Strides in Peripheral Artery Disease

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Introduction

- Peripheral arterial disease (PAD) = atherosclerosis involving the aorta, iliac, and lower extremity arteries as well as their major branches.
- PAD affects ~8.5 million Americans >40yo (5.9% of patients >40yo)
  - Higher prevalence and severity in African Americans and Hispanics
- Associated with an increased risk of MI, stroke, cardiovascular (CV) death
  - 3-4x increase in CV events
  - At 5 years, ~20% of PAD patients will have a CV event
- Associated with a decreased quality of life (QoL) due to activity limitation and progression to critical limb ischemia (CLI)

- Outline:
  - Focus on lower extremity (LE) PAD and claudication
  - Discuss guideline directed medical therapy (GDMT)
  - Discuss endovascular therapy for lower extremity PAD

Olin et al, Management of patient with PAD. JACC 2016
2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines


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### Definition of PAD Key Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Claudication</td>
<td>Fatigue, discomfort, cramping, or pain of vascular origin in the muscles of the lower extremities that is consistently induced by exercise and consistently relieved by rest (within 10 min).</td>
</tr>
<tr>
<td>Acute limb ischemia (ALI)</td>
<td>Acute (&lt;2 wk), severe hypoperfusion of the limb characterized by these features: pain, pallor, pulselessness, poikilothermia (cold), paresthesias, and paralysis.</td>
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<tr>
<td></td>
<td>1. Viable—Limb is not immediately threatened; no sensory loss; no muscle weakness; audible arterial and venous Doppler.</td>
</tr>
<tr>
<td></td>
<td>2. Threatened—Mild-to-moderate sensory or motor loss; inaudible arterial Doppler; audible venous Doppler; may be further divided into IIa (marginally threatened) or IIb (immediately threatened).</td>
</tr>
<tr>
<td></td>
<td>3. Irreversible—Major tissue loss or permanent nerve damage inevitable; profound sensory loss, anesthetic; profound muscle weakness or paralysis (rigor); inaudible arterial and venous Doppler (33,34).</td>
</tr>
<tr>
<td>Tissue loss</td>
<td>Type of tissue loss:</td>
</tr>
<tr>
<td></td>
<td>1. Minor—nonhealing ulcer, focal gangrene with diffuse pedal ischemia.</td>
</tr>
<tr>
<td></td>
<td>2. Major—extending above transmetatarsal level; functional foot no longer salvageable (33).</td>
</tr>
<tr>
<td>Critical limb ischemia (CLI)</td>
<td>A condition characterized by chronic (&gt;=2 wk) ischemic rest pain, nonhealing wound/ulcers, or gangrene in 1 or both legs attributable to objectively proven arterial occlusive disease.</td>
</tr>
<tr>
<td></td>
<td>The diagnosis of CLI is a constellation of both symptoms and signs. Arterial disease can be proved objectively with ABI, TBI, TcPO₂, or skin perfusion pressure. Supplementary parameters, such as absolute ankle and toe pressures and pulse volume recordings, may also be used to assess for significant arterial occlusive disease. However, a very low ABI or TBI does not necessarily mean the patient has CLI. The term CLI implies chronicity and is to be distinguished from ALI (35).</td>
</tr>
</tbody>
</table>
**Functional classification for claudication**

**TABLE 2  Classifications of Severity of PAD**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fontaine</th>
<th>Clinical</th>
<th>Rutherford</th>
<th>Grade</th>
<th>Category</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic</td>
<td>0</td>
<td>0</td>
<td>Asymptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>Mild claudication</td>
<td>I</td>
<td>1</td>
<td>Mild claudication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>Moderate-severe claudication</td>
<td>I</td>
<td>2</td>
<td>Moderate claudication</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>I</td>
<td>3</td>
<td>Severe claudication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Ischemic rest pain</td>
<td>II</td>
<td>4</td>
<td>Ischemic rest pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Ulceration or gangrene</td>
<td>III</td>
<td>5</td>
<td>Minor tissue loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV</td>
<td>6</td>
<td>Ulceration or gangrene</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PAD = peripheral artery disease.*

Limiting claudication is defined by the patient.
Clinical presentation

- Classic claudication (10-30%)
- Atypical leg pain (20-40%)
- Asymptomatic (nearly 50%)

- Patient reported symptoms underestimate the prevalence of PAD

- Risk factors: **diabetes mellitus**, **smoking**, CKD, HTN, dyslipidemia, family history
Class I recommendations – H&P

• Patients at risk for PAD should undergo a detailed history for exertional leg symptoms, ischemic rest pain, non-healing wounds
  – Majority of PAD patients do not have classic claudication
• Vascular examination including palpation of pulses (femoral, popliteal, DP, and PT), auscultation for femoral bruits, and inspection of the legs and feet.
• Non-invasive BP measurement in both arms on initial assessment
  – >15mmHg difference suggestive of subclavian/innominate stenosis

Table 3. Patients at Increased Risk of PAD

- Age ≥65 y
- Age 50–64 y, with risk factors for atherosclerosis (e.g., diabetes mellitus, history of smoking, hyperlipidemia, hypertension) or family history of PAD (52)
- Age <50 y, with diabetes mellitus and 1 additional risk factor for atherosclerosis
- Individuals with known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or AAA)
Ankle-brachial index (ABI)

- **Class I** recommendation
  - H&P consistent with PAD
  - ABI should be reported as abnormal (<0.9), borderline (0.91-0.99), normal (1-1.4), or non-compressible (>1.4)
  - Check TBI (toe-brachial index) if ABI >1.4; useful in setting of CLI as well
  - Exertional leg symptoms and normal or borderline ABI $\rightarrow$ exercise ABI

- **Class IIa** (reasonable):
  - Increased risk of PAD with H&P suggestive of PAD
  - Exercise ABI to assess functional status

- ABI measurement - **ABI <0.9 is 90% sensitive and 95% specific for PAD**
  - Bilateral arms pressures (brachial) and DP/PT pressures using a Doppler
  - Ratio of the highest brachial and highest DP/PT pressure

- Segmental pressures often also done to delineate the level of disease
ABI
Choice of imaging modality influenced by a number of factors: cost, availability, renal function, etc.
Imaging for Anatomic Assessment

- **Class I:**
  - Symptomatic PAD and revascularization being considered → Duplex ultrasound, CTA, or MRA
  - Invasive angiography in patients with CLI whom revascularization is being considered

- **Class IIa:**
  - Invasive angiography in patients with lifestyle limiting claudication with inadequate response to GDMT and revascularization is being considered

- **Class III:** Asymptomatic PAD
Should I screen for atherosclerotic disease in other vascular beds?

- AAA (class IIa if symptomatic PAD)

- No evidence that screening for CAD, carotid disease, or renal artery stenosis reduces the risk of MI, stroke, or death. Thus, screening in the absence of symptoms is NOT recommended
  - Intensive medical therapy of CV risk factors is recommended to prevent adverse ischemic CV events from asymptomatic disease in other vascular beds
Medical therapy for PAD

- Anti-platelet agents
- Statins
- HTN therapy
- Smoking cessation
- Glycemic control
- Cilostazol
- Structured exercise therapy
Anti-platelet Rx and PAD

- **Class I:** *Symptomatic PAD*
  - Anti-platelet therapy (aspirin 75-325mg daily or clopidogrel 75mg daily) to reduce the risk of MI, CVA, or vascular death (22% risk reduction)
    - Only ~20% of patient in clinical practice receive clopidogrel rather than aspirin
    - CAPRIE trial PAD subgroup (clopidogrel versus ASA 325mg): 24% RRR, 1.2% ARR in the composite of stroke, MI, or vascular death.
    - EUCLID trial - no benefit of ticagrelor over clopidogrel

- **Class IIa:** Asymptomatic PAD (ABI <0.9)

- **Class IIb:**
  - Asymptomatic patients with borderline ABI (uncertain)
  - DAPT in Symptomatic PAD patients to reduce CV events is not well established (possible benefit in the PAD subgroup of the CHARISMA trial: decreased MI, ARR =1.4%)
  - DAPT may be reasonable to reduce limb-related events in patient after PAD revascularization
  - Overall clinical benefit of vorapaxar (PAR-1 antagonist) added to existing anti-platelet therapy in patients with symptomatic PAD is uncertain (increased moderate to severe bleeding risk; increased ICH in patients with a history of stroke)

CAPRIE Steering Committee. CAPRIE. *Lancet.* 1996
Cacoub et al. CHARISMA. *Eur Heart J* 2009
Bohula et al. TRA2P-TIMI50. *Circulation* 2015
Statins and PAD

• **Class I:**
  – Treatment with statins is indicated for all patients with PAD
  • Recommend at least a moderate dose statin
  • Heart Protection Study sub-group analysis (~6,700 patients with PAD): 22% relative reduction in the rate of the first major vascular event (coronary or non-coronary revascularization, stroke) with simvastatin 40mg daily
    • ARR = 5.4%
  • 18% reduction in limb events (worsening claudication, CLI, revascularization, or amputation) in a multi-national registry of ~6K patients

Kumbhani et al. REACH registry. *Eur Heart J.* 2014
Anti-hypertensives and PAD

- Class IIa:
  - ACE-I or ARB can be effective to reduce the risk of CV ischemic events in patients with PAD
- Subset of the HOPE (Heart Outcomes Prevention Evaluation) trial - ~4k patients with PAD; ramipril reduced the risk of MI, stroke, or vascular death by 25%

Ostergren et al. Eur Heart J. 2004
Smoking cessation

• **Class I** recommendation

• In PAD patients, a comprehensive smoking cessation program combining counseling and pharmacologic agents (nicotine replacement, varenicline, or bupropion) increased cessation rates to 21.3% versus 6.8% with standard advice

• Smoking cessation is of paramount importance in preventing CLI, amputation, and adverse CV events.

• **GHS resource:**
  – Center for Integrative Oncology and Survivorship (CIOS)
  – Quit Well program

Hennrikus et al. *JACC* 2010
Smoking cessation resource at GHS

- Center for Integrative Oncology and Survivorship (CIOS)
  - Referral can be made through Epic

- Billed to insurance including Medicare
- Personal visit with a NP and nurse navigator
- Does not ask the patient to quit immediately but they formulate a plan and evaluate readiness to quit.
- Up to 4 visits about 1x month
- Will prescribe Chantix and Wellbutrin. Also will manage nicotine replacement with teaching
Smoking and PAD

Mortality 14% vs 31%

Adherence to GDMT and Outcomes

Aspirin, statin, ACE-I, tobacco cessation

Armstrong et al. J Am Heart Assoc. 2014
GDMT and outcomes (cont.)

• National Health and Nutrition Examination Survey (NHANES)
  ➢ 647 patients in the survey had PAD (ABI <0.9)
  ➢ Only 30% were on statins, 25% on ACE-i, and 35% on aspirin

• PAD patients without known CAD (n =451)
  ➢ 65% lower all cause mortality in those receiving multiple preventative therapies

Other medical therapies

• **Class I** recommendation:
  – *Cilostazol* 100mg BID to increase walking distance in patient with claudication (~50% increase)
    • Common side effects: headache, diarrhea, dizziness, palpitations
    • Contraindicated in heart failure (PDE III inhibitor)
    • Reduce dose to 50mg BID if on diltiazem
    • May take up to 4 months to see maximum benefit
    • Low adherence (>60% discontinuation rate at 3 years)

• **Class III**: *Pentoxifylline*, chelation therapy, B-complex vitamins to reduce homocysteine levels

Rivaroxaban and PAD

- COMPASS Trial
  - Primary outcome: CV death, stroke, or non-fatal MI
  - Study terminated early by DSMB b/c of the benefit of low dose rivaroxaban+ASA over ASA alone (ARR 1.3%, RRR 24%); mean f/u 23 months
  - Increased bleeding with combined therapy vs. ASA alone (3.1% vs. 1.9%); mostly GI bleeds (no significant difference in fatal bleeding or ICH)
  - **PAD subset**: 7,470 patients (1/3 tob, 44% with DM), showed low-dose rivaroxaban plus aspirin reduced major adverse cardiovascular events and limb-threatening ischemia by 30%.
  - FDA approval pending
Exercise therapy - Mainstay of treatment for symptomatic PAD

- **Class I** recommendations:
  - In patient with claudication, *supervised* exercise is recommended to improve functional status and QoL and to reduce leg symptoms
  - *Supervised* exercise program should be discussed as a treatment option for claudication prior to revascularization

- **Class Ila:**
  - Structured community or home-based exercise program
Structured walking program versus aorto-iliac stenting

COT = claudication onset time
PWT = peak walking time

CLEVER Trial

Structured exercise program

**TABLE 8  Structured Exercise Programs for PAD: Definitions**

**Supervised exercise program (COR I, LOE A)**
- Program takes place in a hospital or outpatient facility.
- Program uses intermittent walking exercise as the treatment modality.
- Program can be standalone or within a cardiac rehabilitation program.
- Program is directly supervised by qualified healthcare provider(s).
- Training is performed for a minimum of 30–45 min/session; sessions are performed at least 3 times/wk for a minimum of 12 wk (36–46).
- Training involves intermittent bouts of walking to moderate-to-maximum claudication, alternating with periods of rest.
- Warm-up and cool-down periods precede and follow each session of walking.

**Structured community- or home-based exercise program (COR IIa, LOE A)**
- Program takes place in the personal setting of the patient rather than in a clinical setting (41,47–51).
- Program is self-directed with guidance of healthcare providers.
- Healthcare providers prescribe an exercise regimen similar to that of a supervised program.
- Patient counseling ensures understanding of how to begin and maintain the program and how to progress the difficulty of the walking (by increasing distance or speed).
- Program may incorporate behavioral change techniques, such as health coaching or use of activity monitors.

COR indicates Class of Recommendation; LOE, Level of Evidence; and PAD, peripheral artery disease.

**Benefit usually after 12 weeks of therapy**

**Improves:**
- Skeletal muscle metabolism
- Endothelial function
- Gait biomechanics
**Home exercise program**

**TABLE 1 A Practical Home Exercise Program for Patients With PAD**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>3-5 days per week</th>
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</thead>
<tbody>
<tr>
<td>Modality</td>
<td>Treadmill (this program can be adapted for walking outside)</td>
</tr>
</tbody>
</table>
| Method      | 1. Begin at 2 mph and a grade of 0 (flat)  
2. Try not to hold onto the treadmill. Use the side panels for balance only.  
3. Stop the treadmill completely when pain is 3-4 on claudication discomfort scale*  
4. When the discomfort has ceased, resume exercise at the same intensity  
5. Repeat rest/exercise cycles  
6. Progress to a higher workload when you can walk for 8 min without having to stop for leg symptoms  
a) Increase speed by 0.2 mph each time you can walk for 8 min  
b) Once you are able to walk at 3.4 mph, or reach a speed at which you can no longer keep up, begin increasing the grade by 1% |

**Duration**

The total exercise period, including rest periods, should equal 45 min per day

**Tips for success**

1. Do not continue walking past 3-4 on claudication pain/discomfort scale. This way the pain/discomfort should go away in 2-5 min. If you walk until you are in severe pain, you will build up lactic acid in your muscles, and it will take much longer for the pain to go away.

2. When at 3-4 on pain/discomfort scale, stop walking completely. Do not slow down, but stop and stand on the treadmill until the discomfort is gone.

This works if you do it! Not only will this improve your walking performance, decrease your discomfort, and improve your quality of life, this type of program is also beneficial for your heart, blood pressure, and lipid (cholesterol and triglyceride) levels.

*Claudication pain scale: 1 = no pain or discomfort; 2 = onset of claudication; 3 = mild pain or discomfort; 4 = moderate pain or discomfort; 5 = severe pain or discomfort. Adapted from Weinberg et al. (49).  
PAD = peripheral artery disease.

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**Adherence >80% in one small study**

Gardner et al. *Circulation* 2011
Issues with exercise therapy

- Long-term adherence
- Patient or physician preference for revascularization (more immediate results)
- Availability of supervised exercise programs (coming soon to GHS cardiac rehab / HeartLife...)
Cardiac rehab at GHS

HeartLife Program

• Symptomatic PAD (ABI, ultrasound, imaging)
• CMS will cover up to 36 sessions over 12 weeks:
  – Face to face visit with the physician treating the patient’s PAD to obtain the referral
  – Must also document counseling on CV and PAD risk factor modification at the office visit

Plan to start at the GHS Life Center in the next few months
Revascularization for claudication

- **Class IIa**
  - Reasonable treatment option for patients with life-style limiting claudication with an inadequate response to GDMT
  - Minority of patients (<10% over 5 years) will progress to CLI
  - Lifestyle limiting claudication is defined by the patient
TASC anatomic classification

**Type A Lesions**
- Unilateral or Bilateral Stenoses of CIA
- Unilateral or Bilateral Single Short (≤3 cm) Stenosis of EIA

**Type B Lesions**
- Short (≤3 cm) Stenosis of Infrarenal Aorta
- Unilateral CIA Occlusion
- Single or Multiple Stenosis Totaling 3-10 cm Involving the EIA Not Extending Into the CFA
- Unilateral EIA Occlusion Not Involving the Origins of Internal Iliac or CFA

**Type C Lesions**
- Bilateral CIA Occlusions
- Bilateral EIA Stenosis 3-10 cm
- Long Not Extending Into the CFA
- Unilateral EIA Stenosis Extending Into the CFA
- Unilateral EIA Occlusions That Involves the Origins of Internal Iliac and/or CFA
- Heavily Calcified Unilateral EIA Occlusion With or Without Involvement of Origins of Internal Iliac and/or CFA

**Type D Lesions**
- Infra-renal Aortoiliac Occlusion
- Diffuse Disease Involving the Aorta and Both Iliac Arteries Requiring Treatment
- Diffuse Multiple Stenoses Involving the Unilateral CIA, EIA, and CFA
- Unilateral Occlusions of both CFA and EIA
- Bilateral Occlusions of EIA
- Iliac Stenoses in Patients with AAA Requiring Treatment and Not Amenable to Endograft Placement or Other Lesions Requiring Open Aortic or Iliac Surgery

**Type A Lesions**
- Single Stenosis ≤10 cm in Length
- Single Occlusion ≤5 cm in Length

**Type B Lesions**
- Multiple Lesions (Stenoses or Occlusions), Each ≤5 cm
- Single Stenosis or Occlusions ≤15 cm Not Involving the Infrageniculate Popliteal Artery
- Single or Multiple Lesions in the Absence of continuous Tibial Vessels to Improve Inflow for a Distal Bypass
- Heavily Calcified Occlusion ≤5 cm in Length
- Single Popliteal Stenosis

**Type C Lesions**
- Multiple Stenoses or Occlusions Totaling >15 cm With or Without Heavy Calcification
- Recurrent Stenoses or Occlusions That Need Treatment After 2 Endovascular Interventions

**Type D Lesions**
- Chronic Total Occlusions of CFA or SFA (>20 cm, Involving the Popliteal Artery)
- Chronic Total Occlusion of Popliteal Artery and Proximal Trifurcation Vessels
Endovascular Revascularization for Claudication

- “Endovascular first” approach: high procedural success rates and low risk
  - Consider surgery for TASC D or CFA disease

- **Class I**
  - Endovascular procedures are effective as a revascularization option for patient with limiting claudication and significant *aortoiliac* disease
  - BRAVISSIMO trial: 87.9% primary potency at 2 years

- **Class IIa**
  - Endovascular procedures are effective as a revascularization option for patient with limiting claudication and significant *femoropopliteal* disease
    - Lower long-term patency than iliac interventions (60-75% due to recoil and neointimal hyperplasia)
    - Poor tibial run-off, DM, lesion characteristics, smoking and CKD/ESRD effect long-term patency

Aorto-iliac intervention
SFA - PTA vs stenting

Angioplasty for short lesions

- Mean lesion length 45mm
- ISR rates 39% vs 32% p=NS

Stent for intermediate lesions

- Mean 132mm
- Mean 71mm

Krakenberg et al. FAST trial. Circulation. 2007
Schillinger et al. NEJM 2006
Laird et al. RESILIENT Trial. Circ Cardiovasc Interv. 2010
SFA intervention
SFA intervention
ISR risk factors across all TASC classes:
1. DM
2. CTO
3. Lack of stent use
4. Poor below the knee runoff

Patency after femoral-popliteal stenting

Ilida et al. JACC Cardiovasc Interv. 2014
Drug-Coated balloon (DCB) for fem-pop disease - Paclitaxel

IN.PACT Admiral DCB (Medtronic)

Lutonix DCB (BARD)

Primary Patency Results through 2 Years

- 78.9% Patency for DCB
- 50.1% Patency for PTA

Log-rank $P < 0.001$

58% fewer re-interventions in the DCB group

Advantages of DCB:
- Improved patency
- Reduced need for stents (stent fracture risk)

Laird. IN.PACT SFA study - 2-year trial results. TCT 2015
Rosenfield et al. LEVIANT. NEJM. 2015
DES for femoral-popliteal disease

Zilver Paclitaxel DES 5 year f/u vs. angioplasty/BMS

DCB for restenosis
Endovascular Revascularization for Claudication

- **Class IIB**
  - Usefulness unknown for patients with claudication due to isolated *infraopliteal* disease (higher rates of restenosis)
    - Non-healing ulcers/CLI
    - DES > BMS/angioplasty (4 randomized trials demonstrated increased patency, less re-intervention, reduced amputations, and improved event free survival with DES over BMS/angioplasty/DCB)

- **Class III**: Intervention to solely to prevent progression to CLI (increased mortality with PAD from cardiac events not limb events)

Scheinert et al. ACHILLES. *JACC* 2012
Siablis et al. IDEAS. *JACC* 2014
Rastan et al. *JACC* 2012
Infrapopliteal DES

A. ITT – Population
   Primary Endpoint
   - In-Segment Restenosis (%)
   - SES: 22.4 (%), n = 15/67
   - PTA: 41.9 (%), n = 31/74
   - p = 0.019

B. "As Treated" – Population
   - In-Segment Restenosis (%)
   - SES: 21.3 (%), n = 16/75
   - PTA: 45.5 (%), n = 30/66
   - p = 0.004

C. Diabetic Patients
   - In-Segment Restenosis (%)
   - SES: 17.6 (%), n = 9/51
   - PTA: 53.2 (%), n = 25/47
   - p < 0.001

*Post hoc Analysis

Scheinert et al. ACHILLES. JACC 2012
Tibial intervention
Atherectomy

• Theoretical advantages of atherectomy
  – Remove or “debulk” plaque
  – Lower pressure angioplasty so less trauma/dissection
  – “Prepare” vessel for stenting to obtain symmetric and full expansion

Directional atherectomy

Orbital atherectomy

Dattilo et al. COMPLIANCE 360 trial. J Invasive Cardiol. 2014
Atherectomy
Percutaneous therapy

2016 ACC/AHA PAD GUIDELINES

Endovascular Interventions for CLAUDICATION

I A

IIa B-R

IIb C-LD

Deep femoral

Iliac

Superficial femoral

Popliteal

Anterior tibial

Posterior tibial

### Additive benefit of exercise and percutaneous revascularization

#### Table: Results of Functional Performance Measures

<table>
<thead>
<tr>
<th>Functional Performance Measures</th>
<th>Mean (99% CI)</th>
<th>Endovascular Revascularization Plus Supervised Exercise (n = 106)</th>
<th>Between-Group Difference (99% CI)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum walking distance, m</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>285 (244 to 326)</td>
<td>264 (228 to 300)</td>
<td></td>
<td></td>
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<tr>
<td>1 mo</td>
<td>438 (282 to 595)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1004 (835 to 1174)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>566 (358 to 774)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>851 (683 to 1018)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1260 (1076 to 1444)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>409 (183 to 636)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12 mo</td>
<td>955 (786 to 1124)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1237 (1058 to 1418)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>282 (60 to 505)</td>
<td>.001</td>
</tr>
<tr>
<td><strong>Pain-free walking distance, m</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>135 (113 to 157)</td>
<td>117 (96 to 138)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>181 (23 to 339)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>724 (561 to 886)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>543 (340 to 744)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>542 (378 to 707)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1071 (900 to 1243)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>529 (315 to 743)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12 mo</td>
<td>712 (549 to 876)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1120 (948 to 1293)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>408 (195 to 622)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Fakhry et al. ERASE trial. *JAMA* 2015
Critical Limb Ischemia

- High risk of amputation (25% at 1 year)
- 10% will experience a fatal CV event at 1 year
- Care focused on revascularization to aid in wound healing if possible (attempt to revascularize at least one artery to the foot), minimize tissue loss, and preserve the functional foot.

<table>
<thead>
<tr>
<th>Findings That Favor Consideration of Surgical Revascularization</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors associated with technical failure or poor durability with endovascular treatment</td>
<td>Lesion involving common femoral artery, including origin of deep femoral artery</td>
</tr>
<tr>
<td>Long segment lesion involving the below-knee popliteal and/or infrapopliteal arteries in a patient with suitable single-segment autogenous vein conduit</td>
<td></td>
</tr>
<tr>
<td>Diffuse multilevel disease that would require endovascular revascularization at multiple anatomic levels</td>
<td></td>
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<tr>
<td>Small-diameter target artery proximal to site of stenosis or densely calcified lesion at location of endovascular treatment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Findings That Favor Consideration of Endovascular Revascularization</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endovascular treatment likely to preclude or complicate subsequent achievement of in-line blood flow through surgical revascularization</td>
<td>Single-vessel runoff distal to ankle</td>
</tr>
<tr>
<td>The presence of patient comorbidities may place patients at increased risk of perioperative complications from surgical revascularization. In these patients, an endovascular-first approach should be used regardless of anatomy</td>
<td>Patient comorbidities, including coronary ischemia, cardiomyopathy, congestive heart failure, severe lung disease, and chronic kidney disease</td>
</tr>
<tr>
<td>Patients with rest pain and disease at multiple levels may undergo a staged approach as part of endovascular-first approach</td>
<td>In-flow disease can be addressed first, and out-flow disease can be addressed in a staged manner, when required, if clinical factors or patient safety prevent addressing all diseased segments at one setting</td>
</tr>
<tr>
<td>Patients without suitable autologous vein for bypass grafts</td>
<td>Some patients have had veins harvested for previous coronary artery bypass surgery and do not have adequate remaining veins for use as conduits. Similarly, patients may not have undergone prior saphenous vein harvest, but available vein is of inadequate diameter</td>
</tr>
</tbody>
</table>

CLI indicates critical limb ischemia.
Critical limb ischemia

FIGURE 2 Diagnostic Testing for Suspected CLI

Diagnostic Testing for Suspected CLI

History and physical examination suggestive of PAD with rest pain, nonhealing wound, or gangrene (Table 5)

Yes \(\rightarrow\) Search for alternative diagnosis (Tables 6 and 7)

No \(\rightarrow\) ABI (Class I)

- Noncompressible arteries ABI: \(>1.40\)
  - TBI (Class I)
    - Normal (>0.70)
    - Abnormal (≤0.70)
      - Perfusion assessment:
        - TBI with waveforms
        - TcPO₂
        - Skin perfusion pressure
        (Class IIa)
      - Search for alternative diagnosis (Table 7)
    - Normal \(\rightarrow\) Abnormal

- Normal ABI: 1.00–1.40
  - Borderline ABI: 0.91–0.99
    - Nonhealing wound or gangrene
      - Search for alternative diagnosis (Table 6)

- Abnormal ABI: ≤0.90
  - Additional perfusion assessment, particularly if ABI >0.70:
    - TBI with waveforms
    - TcPO₂
    - Skin perfusion pressure
      (Class IIa)
  - Abnormal \(\rightarrow\) Anatomic assessment:
    - Duplex ultrasound
    - CTA or MRA
    - Invasive angiography
      (Class I)
Acute limb ischemia

**FIGURE 3** Diagnosis and Management of ALI (33,34)

Diagnosis and Management of ALI

- Acutely cold, painful leg
- Suspected ALI
  - Clinical evaluation, including: symptoms, motor and sensory assessment, arterial and venous Doppler signals (Class I)

1. Audible arterial Audible venous
2. Inaudible arterial Audible venous
3. Inaudible arterial Inaudible venous

Revascularization (urgent) AND anticoagulation, unless contraindicated (Class I)

- **Category I:** Viable limb
  - Normal motor function
  - No sensory loss
  - Intact capillary refill
  - Revascularization (emergency) AND Anticoagulation, unless contraindicated (Class I)

- **Category III:** Irreversible
  - Complete loss of motor function
  - Complete sensory loss
  - Absent capillary refill
  - Primary amputation (Class I)

- **Category IIA:** Marginally threatened
  - Slow-to-intact capillary refill
  - Sensory loss limited to toes if present
  - No muscle weakness
  - Salvageable if treated promptly
  - Revascularization (emergency) AND Anticoagulation, unless contraindicated (Class I)

- **Category IIB:** Immediately threatened
  - Slow-to-absent capillary refill
  - Sensory loss more than toes and with rest pain
  - Mild or moderate muscle weakness
  - Salvageable if treated emergently
  - Revascularization (emergency) AND Anticoagulation, unless contraindicated (Class I)

Colors correspond to Class of Recommendation in Table 1.
ALI indicates acute limb ischemia.
Follow-up post revascularization

- Clinical follow-up (at least every 6 months)
- Limited data on routine ultrasound evaluation (class IIa)
  - One small study supports u/s at 1, 3, 6, and 12 months followed by yearly ultrasounds
  - Complexity of the intervention may influence this decision
- Yearly ABI measurements (change of 0.15 is significant)
### Treatment for PAD patients

**Central Illustration: The Peripheral Artery Disease Prescription**

<table>
<thead>
<tr>
<th>Decrease the Risk of MI, Stroke, and CV Death</th>
<th>Improve Symptoms, Quality of Life, and Prevent Amputation</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Discontinue Tobacco Use</td>
<td>- Discontinue Tobacco Use</td>
</tr>
<tr>
<td>- Walking Program</td>
<td>- Walking Program</td>
</tr>
<tr>
<td>- Control Blood Pressure to Goal - ACE Inhibitor</td>
<td>- Cilostazol</td>
</tr>
<tr>
<td>- High-Dose Statin Therapy</td>
<td>- Good Foot Care</td>
</tr>
<tr>
<td></td>
<td>- Moisturizing cream, nail care, treat and prevent tinea, orthotics to prevent abnormal pressure points</td>
</tr>
<tr>
<td>- Antiplatelet Therapy</td>
<td>- Revascularization</td>
</tr>
</tbody>
</table>


Management of patients with peripheral artery disease: recommendations for improving outcomes and quality of life. ACE = angiotensin-converting enzyme; CV = cardiovascular; MI = myocardial infarction.
Conclusions

• PAD is underdiagnosed and carries with it significant CV morbidity and mortality
• PAD therapy needs to address:
  1. Limb-related outcomes (claudication, prevention of CLI and amputation)
  2. Prevention of major CV events
• Optimal PAD treatment includes pharmacologic therapy, lifestyle modification, a structured exercise program, and revascularization.

![Graph showing hazard ratio, major adverse cardiovascular events, and maximum walking distance over time.](image-url)
MOC question

A 49 year old male complains of pain and cramping in his right calf for the past 6 months. It occurs after walking approximately 50 yards and is relieved by rest within a few minutes. PMH includes hypertension and tobacco abuse. BP in the office today is 155/90mmHg. He is not currently taking any medications. ABIs are ordered and are abnormal. ABI on the right is 0.8. The next best guideline directed step is:

a) Referral for peripheral angiography and possible intervention
b) Start the patient on aspirin 81mg daily, atorvastatin 40mg daily, lisinopril 5mg daily, discuss a structured exercise program, and counsel on smoking cessation
c) Start aspirin 81mg daily, rivaroxaban 2.5mg BID, and discuss a structured exercise program
d) Start cilostazol 100mg BID and order a duplex ultrasound
e) Order a CTA of the lower extremities and refer to a vascular specialist