervention vs. usual care</td>
<td>9</td>
<td>1,593</td>
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<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>
Medical Therapy vs. Usual Care

- Cilostazol resulted in increased number of headaches
  Strength of Evidence: High
- Cilostazol resulted in increased rates of diarrhea and palpitations
  Strength of Evidence: Moderate
- Cilostazol may result in improved quality of life
  Strength of Evidence: Low
Medical Therapy vs. Usual Care

• No difference: all-cause mortality, maximal walking distance (MWD) or absolute claudication distance (ACD) (cilostazol), initial claudication distance (ICD) or pain-free walking distance (PFWD) (cilostazol)

  Strength of Evidence: Low

• Inconclusive evidence: nonfatal MI, nonfatal stroke, amputation, MWD or ACD (pentoxifylline), modifiers of effectiveness

• 0 studies: primary and secondary patency, composite cardiovascular events, wound healing, pain, safety (subgroups)

  Strength of Evidence: Insufficient
Exercise Training vs. Usual Care

- Exercise resulted in improved MWD or ACD
  Strength of Evidence: Moderate
- Exercise may result in improved quality of life and ICD or PFWD
- No difference: all-cause mortality
  Strength of Evidence: Low
Exercise Training vs. Usual Care

• Inconclusive evidence: nonfatal MI, nonfatal stroke, amputation, general safety concerns
• 0 studies: composite cardiovascular events, wound healing, pain, safety (subgroups)

Strength of Evidence: Insufficient
Endovascular Intervention vs. Usual Care

- Endovascular intervention may improve quality of life and ICD or PFWD
- No difference: all-cause mortality, MWD, or ACD

Strength of Evidence: Low
Endovascular Intervention vs. Usual Care

- Inconclusive evidence: nonfatal MI, nonfatal stroke, amputation, modifiers of effectiveness, general safety concerns
- 0 studies: composite cardiovascular events, wound healing, pain, safety (subgroups)

Strength of Evidence: Insufficient
Surgical Revascularization vs. Usual Care

• Surgical revascularization may improve quality of life

  Strength of Evidence: Low

• Inconclusive evidence: all-cause mortality, primary and secondary patency, modifiers of effectiveness

• 0 studies: nonfatal MI, nonfatal stroke, amputation, composite cardiovascular events, wound healing, pain, safety

  Strength of Evidence: Insufficient
Endovascular Intervention vs. Exercise Training

• No difference: MWD or ACD
  Strength of Evidence: Moderate

• No difference: all-cause mortality, quality of life, ICD or PFWD
  Strength of Evidence: Low

• Inconclusive evidence: nonfatal MI, stroke, amputation, modifiers of effectiveness, general safety

• 0 studies: composite cardiovascular events, wound healing, pain, safety (subgroups)
  Strength of Evidence: Insufficient
Surgical Intervention vs. Exercise + Pentoxifylline

- Inconclusive evidence: MWD, ACD, ICD, or PFWD
- 0 studies: composite cardiovascular events, wound healing, pain, safety (subgroups)

**Strength of Evidence: Insufficient**
Endovascular Intervention vs. Surgical Revascularization

• No difference: quality of life

**Strength of Evidence: Low**

• Inconclusive evidence: all-cause mortality and modifiers of effectiveness

• 0 studies: MWD or ACD, ICD or PFWD, nonfatal MI, nonfatal stroke, amputation, primary patency, secondary patency, composite cardiovascular events, wound healing, pain, safety

**Strength of Evidence: Insufficient**
• Endovascular intervention + exercise may improve MWD or ACD

Strength of Evidence: Low

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

Strength of Evidence: Insufficient
• Inconclusive evidence: primary or secondary patency
• 0 studies: composite cardiovascular events, wound healing, pain, safety

Strength of Evidence: Insufficient
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**
- Population: IC-CLI mixed
- 12 studies
- 565,168 patients
Endovascular Intervention vs. Usual Care

- Inconclusive evidence: all-cause mortality, amputation, amputation-free survival, length of stay
- 0 studies: nonfatal stroke, nonfatal MI, composite cardiovascular events, MWD or ACD, ICD or PFWD, quality of life, primary or secondary patency, wound healing, pain, modifiers of effectiveness, safety

Strength of Evidence: Insufficient
Patients with CLI:

- At 1 yr, no difference in primary patency
  Strength of Evidence: Moderate

- Endovascular interventions may reduce all-cause mortality (≤ 6 mos), improve secondary patency at 1 yr and 2-3 yrs

- No difference: all-cause mortality (1-2 yrs and ≥ 3 yrs); amputation (< 2 yrs, 2-3 yrs, > 5 yrs); amputation-free survival (1 yr, 2-3 yrs, > 5 yrs)
  Strength of Evidence: Low
Patients with CLI:

• Inconclusive evidence: nonfatal MI, wound healing, primary patency (2-3 yrs), length of stay, modifiers of effectiveness

• 0 studies: nonfatal stroke composite cardiovascular events, MWD or ACD, ICD or PFWD, quality of life, pain, safety

Strength of Evidence: Insufficient
IC-CLI Mixed Populations:

• Endovascular interventions may reduce all-cause mortality (≤ 6 mos, 1-2 yrs), improve primary patency (1 yr), and reduce infection

  Strength of Evidence: Low

• Inconclusive evidence: all-cause mortality (≥ 3 yrs), amputation (< 2 yrs, 2-3 yrs), primary and secondary patency (2-3 yrs), length of stay, modifiers of effectiveness, periprocedural complications

• 0 studies: nonfatal stroke composite cardiovascular events, MWD or ACD, ICD or PFWD, quality of life, pain, safety

  Strength of Evidence: Insufficient
Conclusions
What did we learn?
Conclusions

Aspirin vs. placebo

- No benefit for preventing vascular events in asymptomatic PAD
- Aspirin favored for reducing nonfatal MI and combined vascular events in IC patients

Clopidogrel monotherapy vs. aspirin monotherapy

- Clopidogrel favored for reducing adverse cardiovascular outcomes

Dual antiplatelet therapy vs. aspirin monotherapy

- No difference in reducing stroke or cardiovascular mortality in IC or CLI patients
- Dual therapy favored for reducing nonfatal MI
Conclusions

- Exercise vs. usual care or medical therapy
  - Favors exercise training for improving walking distance

- Endovascular vs. usual care
  - Favors endovascular intervention for functional improvement

- Endovascular + exercise vs. exercise or endovascular intervention alone
  - Endovascular intervention + exercise improved outcomes

- Bypass surgery vs. angioplasty
  - Limited evidence for the effectiveness of bypass surgery compared with angioplasty
Limitations of the Evidence Base

• No large-scale RCTs comparing antiplatelets in PAD.
• Few direct comparisons of treatment strategies in patients with IC.
• Same-treatment strategy comparisons studied previously.
• 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
What should I discuss with patients?
What to Discuss with Patients

- Concerns about the progression of PAD from asymptomatic to IC to CLI
- Factors contributing to PAD:
  - Male sex
  - Increased age
  - Diabetes
  - Smoking
  - Hypertension
  - High cholesterol
  - Renal insufficiency
What to Discuss with Patients

✓ Health consequences of PAD
  - Reduced functional capacity
  - Reduced quality of life
  - Increased risk for MI
  - Increased risk for stroke
  - Increased mortality
  - PAD as a major cause of limb amputation
What to Discuss with Patients

- Effectiveness of strategies to treat PAD
- Goals of treatment for IC and CLI
  - Cardiovascular protection
  - Relief of symptoms
  - Preservation of functional status
  - Prevention of amputation
Interlude

CONTINUING EDUCATION CREDIT
To obtain credit:

► Complete the online evaluation.
► Pass the posttest with a grade of 80% or higher.

If you have any problems receiving certification, please contact:

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