Peripheral Vascular Disease: What the Internist Needs to Know?

Yerem Yeghiazarians, MD
UCSF Medical Center
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Some slides courtesy of Dr. Heather Gornik and Dr. Joseph Garasic
Objectives

- The scope of the problem and the link between peripheral arterial disease and cardiovascular risk
- Identification and diagnosis of patients with peripheral arterial disease
- Management of patients with PAD
Atherosclerosis is a Pan Vascular Process

- Coronary Artery Disease (CAD)
- Peripheral Arterial Disease (PAD)
- Cerebrovascular Disease (CVD)
- Renovascular Hypertension
- Mesenteric Ischemia
- Aortic aneurysm
- Vasculogenic Erectile Dysfunction
PAD Remains a Clinical Challenge

10 Million U.S. PAD Patients

2.5 Million Patients Diagnosed

Just 4% of all PAD patients are treated interventionally
Your Patient Has Never Heard of PAD? (S)He is not alone!

Not Aware of PAD (74%)

PAD Aware (26%)

N=2501 people surveyed

“PAD Aware” defined by “somewhat” or “very familiar” responses

How do we diagnosis PAD?

History
Physical Exam
Diagnostic Testing
Peripheral Artery Disease

Varied spectrum of clinical presentation
- Asymptomatic PAD - abnormal ABI test
- Symptomatic PAD - leg pain
- Critical Limb Ischemia
- Acute Limb Ischemia
Leg Symptoms Among Patients with PAD in Ambulatory Care Setting

- 55% Classic Claudication
- 34% Atypical Leg Pain
- 11% No Pain

N=1857 Patients with ABI ≤ 0.9

Critical Limb Ischemia = Vascular Urgency

- Non-healing ulcer
- Gangrene
- Ischemic Rest pain

→ Urgent consideration of revascularization
Acute Limb Ischemia=
Vascular Emergency

- The 6 Ps:
  - Pain
  - Pallor
  - Paresthesias
  - Pulselessness
  - Paralysis
  - Poikilothermia or Polar (cold leg)

Evaluate for emergent revascularization
The Comprehensive Vascular Examination

- Carotid Bruits
- Subclavian Bruits
- Bilateral Blood Pressures
- Brachial Pulses
- Radial Pulses
- Allen Test
- Abdominal Aorta
- Femoral Pulses and Bruits
- Popliteal Pulses
- Posterior Tibial Pulses
- Dorsalis Pedis Pulses

Inspect feet for ulcers
The Ankle-Brachial Index

\[ \text{ABI} = \frac{\text{Ankle systolic pressure}}{\text{Brachial systolic pressure}} \]

- Cornerstone of PAD Diagnosis
- Ankle and brachial systolic pressures taken using a hand-held Doppler device
- Supine position
- After 5+ minutes of rest

<table>
<thead>
<tr>
<th>Condition</th>
<th>ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.90-1.30</td>
</tr>
<tr>
<td>PAD</td>
<td>&lt;0.91</td>
</tr>
<tr>
<td>Severe PAD</td>
<td>&lt;0.40</td>
</tr>
<tr>
<td>Non-compressible</td>
<td>&gt;1.30</td>
</tr>
</tbody>
</table>
## Performance of the ABI Test

<table>
<thead>
<tr>
<th>TEST</th>
<th>SENSITIVITY</th>
<th>SPECIFICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI</td>
<td>95-97%</td>
<td>99-100%</td>
</tr>
<tr>
<td>PULSE EXAM (DP)</td>
<td>50%</td>
<td>73%</td>
</tr>
<tr>
<td>PULSE EXAM (PT)</td>
<td>71%</td>
<td>91%</td>
</tr>
</tbody>
</table>

Limitations of the ABI

- Appropriately trained staff to perform it
- ABI correlates poorly with symptoms and functional limitations
- Decreased sensitivity for mild disease or inflow disease
  - Exercise ABI critical for patients with suspected PAD and normal resting ABI
- Falsely elevated ABI for patients with “medial calcinosis” or calcified vessels
  - Diabetes mellitus
  - Renal failure
  - Hyperparathyroidism
Do Non-Compressible Vessels Have any Meaning for a Diabetic? Yes!

- Non-compressible vessels (high ABI) independent predictor of adverse outcome

- Significant PAD is generally present though ABI number is not interpretable

- Do not consider an ABI > 1.3 “normal”
**Toe-Brachial Index**

- Ratio of toe pressure to brachial pressure
- Room must be warm to avoid vasoconstriction
- Great toe pressure measured using small digit cuff and a flow sensor
  - Doppler
  - Strain gauge
  - Photoplethysmography
- Digital vessels almost always compressible
- Normal TBI > 0.7

Bonham PA. Nursing. 2003;33:54.
Anatomic Imaging Options for PAD

**Duplex u/s**
- Least expensive
- Labor intensive
- Not a road map
- Generally reserved for f/u

**MRA**
- Angiographic projections
- Tends to overestimate dz
- Pacemaker contraindication
- Stent drop-out
- Careful in setting of renal insufficiency

**CT angiography**
- Requires IV contrast
- Radiation exposure

**Digital Subtraction Arteriography**
- Invasive
- Requires IV contrast
- Radiation exposure
- Typically reserved for intervention
Intermittent Claudication

Atypical or No Symptoms
What is the Prevalence of PAD in the Clinic?

- PARTNERS study (2001)
- 6,979 ambulatory care patients in 350 primary care practices
- ABIs measured for all enrolled patients
  - Aged 70+
  - Aged 50-69+ with diabetes mellitus or tobacco history
- PAD prevalence 29% overall
- Only 11% of patients with abnormal ABI had classic symptoms

Risk Factors for PAD

- Smoking
- Diabetes
- Hypertension
- Hypercholesterolemia
- Hyperhomocysteinemia
- Fibrinogen
- C-Reactive Protein
- Alcohol

Relative Risk

PAD is a Marker of Atherosclerosis and CV Risk

- 60-80% of patients with PAD have CAD in at least one coronary vessel\textsuperscript{1,2}

- Up to 15-25% of patients with PAD have a significant carotid stenoses of >70%\textsuperscript{3,4}

- PAD a true coronary “risk equivalent”

- 21% of patients with P.A.D. will have MI, stroke, cardiovascular death or hospitalization within 1 year\textsuperscript{5}
  - Compared to 15% of patients with established coronary artery disease or prior heart attack!

\textsuperscript{5} Steg, et al. REACH Registry. JAMA 2007
Natural History of PAD

Population > 55 years of age

Intermittent claudication 5%

Peripheral vascular outcomes

Stable claudication 73%
Worsening claudication 16%
Lower extremity bypass surgery 7%
Major amputation 4%

Other cardiovascular morbidity/total mortality

Nonfatal cardiovascular event (MI/stroke) 20%
5-year mortality 30%
Cardiovascular cause 75%

Worsening claudication 16%

Nonfatal cardiovascular event (MI/stroke) 20%
5-year mortality 30%
Cardiovascular cause 75%

Low ABI: Independent Predictor of Survival

ABI and CV Risk


N=4393 American Indians
Strong Heart Study

Optimal ABI?
ABI Increases CV Risk Prediction Beyond the Framingham Score

- Meta-analysis of 16 cohort studies involving 480,325 person-years of data
  - e.g., ARIC, Edinburgh, Framingham offspring, Strong Heart, San Diego, Rotterdam
- Lowest risk of death in ABI 1.11 – 1.4 range
- For each Framingham risk category, low ABI (<.91) doubles CV event and death rate
- ABI adds additive information to Framingham risk score
  - Risk reclassification or modification of treatment
    - 19% of men
    - 36% of women

ACC/AHA Consensus Guidelines: Who should have an ABI test?

Class I recommendation:

The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with:

- Exertional leg symptoms
- Non-healing wounds
- Asymptomatic patients at high risk
  - Adults $\geq$ 70 years of age
  - Adults $\geq$ 50 years of age with diabetes or tobacco use

The USPSTF recommends against routine screening for peripheral arterial disease (PAD) among asymptomatic adults in the general population because:

- the prevalence of PAD in this group is low (!!)
- there is little evidence that treatment of PAD at this asymptomatic stage of disease improves health outcomes.
- screening asymptomatic adults with the ABI could lead to some small degree of harm, including false-positive results and unnecessary work-ups.

Management of PAD: A Three-Pronged Approach

- Prevent MI, Stroke, and Death
- Protect the Feet: Prevent Amputation
- Treat Intermittent Claudication: Improve QOL

All patients with PAD
Symptomatic patients
Foot Care and Ulcer Prevention

- Meticulous foot and nail care
- Daily foot self-inspection
- Appropriate footwear
- PAD patients with diabetes at highest risk for amputation
- Collaborate with podiatry colleagues when appropriate
- Review warning signs of critical limb ischemia (CLI)
  - Advise patients when to call in to report an ulcer
- Reinforce importance of foot care at each office visit
Preventing Cardiovascular Events in Patients with PAD

- Smoking cessation
- Antiplatelet therapy
- Lipid lowering therapy
  - Statins
  - Other agents
- Antihypertensive therapy
  - Ace-inhibitors or ARBs
  - Other agents
- Glycemic control for the diabetic patient
Beneficial Effects of Smoking Cessation in Patients with PAD

- Decreases likelihood of:
  - Amputation\(^1\)
  - Need for revascularization\(^2\)
  - Failure of arterial bypass grafts\(^3\)

- Improves pain free and maximal walking times compared to patients who continue to smoke\(^4,5\)

- Improves survival\(^6\)

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Anti-Platelet Therapy: Antithrombotic Trialists’ Collaboration Meta-analysis

- Meta-analysis of anti-platelet therapy for cardiovascular disease
- 42 clinical trials enrolled patients with PAD
- 9,214 patients with PAD
- 23% reduction in serious adverse vascular events (P=.004)
- Benefits similar among PAD subtypes (intermittent claudication, peripheral grafting, and peripheral angioplasty)

CAPRIE: Efficacy of Clopidogrel vs. Aspirin in MI, Ischemic Stroke, or Vascular Death


Aspirin 325 mg/d vs. Clopidogrel 75 mg/day

N = 19,185

Cumulative Event Rate (%) vs. Months of Follow-Up

Aspirin
5.83%

Clopidogrel
5.32%

Overall Relative Risk Reduction
8.7%*

p = 0.043
Antiplatelet therapy is indicated to reduce the risk of myocardial infarction, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD.

Aspirin, in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of myocardial infarction, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD.

Clopidogrel (75 mg per day) is recommended as an effective alternative antiplatelet therapy to aspirin to reduce the risk of myocardial infarction, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD.

**CHARISMA: Effect of Combination Anti-Platelet Therapy on Major CV Events**

*All patients received ASA 75-162 mg/day*

Placebo + ASA*  
7.3%

Clopidogrel + ASA*  
6.8%

RRR: 7.1% [95% CI: -4.5%, 17.5%]  
p=0.22

N=15,603

CHARISMA Study: Subset Analysis by Category of Inclusion Criteria

N=9,478 subset with prior MI, ischemic stroke (IS), or symptomatic PAD (8)

<table>
<thead>
<tr>
<th>Category of Inclusion Criteria</th>
<th>Placebo</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI</td>
<td>10.7%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Prior IS</td>
<td>8.7%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Prior PAD</td>
<td>8.8%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Entire Cohort</td>
<td>8.8%</td>
<td>7.3%</td>
</tr>
</tbody>
</table>

HR (95% & CI)                  P-value

- Prior MI: 0.780 (0.624, 0.976) 0.029
- Prior IS: 0.869 (0.671, 1.125) 0.085
- Prior PAD: 0.829 (0.719, 0.956) 0.010

But 60% Increase in Moderate Bleeding with Dual Anti-Platelet Therapy

Dual anti-platelet therapy not for everyone

Multiple Benefits of Statins in PAD

- Prevent MI, stroke, and CV death
- Other benefits
  - Shown to improve claudication in single-center studies\(^1\)
  - May slow rate of functional decline among patients with PAD\(^2\)
  - Use associated with improved patency of infrainguinal bypass grafts\(^3\)
  - Use associated with decreased perioperative complication rate among patients undergoing major vascular surgery\(^4,5,6\)

ACC/AHA Guidelines for the Management of Patients with PAD

Class I
Statins are indication for all patient with PAD to achieve an LDL<100mg/dl

Class IIa
Treatment with a statin to achieve a target LDL of <70 mg/dl is reasonable for patients with LE PAD at very high risk for ischemic events.

Hirsch et al. JACC 2006.
The HOPE Study: Effect of Ramipril on MI, Stroke or Cardiovascular Death

## The HOPE Study: PAD Subgroup Analysis

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Incidence of Composite Outcome in Placebo Group</th>
<th>Relative Risk in Ramipril Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAD</td>
<td>4051</td>
<td>22.0</td>
</tr>
<tr>
<td>No PAD</td>
<td>5246</td>
<td>14.3</td>
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</table>

ONTARGET: ARBs as Alternatives to ACE-I Inhibitors


<table>
<thead>
<tr>
<th></th>
<th>Years of Follow-up</th>
<th>No. at Risk</th>
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<tbody>
<tr>
<td>Telmisartan</td>
<td>0</td>
<td>8542</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>8177</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>7778</td>
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<tr>
<td></td>
<td>3</td>
<td>7420</td>
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<td>7051</td>
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<td>Ramipril</td>
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<td>7022</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1718</td>
</tr>
</tbody>
</table>

N=25,620
2,468 with PAD
Therapies for Intermittent Claudication

- Supervised exercise rehabilitation
- Medical therapy
  - Pentoxifylline
  - Cilostazol
- Revascularization
  - Percutaneous
  - Surgical

Prevent MI, Stroke, and Death
Management of the Patient with PAD
Treat Intermittent Claudication: Improve QOL

Protect the Feet: Prevent Amputation
Efficacy of Supervised Exercise Training for Claudication: Findings of Meta-analyses

- Up to 180% improvement in pain free walking distance\(^1\)
- 120 – 150% improvement in maximal walking distance\(^1,2\)
- Predictors of greatest clinical response\(^1\):
  - Enrollment in walking only focused program
  - Sessions > 30 minutes each
  - At least 3 sessions per week
  - Training with walking to near-maximal pain
  - ≥ 6 month program

\(^1\)Gardner AW, Poehlman ET. JAMA. 1995;274:975.
Pharmacotherapy for PAD

FDA Approved Drugs

- Pentoxifylline
- Cilostazol
- Naftidrofuryl (Europe)

Investigational

- Niacin
- Propionyl-L-carnitine
- New PDE inhibitors
- Serotonin antagonists
- Angiogenic Factors
  - HiF 1α
  - VEGF
  - bFGF
- Stem cell therapy

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<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentoxifylline (Trental®)</td>
<td>• ↓ Blood viscosity</td>
</tr>
<tr>
<td></td>
<td>• ↓ Platelet aggregation</td>
</tr>
<tr>
<td>Cilostazol (Pletal®)</td>
<td>• Trigger vasodilation</td>
</tr>
<tr>
<td></td>
<td>• Improve lipid profile</td>
</tr>
</tbody>
</table>

Cilostazol (100 mg orally 2 times per day) is indicated as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity PAD and IC.

A therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure).

Pentoxifylline (400 mg 3 times per day) may be considered as second-line alternative therapy to cilostazol to improve walking distance in patients with IC. The clinical effectiveness of pentoxifylline as therapy for IC is marginal and not well established (C).

Cilostazol Caveats and Cautions

- **BLACK BOX WARNING:** Cilostazol is contraindicated in patients with congestive heart failure of any severity

- **Extensive CYP 3A4 (and CYP2C19) Metabolism**
  - Consider 50 mg BID starting dose
  - With CYP 3A4 inhibitors (e.g., ketoconazole, erythromycin, diltiazem, fluoxetine, others)
  - With CYP2C19 inhibitors (e.g., omeprazole)
  - Cilostazol blood levels may be increased

- **Cilostazol does not increase blood levels of statins**

- **Side effects of cilostazol are common**
  - Abnormal stools or diarrhea (~15-20%)
  - Palpitations or tachycardia (~15%)
  - Headaches (25-35%)

1Source: cilostazol package insert
Indications for Revascularization

**Absolute Indications**
- Acute limb ischemia
- Critical limb ischemia
  - Rest pain
  - Tissue loss
    - Non-healing ulceration
    - Tissue necrosis – gangrene

**Relative Indications**
- Lifestyle-limiting claudication with poor response to pharmacotherapy +/- exercise training
- Lifestyle-limiting claudication with impaired QOL (primary therapy)
Which Intervention is Best for Lower Extremity PAD?
The SFA is Unique

Knee Extension

Knee Flexion
Forces Exerted on Stents in SFA

1. Extension / Contraction
2. Torsion
3. Compression
4. Flexion
The Changing Landscape of Peripheral Revascularization

# Durability of Surgical vs. Endovascular Outcomes for Claudication

## Aortoiliac Revascularization
- **Aorto-bifem BPG**
  - 5-year: 85-91%
  - 10-year: 79-86%
- **Iliac PTA**
  - 5-year: 71%

## Femoropopliteal Revascularization
- **Fem-pop BPG vein**
  - 5-year: 80%
- **Fem-pop BPG PTFE**
  - 5-year: 65-75%
- **Fem-pop PTA**
  - 3-year: 48-61%
- **Fem-pop PTA + stent**
  - 3-year: 64-66%

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Summary

- Vascular disease is a multi-system disease
- Classic coronary risk factors are also predictive of PAD occurrence
- Conservative management involves a combination of risk factor modification, pharmacologic, and non-pharmacologic therapies
- The best therapy for patients with PAD is the best therapy for patients with CAD!
- The utility and durability of lower extremity revascularization varies with anatomic level of disease
PAD Patient Education Resources

- Stay in Circulation Campaign
  www.aboutpad.org
- NHLBI Health Information Center
  www.nhlbi.nih.gov/health/infoctr
- P.A.D. Coalition
  www.PADCoalition.org

For referrals:
Yerem Yeghiazarians, MD
yeghiaza@medicine.ucsf.edu
415-353-3817
THANK YOU