Peripheral Arterial Disease: Why You Should Care & How You Can Help

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Today’s Objectives

• Review the assessment, diagnosis and treatment of peripheral arterial disease (PAD)

• Provide an appreciation of the significant morbidity and mortality of patients with PAD

• Demonstrate the magnitude and severity of asymptomatic PAD
What is Peripheral Arterial Disease?

- PAD is atherosclerosis of the extremities
  - Asymptomatic or symptomatic (claudication)
  - Diagnosed with ABI (ankle-brachial index)
  - Significant increase in mortality
  - Substantial decrease in quality of life
  - Underdiagnosed and undertreated
How Common is PAD?

• PARTNERS  \( n = 6979 \)
  – Age > 70 or > 50 with DM or smoking
  – \( \approx 29\% \) had PAD

• getABI  \( n = 6880 \)
  – 6880 patients age \( \geq 65 \)
  – \( \approx 21\% \) had PAD
How is PAD Diagnosed?

Ankle Brachial Index (ABI)
Right ABI
- Higher right ankle pressure
- Higher arm pressure

Left ABI
- Higher left ankle pressure
- Higher arm pressure

**Interpretation of ABI**

- > 1.4: Noncompressible
- 0.91-1.40: Normal
- 0.41-0.90: Mild to moderate PAD
- 0.00-0.40: Severe PAD

Adapted from NEJM 2001;344(21):1608-1621
What is Claudication?

- Cramping . . .
- Aching . . .
- Fatigue . . .

in the calf, thigh, or buttock induced by walking a reproduceable distance and relieved by standing still for 2-5 minutes
Comparing Physical Health for Chronically Ill U.S. Adults

What if you could only walk 1 block before you had to stop and rest???
Survival of Patients with Claudication

J Vasc Surg 2000;31:S1-S296
Relative 5-Year Mortality Rates

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Cancer</td>
<td>8</td>
</tr>
<tr>
<td>Hodgkin's Disease</td>
<td>18</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>23</td>
</tr>
<tr>
<td>PAD</td>
<td>32</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>39</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>86</td>
</tr>
</tbody>
</table>

American Cancer Society. Cancer Facts and Figures, 2000
Criqui NEJM 1992;326:381-6
Causes of Death

General Population

- Cardiac: 36%
- Non-vascular: 48%
- Cerebral: 4%
- Other vascular: 12%

Intermittent Claudication

- Cardiac: 55%
- Non-vascular: 25%
- Cerebral: 11%
- Other vascular: 9%

J Vasc Surg 2000;31:S1-S296
What About **Asymptomatic** PAD?

- Several studies demonstrate a consistent and significant increase in mortality for **asymptomatic** patients with low ABI results.

Circulation 2009;120(21):2053-61


Angiology 1995;46(3):211-219
What About Asymptomatic PAD?

Both walk without pain

ABI > 0.9

ABI < 0.9

Relative risk for death is 3 times higher for those with ABI < 0.9
getABI

- 6880 patients age ≥ 65 in the primary care setting
- ≈ 21% had PAD
  - ≈ 12% with asymptomatic disease
    - ABI < 0.90 without symptoms of intermittent claudication or prior revascularization
  - ≈ 9% with symptomatic disease
Death in getABI

• Big difference in MORTALITY between patients with and without PAD:
  – No PAD 19.5/1000 patient-years
  – PAD 46.3/1000 patient-years

• By 5 years, about 1 in 5 patients with PAD had died

Circulation 2009;120(21):2053-61
Death in getABI

• No difference in MORTALITY between symptomatic & asymptomatic PAD patients!
  – Death from any cause
  – Death from stroke
  – Death from cardiovascular event
  – Death from other/unknown causes

Circulation 2009;120(21):2053-61
If you care about death & severe vascular events . . .

Which would you rather not have?

Diabetes

Obesity

Smoking History

Hypertension

PAD

Lipid Disorder
Since you care about death & severe vascular events . . .

For Which Do You Currently Screen?

- Diabetes
- Obesity
- Smoking History
- Hypertension
- PAD?
- Lipid Disorder
For Which Do You Screen?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence of death from any cause or severe vascular events (per 1000 PY, 95% CI)</th>
<th>Hazard Ratio (adjusted, 95% CI) Cox regression analysis adjusted for all other variables in the Table</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAD</td>
<td>no/unknown: 27.2 (25.1 - 29.4) / yes: 77.5 (70.0 - 85.0)</td>
<td>2.17 (1.90 - 2.48)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>no/unknown: 30.6 (28.2 - 32.9) / yes: 56.0 (50.3 - 61.6)</td>
<td>1.50 (1.31 - 1.71)</td>
</tr>
<tr>
<td>Smoker (ever)</td>
<td>no: 25.4 (22.9 - 28.0) / yes: 50.7 (46.7 - 54.7)</td>
<td>1.37 (1.19 - 1.59)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>no/unknown: 27.1 (23.6 - 30.5) / yes: 41.1 (38.2 - 43.9)</td>
<td>1.13 (0.96 - 1.31)</td>
</tr>
<tr>
<td>BMI (≥ 30 kg/m²)</td>
<td>no/unknown: 36.4 (33.8 - 39.0) / yes: 37.4 (32.7 - 42.2)</td>
<td>1.05 (0.90 - 1.22)</td>
</tr>
<tr>
<td>Lipid disorders</td>
<td>no/unknown: 36.0 (30.6 - 41.4) / yes: 36.7 (34.3 - 39.2)</td>
<td>1.01 (0.85 - 1.19)</td>
</tr>
</tbody>
</table>

PY = person-years; CI = confidence interval

Severe vascular events: myocardial infarction, coronary revascularization, stroke, carotid revascularization, lower-extremity peripheral revascularization, or amputation.
“I don’t need to screen with an ABI. A good history and physical will tell me if my patients have PAD or not.”

Is this a true statement???
How Good is the History???

Peripheral Arterial Disease Detection, Awareness and Treatment in Primary Care

• 6979 patients from 350 primary care practices in the USA aged > 70, or > 50 plus diabetes and/or smoking

• 29% had PAD diagnosed by in-office ABI ≤ 0.9
How Good is the History???

• Only 9.6% of patients with PAD alone had “classic” claudication
  – 52% had atypical leg symptoms
  – 38% of patients had no pain

If you rely on a classic claudication history, you will miss the vast majority of PAD!!!
Our Fingers Are Liars

• We may think, and our practice may reveal that:
  – Normal pulses “rule out” PAD
  – Abnormal pulses “rule in” PAD

• Abnormal dorsalis pedis pulse on exam:
  – 50% Sensitivity
  – 73% Specificity
  – 18% PPV
  – 93% NPV
Our Fingers Are Liars

- Abnormal posterior tibial pulse on exam:
  - 71% Sensitivity → A normal pulse will miss 29% of patients with PAD
  - 91% Specificity
  - 49% PPV → An abnormal pulse will incorrectly diagnose PAD in 51% of “normals”
  - 97% NPV
What now???

• There is an **alarmingly high risk** for those with asymptomatic PAD

• Relying on a history of classic claudication misses the majority of patients with PAD

• Examination is not reliable to rule in or rule out PAD
PAD: Who should be evaluated???

• ABI is recommended if:
  – Age ≥ 65
  – Age 50-64 + history of smoking or diabetes
  – Leg pain with exertion
  – Non-healing wounds

ACC/AHA Class I, LOE B
The Ankle Brachial Index (ABI)

• Diagnostic accuracy **EXCELLENT!**
  – Sensitivity 95-97%
  – Specificity ≈ 99%
  – Positive Predictive Value ≈ 99%
  – Negative Predictive Value 98-99%

Surgery 1982;91:686-693
Asymptomatic
Screening Recommendations
• Age 65 or older
• Age 50-64 with history of smoking or diabetes

Exertional leg symptoms (Claudication)

Non-healing lower extremity ulcer without known PAD

ABI
ABI

0.91-1.40

≤ 0.90 on either side

>1.40 (Noncompressible)
>1.40 (Noncompressible)

Need TBI in Vascular Lab to rule out PAD
< 0.67 is abnormal
≤ 0.90 on either side

PAD Present
Start Treatment*
0.91-1.40

Exertional Symptoms?

Yes

Provocation 50 toe lifts

0.91-1.40

≤ 0.90 on either side

No PAD

PAD Present
Start Treatment*
Who “Owns” This Disease?

To diagnose and treat peripheral arterial disease, what was drilled into your head during medical school and residency?

Consult to ________________
The Most Common Foot with PAD?

OR

OR
Natural History of Atherosclerotic Lower Extremity PAD Syndromes

PAD Population (50 Years and Older)

Initial clinical presentation

Asymptomatic PAD 20%-50%

Atypical leg pain 40%-50%

Claudication 10%-35%

Critical limb ischemia 1%-2%

1 year outcomes

Alive with two limbs 50%
Amputation 25%
CV Mortality 25%

5 year outcomes

Limb morbidity

Stable claudication 70%-80%
Worsening claudication 10%-20%
Critical limb ischemia 1%-2%

CV morbidity & mortality

Nonfatal cardiovascular event (MI or stroke) 20%
Mortality 15%-30%

Amputation (see CLI data)

CV causes 75%
Non-CV causes 25%

Circulation 1996;94:3026-49
Treatment Goals in PAD

- Prevent Heart Attacks and Strokes!!!
- Prevent Progression of Disease
  - Preserve the Limb
  - Decrease need for revascularization
- Improve Functional Status
  - Symptoms
  - Exercise Capacity
  - Quality of Life
Undertreated . . .

• PARTNERS
  – 50% received cholesterol medication
  – 42% received antiplatelet therapy

• GetABI
  – 23% received a statin
  – 56% received antiplatelet therapy
Undertreated . . . And It Matters!

• NHANES observational study

• 7458 aged ≥ 40 were screened for PAD
  – Mean follow up of 4.4 years

• Those with PAD:
  – Statin use in only 30.5%
  – ACE/ARB use in only 24.9%
  – Antiplatelet use in only 39%
Undertreated . . . And It Matters!

<table>
<thead>
<tr>
<th></th>
<th>PAD without CAD</th>
<th>PAD with CAD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 451</td>
<td>n = 196</td>
<td></td>
</tr>
<tr>
<td>Statin Use</td>
<td>18.3%</td>
<td>57.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACEI/ARB Use</td>
<td>20.8%</td>
<td>34.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiplatelet Use</td>
<td>27.4%</td>
<td>65.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None of these</td>
<td>53.7%</td>
<td>14.9%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Taking at least 2 of these medications compared with none reduced all-cause mortality by 65%
Smoking

• Cigarette smoking:
  – 2-3 times more likely to cause PAD than CAD
  – Increases the risk of PAD by 2-6 times
  – Increases the risk of claudication by 3-10 times

NEJM 2001;344(21):1608-1621
Smoking Cessation

• The patient with PAD who quits . . .
  – Improves ankle blood pressure
  – Improves exercise tolerance
  – Decreases chance of critical leg disease
  – Decreases chance of MI
  – Decreases chance of cardiac death
  – Improves overall survival

Br J Surg 1982;69:S24-26
Acta Med Scand 1987;221(3):253-60
Smoking Cessation

• Keep on smoking, big guy . . .
  – Decreased patency rates after limb angioplasty or bypass surgery
  – Increased unplanned urgent re-do revascularization
  – Increased risk of death
  – 11 times the risk of amputation

Vasc Med 1997;2:243-251
Acta Med Scand 1987;221:253-60
J Invasive Cardiol 2003;15:242-6
Aspirin in PAD

- 43% improvement in vascular graft patency in peripheral bypass or angioplasty

- Reduced the need for first time peripheral artery surgery in the Physician’s Health Study

*Lancet 1992;349:143-5*
Aspirin in PAD

• Meta-analysis of 18 trials with 5269 patients
  – Admittedly underpowered
  – No decrease in cardiovascular events
    • 8.9% aspirin vs. 11.0% control
  – No difference in mortality or major bleeding
  – Reduced nonfatal stroke
    • 1.8% aspirin vs. 3.1% control

JAMA 2009;301:1909-19
Aspirin in Asymptomatic PAD

• POPADAD trial of patient with diabetes and asymptomatic “PAD”
  – Used ABI cut off of $\leq 0.99$
  – No decrease in vascular events

• Aspirin in Asymptomatic Atherosclerosis
  – Used ABI cut off of $< 0.95$
  – Calculated ABI incorrectly to include “normals”
  – Only 60% medication adherence
  – No decrease in vascular events

BMJ 2008;337:a1840
JAMA 2010;303:841-48
Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE)

- 19,185 patients with recent MI, CVA, or symptomatic PAD
- Randomized to clopidogrel 75 mg or aspirin 325 mg daily for 3 years
- Combined endpoint of fatal or nonfatal CVA, fatal or nonfatal MI, or vascular death

Lancet 1996;348:1329-39
CAPRIE Symptomatic PAD Subgroup

- Events with aspirin: 4.86%
- Events with clopidogrel: 3.71%
- RRR = 23.7%
- ARR = 1.15% per year
- NNT = 87 per year to prevent one event

Lancet 1996;348:1329-39
Antiplatelet Guidelines - Chest

• Symptomatic PAD
  – Aspirin 75-100 mg/day, or
  – Clopidogrel 75 mg/day (Grade 1A)

• Asymptomatic PAD
  – Aspirin 75-100 mg/day (Grade 2B)
Statins Reduce Events in PAD

• Heart Protection Study subgroup of 6748 patients with symptomatic PAD randomized to simvastatin 40 mg/day or placebo

• Big event reductions in first and subsequent vascular events and death, regardless of baseline LDL levels

<table>
<thead>
<tr>
<th>Major vascular event &amp; prior disease group</th>
<th>Simvastatin -allocated</th>
<th>Placebo -allocated</th>
<th>Event rate ratio (95% CI)</th>
<th>Heterogeneity p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major coronary events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>369 (10.9%)</td>
<td>465 (13.8%)</td>
<td></td>
<td>p=0.3</td>
</tr>
<tr>
<td>No PAD</td>
<td>529 (7.7%)</td>
<td>747 (10.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal: coronary</strong></td>
<td>898 (8.7%)</td>
<td>1212 (11.8%)</td>
<td>0.73 (0.67 - 0.79)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td><strong>Strokes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>179 (5.3%)</td>
<td>242 (7.2%)</td>
<td></td>
<td>p=0.7</td>
</tr>
<tr>
<td>No PAD</td>
<td>265 (3.8%)</td>
<td>343 (5.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal: stroke</strong></td>
<td>444 (4.3%)</td>
<td>585 (5.7%)</td>
<td>0.75 (0.66 - 0.85)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td><strong>Revascularisations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>466 (13.8%)</td>
<td>603 (17.9%)</td>
<td></td>
<td>p=0.7</td>
</tr>
<tr>
<td>No PAD</td>
<td>473 (6.9%)</td>
<td>602 (8.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal: revascularisation</strong></td>
<td>939 (9.1%)</td>
<td>1205 (11.7%)</td>
<td>0.76 (0.70 - 0.83)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td><strong>MAJOR VASCULAR EVENTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>895 (26.4%)</td>
<td>1101 (32.7%)</td>
<td></td>
<td>p=0.5</td>
</tr>
<tr>
<td>No PAD</td>
<td>1138 (16.5%)</td>
<td>1484 (21.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALL PATIENTS</strong></td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td>0.76 (0.72 - 0.81)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>
Statins Prevent Development of PAD

- PANDORA ABI screening study of 10,287 patients
  - ≥ 1 cardiovascular risk factor
  - No diabetes

- Patients treated with statins were 38% less likely to have asymptomatic PAD than those who were not \( (p < 0.0001) \)
Statins Improve Walking in PAD

- 86 patients with PAD and intermittent claudication with cholesterol levels over 220 mg/dl
- Randomized to Simvastatin 40 mg or placebo for 6 months
Statins Improve Walking in PAD

• Improved ABI:
  – 0.09 at rest and 0.19 after exercise

• Improved walking:
  – Pain-free: 125% improvement
  – Maximum: 131% improvement

• A study of atorvastatin 80 mg showed significant results as well

Circulation 2003;108(12):1481-1486
Ramipril Reduces Events in PAD

Heart Outcomes Prevention Evaluation (HOPE)

- 9297 patients ≥ 55 years with vascular disease or diabetes plus one other risk factor without heart failure

- Ramipril 10 mg daily vs. placebo for 5 years

- Outcome was MI, CVA, and/or vascular death

NEJM 2000;342(3):145-153
Ramipril Reduces Events in PAD

• Included 4051 patients with claudication, known PAD, or ABI < 0.9
  
• Events with placebo: 17.8%
• Events with ramipril: 14.0%
  
• RRR = 22%
• ARR = 3.8%
• NNT = 26.3
HOPE PAD Subgroup Results

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Patients</th>
<th>Incidence of Composite Outcome in Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral arterial disease</td>
<td>4046</td>
<td>22.0</td>
</tr>
<tr>
<td>No peripheral arterial disease</td>
<td>5251</td>
<td>14.3</td>
</tr>
</tbody>
</table>
Ramipril Improves Walking in PAD

• Pilot study of 40 patients with symptomatic PAD
  – No diabetes
  – No blood pressure greater than 160/90 mmHg
  – No aortoiliac disease

• Ramipril 10 mg daily vs. placebo for 6 months

• Not asked to exercise during the trial
  – “Maintain all aspects of your lifestyle”
Ramipril Improves Walking in PAD

- ABI change of 0.12 mmHg at rest (P < 0.001)

- Improved walking:
  - Pain-free: 202 meter improvement (P < 0.001)
  - Maximum: 401 meter improvement (P < 0.001)

- Improvement in Walking Impairment Questionnaire scores (P < 0.001)
Ramipril Improves Walking in PAD

• 343 patients with symptomatic PAD
  – Included patients with diabetes and aortoiliac disease

• Ramipril 10 mg daily vs. placebo for 6 months

• Improved walking:
  – Pain-free: 87% improvement
  – Maximum: 139% improvement

• Improved functional capacity & quality of life

Ahimastos, A. 2011 American Heart Association Meeting
Cilostazol Improves Walking in PAD

- Type III phosphodiesterase inhibitor
  - Black box warning for CHF of any severity
- Inhibits platelet aggregation and increases vasodilation
- Adverse effects: Headache in 34%; diarrhea

- Improved walking:
  - Pain free: 67% improvement
  - Maximal: 50% improvement

Am J Cardiol. 2002;90(12):1314
Pentoxifylline Anyone?


n = 698
Exercise Rehabilitation Works

- Optimal Program:
  - Frequency of at least 3 sessions per week
  - Duration > 30 minutes per session
  - Walking used as the mode of exercise
  - Use of near-maximal pain during training as temporary end point
  - Program length of at least 6 months
Exercise Rehabilitation Works

- Distance to Pain Onset: 126 m to 351 m (179% increase, p < 0.001)
- Distance to Maximal Pain: 326 m to 723 m (122% increase, p < 0.001)

JAMA 1995;274:975-980
Exercise Rehabilitation Works

• Rehabilitation programs across the nation are rare
  – No Medicare/Private Insurance reimbursement

• Noncompliance with simple exercise recommendations from providers is high
## Walking Improvement in PAD

### Summary

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Pain Free Time/Distance</th>
<th>Maximal Time/Distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin*</td>
<td>125%</td>
<td>131%</td>
</tr>
<tr>
<td>Ramipril*</td>
<td>87%</td>
<td>139%</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>67%</td>
<td>50%</td>
</tr>
<tr>
<td>Supervised Exercise</td>
<td>179%</td>
<td>122%</td>
</tr>
</tbody>
</table>

* Also reduces vascular events and death in patients with PAD
Timing of Revascularization

• Rest pain from ischemia

• Non-healing ischemic wounds

• “Lifestyle limiting” claudication
  – More aggressive if disease is aortoiliac on history and/or segmental pressure studies
Take Home Points

• PAD, both symptomatic and asymptomatic, is common and deadly

• History and physical exam are unreliable to diagnose PAD in most patients

• Diagnose and screen for PAD with the ABI
Take Home Points

• ABI is recommended if:
  – Age ≥ 65
  – Age 50-64 + history of smoking or diabetes
  – Leg pain with exertion
  – Non-healing wounds

ACC/AHA Class I, LOE B
Take Home Points

• Aggressively treat this disease!
  – Complete smoking cessation
  – Antiplatelet agents
  – Statins
  – Ramipril
  – Exercise rehabilitation for claudication
Thank You!