PAD and CRITICAL LIMB ISCHEMIA: EVALUATION AND TREATMENT
2014

Van Crisco, MD, FACC, FSCAI
First Coast Heart and Vascular Center, PLLC
Jacksonville, FL
678-313-6695
Conflict of Interest
- Bayer Healthcare Speakers Bureau
- AstraZeneca Speakers Bureau

Off-label Use
- I will discuss experimental therapies in this talk, covering Drug Eluting Stents and Drug Eluting Balloons currently in PAD and CLI clinical trials
PAD Clinical Manifestations

- Chronic Peripheral Arterial Disease
  - Claudication, symptoms vary
- Critical Limb Ischemia
  - Gangrene
- Acute Limb Ischemia
  - Cold Foot

The American College of Cardiology Foundation and American Heart Association (ACCF/AHA)—in collaboration with the Society of Vascular Medicine, Society for Vascular Surgery, and Society of Interventional Radiology - 2011

- The prevalence of PAD remains very high and is likely to increase, especially with an aging, more obese, and more diabetic population.

- New guidelines are intended to:
  - facilitate the identification of PAD patients earlier
  - use of effective measures of prevention, such as smoking cessation and antiplatelet therapy
  - highlight effective treatment strategies supported by clinical outcome data

- Short-term risk and cost of PAD are high.
  - extremely common patients
  - outcomes over one to five years are as adverse, or worse, as patients who suffer with STEMI
  - the costs are equal to or higher than treating patients with STEMI.
Lower Extremity PAD: Class 1 Recommendations

- The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with 1 or more of the following (Level of Evidence: B):
  - exertional leg symptoms
  - non-healing wounds
  - age 65 years and older
  - or 50 years and older with a history of smoking or diabetes.

- The ABI should be measured in both legs in all new patients with PAD of any severity to confirm the diagnosis of lower extremity PAD and establish a baseline. (Level of Evidence: B)
Lower Extremity PAD: Class 1 Recommendations

- The TBI should be used to establish the lower extremity PAD diagnosis in patients in whom lower extremity PAD is clinically suspected but in whom the ABI test is not reliable due to non-compressible vessels (usually patients with long-standing diabetes or advanced age). (Level of Evidence: B)

- Leg segmental pressure measurements are useful to establish the lower extremity PAD diagnosis when anatomic localization of lower extremity PAD is required to create a therapeutic plan. (Level of Evidence: B)

- ABI results should be uniformly reported with non-compressible values defined as greater than 1.40, normal values 1.00 to 1.40, borderline 0.91 to 0.99, and abnormal 0.90 or less (24). (Level of Evidence: B) *

* = NEW RECOMMENDATION
Recommendations for Smoking Cessation: Class 1 Recommendation

- Smokers or former smokers should be asked about status of tobacco use at every visit. (Level of Evidence: A)*
- Patients should be assisted with counseling and developing a plan for quitting that may include pharmacotherapy and/or referral to a smoking cessation program. (Level of Evidence: A)*
- Individuals with lower extremity PAD who smoke cigarettes or use other forms of tobacco should be advised by each of their clinicians to stop smoking and offered behavioral and pharmacological treatment. (Level of Evidence: C)
- In the absence of contraindication or other compelling clinical indication, 1 or more of the following pharmacological therapies should be offered: varenicline, bupropion, and nicotine replacement therapy. (Level of Evidence: A)*

* = NEW RECOMMENDATION
2011 Focused Update
Recommendations: Antiplatelet Therapy

- Class I
  - Antiplatelet therapy is indicated to reduce the risk of MI, stroke, and vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or CLI, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. (Level of Evidence: A)
  - Aspirin, typically in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or CLI, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. (Level of Evidence: B)
2011 Focused Update
Recommendations: Antiplatelet Therapy

- **Class 1**
  - Clopidogrel (75 mg per day) is recommended as a safe and effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, ischemic stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. (Level of Evidence: B)

- **Class 2a**
  - Antiplatelet therapy can be useful to reduce the risk of MI, stroke, or vascular death in asymptomatic individuals with an ABI less than or equal to 0.90. (Level of Evidence: C)
Antiplatelet Therapy

- Class 2b
  - The usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in asymptomatic individuals with borderline abnormal ABI, defined as 0.91 to 0.99, is not well established. (Level of Evidence: A)

- The combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or CLI, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia and who are not at increased risk of bleeding and who are at high perceived cardiovascular risk. (Level of Evidence: B)
2011 Focused Update Recommendations: Antiplatelet Therapy

- Class 3: No benefit
  - In the absence of any other proven indication for warfarin, its addition to antiplatelet therapy to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD is of no benefit and is potentially harmful due to increased risk of major bleeding. (Level of Evidence: B)
Medical Management of PAD

- Statins:
  - Reduce your risk factor of heart attack and stroke.
  - Goals: LDL <100 and lower for prior MI, CVA, DM2, smokers

- High blood pressure medications:
  - Goal: Non-diabetics <140/90, Diabetics ≤130/80 mm Hg.
  - Consider ACEI/ARB’s first-line

- Medication to control blood sugar.

- Medications to prevent blood clots: Aspirin or clopidogrel (Plavix).

- Symptom-relief medications:
  - Cilostazol (Pletal)
  - Pentoxifylline (Trental, however, it's generally less effective).
Rutherford Categories and Fontaine Stages of PAD

<table>
<thead>
<tr>
<th>PAD Classification</th>
<th>Clinical Symptom</th>
<th>Rutherford</th>
<th>Fontaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Asymptomatic</td>
<td>0</td>
<td>I</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>Mild claudication</td>
<td>1</td>
<td>IIa</td>
</tr>
<tr>
<td></td>
<td>Moderate claudication</td>
<td>2</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Severe claudication</td>
<td>3</td>
<td>IIb</td>
</tr>
<tr>
<td>Critical limb ischemia</td>
<td>Ischemic rest pain</td>
<td>4</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Minor tissue loss</td>
<td>5</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Ulceration or gangrene</td>
<td>6</td>
<td>IV</td>
</tr>
</tbody>
</table>
Prognosis for CLI Patients

- Within 3 months of presentation:
  - death in 9%
  - MI in 1%
  - stroke in 1%
  - amputation in 12%
  - persistent CLI in 18%
- 1-year mortality: 21.0%
- 2-year mortality: 31.6%
CLI = Multi-level arterial obstruction
Limb Ischemia

Straight line flow  Intact Plantar Arch

LIMB SALVAGE

Appropriate Surveillance

Do whatever it takes to get a pulse !!!!!
Recommendations for Critical Limb Ischemia (CLI) : Endovascular and Open Surgical Treatment for Limb Salvage

- Class I
  - For individuals with combined inflow and outflow disease with critical limb ischemia, inflow lesions should be addressed first. (Level of Evidence: C)
  - For individuals with combined inflow and outflow disease in whom symptoms of critical limb ischemia or infection persist after inflow revascularization, an outflow revascularization procedure should be performed. (Level of Evidence: B)
  - If it is unclear whether hemodynamically significant inflow disease exists, intra-arterial pressure measurements across lesions should be measured before and after the administration of a vasodilator. (Level of Evidence: C)
Recommendations for Critical Limb Ischemia: Endovascular and Open Surgical Treatment for Limb Salvage

- **Class 2a**
  - For patients with limb-threatening lower extremity ischemia and an estimated life expectancy of 2 years or less or in patients in whom an autogenous vein conduit is not available, balloon angioplasty is reasonable to perform when possible as the initial procedure to improve distal blood flow. (Level of Evidence: B)
  - For patients with limb-threatening ischemia and an estimated life expectancy of more than 2 years, bypass surgery, when possible and when an autogenous vein conduit is available, is reasonable to perform as the initial treatment to improve distal blood flow. (Level of Evidence: B)
Management of Limb Ischemia

Surgical

Endovascular
Outcome of Fem-pop Surgery for CLI

- Pooled data, 1194 saphenous vein
  - 5 year primary patency
    - 80% in claudicants
    - 66% in critical ischemia

- Results with PTFE
  - 75% in claudicants
  - 47% in critical ischemia

JAMA 1995: 274:71
The Dirty Little Secret: Poor Healing
Infrainguinal Surgery: Outcomes

- Wound Infection 10 - 30%
- Myocardial Infarction 1.9 - 3.4%
- Early graft failure 0 - 24%
- Acute leg ischemia 1.0 - 2.0%
- Op. Mortality 1.3 - 6%
- Surgical Revision rate > 20%

TASC J Vasc Surg 2000
Vascular Access for Endovascular Intervention

Antegrade Puncture

Pedal Punctures

Popliteal access
Endovascular Lesion Crossing Devices
Endovascular Lesion Modification Devices (Rotational/Orbital Atherectomy

2.1 mm

3.0 mm
Endovascular Devices to Increase Patency (Stents/Cryoplasty)
What about Drug-eluting stents in CLI Revascularization?

The PaRADISE (PReventing Amputations using Drug eluting StEnts) Trial

The PARADISE Trial

Patient Flow Diagram

(A) Clinical outcomes.
(B) Angiographic outcomes.
RS = binary restenosis
TO = total occlusion.

Bare-Metal In-Stent Restenosis Successfully Treated With DES

(A) An 87-year-old patient, Rutherford 5 CLI. The arrow indicates popliteal artery occlusion.

(B) After placing a proximal 4.0 mm bare-metal stent (BMS) and 2 overlapping 3.5-mm Cypher drug-eluting stents (DES).

(C) The patient returned 17 months later with rest pain. Note in-stent restenosis of the BMS (dotted brackets) and the patent DES (solid brackets).

(D) Incidental angiography 18 months after treating in-stent restenosis with a 3.5-mm $\times$ 23-mm Cypher stent.
Demonstration of the Technical Ease With Which DES Can Be Delivered to Challenging Tibial Anatomy

(A) A 68-year-old patient with Rutherford 6 critical limb ischemia (CLI) 1 year after femoral-posterior tibial bypass. Toe amputation (arrow) and ankle ulcer failed to heal. (B) The solid arrow points to bypass graft insertion proximal to posterior tibial lesion; the dotted arrows note additional tibial lesions. (C) The ability to place drug-eluting stent (DES) in challenging anatomy from the retrograde contralateral approach is demonstrated. The arrows trace wire course into the anterior tibial artery. (D) Completion angiogram. (E) Angiography 4 years after initial implant. (F) Clinical response 3 months after intervention.
Rate of Major Amputations in Patients Treated With Below-the-Knee Drug-Eluting Stents
(A) 1 - cumulative incidence of amputation curve and confidence limits.
(B) 1 - cumulative incidence of amputation stratified according to entry Rutherford category.

All-Cause Mortality in Patients Treated With Below-the-Knee Drug-Eluting Stents
(A) Kaplan-Meier survival curve with confidence limits.
(B) Kaplan-Meier survival curves stratified according to entry Rutherford category.
Preventing Leg Amputations in Critical Limb Ischemia With Below-the-Knee Drug-Eluting Stents: The PaRADISE (PReventing Amputations using Drug eluting StEnts) Trial

The PaRADISE Trial Amputation-Free Survival
Kaplan-Meier amputation-free survival curve (combined death and major amputation).
68-YEAR-OLD MAN WITH LEFT 5TH TOE GANGRENE: ANTEGRADE PUNCTURE
68-YEAR-OLD MAN WITH LEFT 5TH TOE GANRENE: POPLITEAL AND TIBIAL DISEASE
68-YEAR-OLD MAN WITH LEFT 5TH TOE GANGRENE: FOOT DISEASE

CLI = 3 vessel disease BTK
STEP 1: SUBINTIMAL ANGIOPLASTY LEADING TO EXTENSIVE DISSECTION COVERING POSTERIOR TIBIAL ARTERY OSTIUM

PRE PTA

POST PTA
STEP 2: RETROGRADE POSTERIOR TIBIAL ARTERY ACCESS FOR INTRALUMINAL RE-ENTRY IN THE POPLITEAL
STEP 3: RESIDUAL DISSECTIONS AFTER EXTENSIVE BALLOON-ONLY ANGIOPLASTY WITH 2.5 TO 5.0 MM BALLOONS AT 4 ATM
Drug Eluting Balloon Technology

2014
PT and AT occlusion Dialysis
PT DEB angioplasty

Anphirion In.Pact 2.5x80mm
Peroneal artery long occlusion
12-month Binary Restenosis and Re-Occlusion

- Restenosis:
  - PEB: 29%
  - NEB: 72%
  - P < 0.01

- Re-occlusion:
  - PEB: 14%
  - NEB: 50%
  - P < 0.01
Bilateral SFA disease

Case Study #1

DEB treatment (IN.PACT Pacific™)

Non-DEB treatment

DEB 6x60  Post DEB  Post PTA  PTA 6x60

baseline  6m fu  6m fu  baseline
Case Study # 2

* DEB overlapping zones

<30 cm

baseline

DEB 5x60s and 5x80s

Post DEB

6m fu
Bilateral SFA disease

Case Study # 3
Randomized Trial of IN.PACT Admiral DCB vs PTA for Atherosclerotic Lesions in the SFA and/or PPA

331 patients from Europe and the US received a drug-eluting balloon (DEB; n = 220) or angioplasty (n = 111).

<table>
<thead>
<tr>
<th>ITT Analysis at 1 Year</th>
<th>DEB (n = 220)</th>
<th>Angioplasty (n = 111)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Patency</td>
<td>82.2%</td>
<td>52.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinically Driven TLR</td>
<td>2.4%</td>
<td>20.6%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The primary safety composite (freedom from 30-day device- and procedure-related death and from target limb major amputation and clinically driven TVR through 12 months) was higher in the DEB arm.

**Conclusion:** The IN.PACT Admiral DEB achieves substantially better primary patency at 1 year compared with angioplasty.

Tepe G. Charing Cross International Symposium 2014; London, United Kingdom.
Exercise and Revascularization vs Exercise Alone

- ERASE
Endovascular Revascularization Benefits PAD Patients When Added to Exercise Therapy

212 PAD patients stable intermittent claudication + vascular obstruction > 50% randomized to supervised exercise therapy with (n = 106) or without (n = 106) endovascular revascularization. Walking distances and quality of life measured.

### Improvements From Combination Therapy vs. Exercise Therapy Alone at 1 Year

<table>
<thead>
<tr>
<th></th>
<th>Mean Difference</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Walking Distance, m</td>
<td>282</td>
<td>60-505</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain-free Walking Distance, m</td>
<td>408</td>
<td>195-622</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>VascuQuol</td>
<td>0.62</td>
<td>0.20-1.03</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Conclusion:** The combination of endovascular revascularization plus supervised exercise therapy in patients with peripheral artery disease (PAD) and intermittent claudication results in greater improvements in maximum walking distance and quality of life compared with exercise therapy alone.

Additional Supervised Exercise Therapy After a Percutaneous Vascular Intervention for PAD

70 pts randomized to angioplasty with or without exercise therapy. Exercise consisted of 2 to 3 30-minute weekly sessions with a physiotherapist plus encouragement to walk every day.

<table>
<thead>
<tr>
<th>Claudication Distance at 6 Months</th>
<th>Angioplasty Alone (n = 27)</th>
<th>Angioplasty + Exercise (n = 34)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute, m</td>
<td>685.0 ± 313.5</td>
<td>956.3 ± 490.4</td>
<td>0.011</td>
</tr>
<tr>
<td>Functional, m</td>
<td>547.2 ± 263.5</td>
<td>842.4 ± 478.3</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Conclusion: For PAD patients, supplementing percutaneous intervention with supervised exercise is more effective at improving walking ability than angioplasty alone.

New consensus guidelines for PAD evaluation and treatment recently published 2011
- Focus on Smoking Cessation, Counseling and Drug Rx
- Focus on appropriate Antiplatelet Rx
- Continue Rx that matters: Statins, BP Rx, DM2 Rx, ACEI’s

Endo and Surgical Revascularization are both options

Many endovascular technologies exist to modify lesions and improve patency
- Lesion Specific Device Selection Likely Contributes to Better Outcomes

Newer endovascular technology may offer better long-term patency outcomes
- Drug Eluting Balloon reduces restenosis rates significantly at 1 year

Supervised Exercise 2-3 days per week improves outcomes with endovascular revascularization more than revascularization alone
Thank You

Questions?