Peripheral Arterial Disease
Diagnosis and Treatment of the Ischemic Limb

Peter P. Monteleone, MD
To that end...

- Claudication
- Critical limb ischemia (CLI)
- Acute limb ischemia (ALI)
Before we get there…
Scope and the “incidence of PAD”

• Who do we even need to sort?

• How do we define the population of patients with peripheral arterial disease?
  • We know it when we see it…
  • But how would we look for it?
  • And should we look for it?

• Ankle brachial index as a testable surrogate?
Segmental ABI
Segmental ABI

>1.4 - non-compressible
0.91-1.4 - “normal”
0.71-0.9 - mild PAD
0.41-0.7 - moderate PAD
0-0.4 - severe PAD
What a straightforward… easy to perform… inexpensive test! Should we screen everyone with an ABI?
If the question is...

• Should we screen everyone with an ABI so that everyone with a severe blockage can get a stent or a bypass?
  • the answer is a strong NO

• Should we screen everyone with an ABI so that everyone with PAD can be medically treated to prevent an increased risk of cardiovascular morbidity/mortality?
  • The answer is a strong MAYBE
**Recommendation**

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for peripheral artery disease (PAD) and cardiovascular disease (CVD) risk assessment with the ankle–brachial index (ABI) in adults.

**Grade**

I
The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for peripheral artery disease (PAD) and cardiovascular disease (CVD) risk assessment with the ankle-brachial index (ABI) in adults.

SVM Calls USPSTF Coronary Heart Disease Recommendations Ill-advised
The U.S. Preventive Services Task Force released recommendations in October discouraging the use of what it deems "nontraditional risk factors" in screening for vascular disease.

The Society for Vascular Medicine (SVM) finds these Task Force recommendations, particularly those discouraging the use of ankle-brachial index (ABI) screening for peripheral arterial disease (PAD), ill-advised and contrary to sound medical research. In a 2006 publication, the Task Force dismissed PAD as an important risk factor in cardiovascular disease. However, PAD is not merely a risk factor for cardiovascular disease, it is cardiovascular disease. PAD is thought to affect 8 - 10 million Americans. Individuals with PAD have a five-times increased risk of suffering an heart attack, stroke, or death within five years.
Like we said...

- “A strong maybe”
If you look at ABIs... you will find PAD...
An ABI $\leq 0.90$ was associated with approximately twice the age-adjusted 10-year total mortality, cardiovascular mortality, and major coronary event rate compared with the overall rate in each FRS category.
Get ABI:

PAD Predicts CV Events Regardless of Symptoms

ACC/AHA 2017 Guideline
<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In patients with history or physical examination findings suggestive of PAD, the resting ABI, with or without segmental pressures and waveforms, is recommended to establish the diagnosis.</td>
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<tr>
<td>I</td>
<td>C-LD</td>
<td>Resting ABI results should be reported as abnormal (ABI ≤0.90), borderline (ABI 0.91–0.99), normal (1.00–1.40), or noncompressible (ABI &gt;1.40).</td>
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<td>IIa</td>
<td>B-NR</td>
<td>In patients at increased risk of PAD but without history or physical examination findings suggestive of PAD, measurement of the resting ABI is reasonable.</td>
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<td>III: No Benefit</td>
<td>B-NR</td>
<td>In patients not at increased risk of PAD and without history or physical examination findings suggestive of PAD, the ABI is not recommended.</td>
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**Identify Patients at Increased Risk of PAD**

**Patients at Increased Risk of PAD**

- Age ≥65 years
- Age 50–64 years, with risk factors for atherosclerosis (*e.g.*, diabetes mellitus, history of smoking, hyperlipidemia, hypertension) or family history of PAD
- Age <50 years, 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)
Not back to symptomatic LE PAD…
Categorizing lower extremity ischemia

- Claudication
- Critical limb ischemia (CLI)
- Acute limb ischemia (ALI)
Categorizing lower extremity ischemia

- Claudication
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The claudication to CLI “spectrum”

| Table 1. Fontaine or Rutherford classification systems of peripheral arterial disease |
|-----------------------------------------------|-----------------------------------------------|
| **Fontaine classification**                  | **Rutherford classification**                 |
| **Stage** | **Clinical** | **Grade** | **Category** | **Clinical** |
| I     | Asymptomatic | 0          | 0            | Asymptomatic |
| IIa   | Mild claudication | I         | 1            | Mild claudication |
| IIb   | Moderate to severe claudication | I         | 2            | Moderate claudication |
| III   | Ischaemic rest pain | II    | 4            | Ischaemic rest pain |
| IV    | Ulceration or gangrene | III    | 5            | Minor tissue loss |
|       |                | III    | 6            | Major tissue loss |
The claudication to CLI “spectrum”

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<tr>
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<td>Moderate claudication</td>
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<tr>
<td>I</td>
<td>3</td>
<td>Severe claudication</td>
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<tr>
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<td></td>
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CRITICAL LIMB ISCHEMIA
Claudication

- Supply & demand mismatch
- 99.9% history taking
- Natural history
- Treatment options
Claudication

• Supply & demand mismatch
• 99.9% history taking
• Natural history
• Treatment options
Natural history key points

• Lower extremity amputation rate 2-5% at 5 years

• But 5 year mortality rate up to 30% (primarily cardiac)
Follow those 2 points forward

- Amputation rate as low as 2% dictates how aggressive we are with the limb procedurally.

- 5 year mortality rate as high as 30% dictates how aggressive you MUST be with preventative medical therapies.
Treatment for patients with PAD (not just “treatment of PAD”)

- Diet/exercise
- Tobacco cessation
- Supervised physical therapy
  - 3 months and significant QOL & walking distances
- GDMT for BP control
- High dose statin therapy
- ASA for MACE reduction
- OR (not and) clopidogrel (see CAPRIE/CHARISMA)
- Cilostazol to increase ambulation (PDE III inhibitor contraindicated in CHF)
What about anticoagulation & the COMPASS trial?
Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial


Summary

Background Patients with peripheral artery disease have an increased risk of cardiovascular morbidity and mortality. Antiplatelet agents are widely used to reduce these complications.

Methods This was a multicentre, double-blind, randomised placebo-controlled trial for which patients were recruited at 602 hospitals, clinics, or community practices from 33 countries across six continents. Eligible patients had a history of peripheral artery disease of the lower extremities (previous peripheral bypass surgery or angioplasty, limb or foot amputation, intermittent claudication with objective evidence of peripheral artery disease), of the carotid arteries (previous carotid artery revascularisation or asymptomatic carotid artery stenosis of at least 50%), or coronary artery disease with an ankle–brachial index of less than 0.90. After a 30-day run-in period, patients were randomly assigned (1:1:1) to receive oral rivaroxaban (2.5 mg twice a day) plus aspirin (100 mg once a day), rivaroxaban twice a day (5 mg with aspirin placebo once a day), or to aspirin once a day (100 mg and rivaroxaban placebo twice a day). Randomisation was computer generated. Each treatment group was double dummy, and the patient, investigators, and central study staff were masked to treatment allocation. The primary outcome was cardiovascular death, myocardial infarction or stroke; the primary peripheral artery disease outcome was major adverse limb events including major amputation. This trial is registered with ClinicalTrials.gov, number NCT01776424, and is closed to new participants.
Figure 4: Analyses of primary and secondary outcomes

Hazard ratios and 95% CI are shown for all subgroups of patients with peripheral artery disease for major adverse cardiovascular events (A) and major adverse limb events including major amputation (B), major adverse cardiovascular or limb events including major amputation (C) and for major bleeding (D). The dotted line indicates the point estimate for the overall COMPASS trial population (n=27,395).
- Not yet in guidelines
- Bayer sponsored trial
- “Very low dose” availability?

Figure 4: Analyses of primary and secondary outcomes
Hazard ratios and 95% CI are shown for all subgroups of patients with peripheral artery disease for major adverse cardiovascular events (A) and major adverse limb events including major amputation (B), major adverse cardiovascular or limb events including major amputation (C) and for major bleeding (D). The dotted line indicates the point estimate for the overall COMPASS trial population (n=27 395).
So which claudicants should you refer for revascularization?

- True “lifestyle-limiting claudication”
  - Different for different people

- Do not “procedurally convert the benign natural history of the disease to something more malignant”
  - Remember that 5 year amputation rate of as low as 2-5%
RESULTS  Peak walking time improved from baseline to 18 months for both SE (5.0 ± 5.4 min) and ST (3.2 ± 4.7 min) significantly more than for OMC (0.2 ± 2.1 min; p < 0.001 and p = 0.04, respectively). The difference between SE and ST was not significant (p = 0.16). Improvement in claudication onset time was greater for SE compared with OMC, but not for ST compared with OMC. Many disease-specific quality-of-life scales demonstrated durable improvements that were greater for ST compared with SE or OMC.

CONCLUSIONS  Both SE and ST had better 18-month outcomes than OMC. SE and ST provided comparable durable improvement in functional status and in quality of life up to 18 months. The durability of claudication exercise interventions merits its consideration as a primary PAD claudication treatment. (Claudication: Exercise Versus Endoluminal Revascularization [CLEVER]; NCT00132743) (J Am Coll Cardiol 2015;65:999-1009) © 2015 by the American College of Cardiology Foundation.
Endovascular Revascularization and Supervised Exercise for Peripheral Artery Disease and Intermittent Claudication

Results  Endovascular revascularization plus supervised exercise (combination therapy) was associated with significantly greater improvement in maximum walking distance (from 264 m to 1501 m for an improvement of 1237 m) compared with the supervised exercise only group (from 285 m to 1240 m for improvement of 955 m) (mean difference between groups, 282 m; 99% CI, 60-505 m) and in pain-free walking distance (from 117 m to 1237 m for an improvement of 1120 m vs from 135 m to 847 m for improvement of 712 m, respectively) (mean difference, 408 m; 99% CI, 195-622 m). Similarly, the combination therapy group demonstrated significantly greater improvement in the disease-specific VascuQol score (1.34 [99% CI, 1.04-1.64] in the combination therapy group vs 0.73 [99% CI, 0.43-1.03] in the exercise group; mean difference, 0.62 [99% CI, 0.20-1.03]) and in the score for the SF-36 physical functioning (22.4 [99% CI, 16.3-28.5] vs 12.6 [99% CI, 6.3-18.9], respectively; mean difference, 9.8 [99% CI, 1.4-18.2]). No significant differences were found for the SF-36 domains of physical role functioning, bodily pain, and general health perceptions.

Conclusions and Relevance  Among patients with intermittent claudication after 1 year of follow-up, a combination therapy of endovascular revascularization followed by supervised exercise resulted in significantly greater improvement in walking distances and health-related quality-of-life scores compared with supervised exercise only.
Claudication

- The right treatment for the right patient
- Preventative medical therapy to decrease risk of MACE
- Targeted revascularization for “life-limiting claudication”
Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Katsanos, MD, PhD, MSc, EBIR; Stavros Spiliopoulos, MD, PhD; Panagiotis Kitrou, MD, PhD; Miltiadis Krokidis, MD, PhD; Dimitrios Karnabatidis, MD, PhD

<table>
<thead>
<tr>
<th>Study</th>
<th>Paclitaxel Events</th>
<th>Paclitaxel Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
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<td>THUNDER</td>
<td>12</td>
<td>48</td>
<td>8</td>
<td>54</td>
<td>1.69</td>
<td>1.69</td>
<td>[0.75; 3.78]</td>
<td>23.9%</td>
<td>26.9%</td>
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<td>ZILVER-PTX</td>
<td>42</td>
<td>297</td>
<td>12</td>
<td>177</td>
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<td>2.09</td>
<td>[1.13; 3.85]</td>
<td>47.7%</td>
<td>46.3%</td>
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<td>IN.PACT SFA</td>
<td>24</td>
<td>184</td>
<td>7</td>
<td>103</td>
<td>1.92</td>
<td>1.92</td>
<td>[0.86; 4.30]</td>
<td>28.5%</td>
<td>26.8%</td>
</tr>
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</table>

Fixed effect model: 529  334
Random effects model: 1.94 [1.28; 2.96] 100.0%  --
1.93 [1.27; 2.93]  --  100.0%

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.92$

Figure 3. Random effects forest plot of all-cause death at 4 to 5 years. Pooled point estimate was expressed as risk ratio (RR).
Categorizing lower extremity ischemia

- Claudication
- Critical limb ischemia (CLI)
- Acute limb ischemia (ALI)
Though on a “spectrum” with claudication, a much more severe natural history

Patients with CLI (rest pain or tissue loss) with % amputation rate at 6-12 months
  • Versus 2-5% amputation rate at 5 years with claudication

s/p BKA for CLI with 48% mortality at 2 years

s/p BKA only 4% ambulating at 2 years
Diagnosis

• History and physical
• Normal ABI does not rule out an ischemic wound etiology
  • “30% of CLI patients w/ rest ABI between 0.7 and 1.4” in INPACT-DEEP DEB CLI study
• Think about anatomy and the “angiosome”
Angiosomes of the lower extremity

- Anterior tibial angiosome
- Posterior tibial angiosome
- Peroneal angiosome

Medical Illustrator: Beth Halasz
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Urgent treatment

- Consider the differential diagnosis of wounds
- Urgent vascular referral (w/ woundcare)
- Delineation of anatomy
  - Rest ABI/PVR (though imperfect)
  - Vascular ultrasound
  - ?maybe CTA (consider renal function)
  - Angiography
- Evaluation for underlying infection/osteomyelitis
Revascularize

• *Urgent* revascularization
Revascularization options

- Endovascular versus surgical
  - BEST-CLI ongoing
  - ? avoid creating a surgical bypass wound to treat a non-healing wound
- Novel techniques
  - Atherectomy, DEB, below-knee revasc, retrograde access
- Do anything you can to save the limb or convert to a lesser amputation
The battle of the cath lab ends but the war has just begun...

- Close followup
- Anti-platelet therapies
- **EXCELLENT** wound care above all else
- Avoidance of further injury (offloading shoes)
- Medical optimization (tobacco cessation!)
Categorizing lower extremity PAD

- Claudication
- Critical limb ischemia (CLI)
- Acute limb ischemia (ALI)
ALI is different...
I will deny the existence of the following slide...
Categorizing lower extremity PAD

- Claudication............................Angina

- Critical limb ischemia (CLI)..........ACS (UA/NSTEMI)

- Acute limb ischemia (ALI)............STEMI
Finally the 6 P’s

### Box 3: Signs and Symptoms of Acute Limb Ischemia

- Pain
- Pallor
- Pulselessness
- Poikilothermia ("coldness")
- Paralysis
- Paresthesia
When you suspect ALI

• Think something has happened rapidly
• A limb is dying
• It needs to be treated *equally rapidly*
Consider certain circumstances

- Most commonly a revascularization that has failed
  - Surgical graft goes down
  - Stent thromboses
- Remember thromboembolic disease
  - Atrial fibrillation or post anterior MI and cardiac thrombus embolization
  - DVT and intracardiac shunt
  - Hypercoagulable states (HITT, lupus anticoag, ? hyperhomocysteine)
Concurrent diagnosis/treatment

• All important physical exam/Doppler pulses
• Anticoagulate with heparin
• Arterial ultrasound, often CTA especially when embolic phenomenon is a concern
• Often the first test is the angiogram
• Revascularize emergently
### Clinical classification of acute limb ischemia

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<tr>
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<th>Doppler signals</th>
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### TABLE 2
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### Evaluation

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Take home points...
• PAD as diagnosed even by screening ABI is associated with increased cardiovascular risk
• Debate re: use of true “screening ABI”
• “Athero somewhere is athero everywhere”
Claudication

• Claudication carries a relatively low risk of amputation ("benign natural history") but is associated with a very real risk of cardiovascular events including mortality

• Therefore aggressively medically manage your claudicants

• Patients with "lifestyle-limiting claudication" benefit from revascularization + exercise with improved walking distance and real QOL improvement
• Ischemic rest pain and/or tissue loss mean CLI
• CLI amputation rates up to 50% at 6-12 months
• s/p BKA for CLI with 50% mortality at 2 years and only 4% ambulating
• Be aggressive with revascularization for CLI when appropriate
• Exceptional followup and wound care required
• ALI is an acutely dying limb
• Remember post-procedure and thromboembolic etiologies
• Anticoagulate, diagnose and treat
Questions?

Peter Monteleone, MD
Interventional Cardiology
Vascular Medicine & Intervention

Pedro Teixeira, MD
Vascular Surgery