CRITICAL LIMB ISCHEMIA: EVALUATION AND TREATMENT 2013

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• **Conflict of Interest**
  
  • I have no conflicts to disclose

• **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
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 !!!!!
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
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:
  - exertional leg symptoms
  - non-healing wounds
  - age 65 years and older
  - or 50 years and older with a history of smoking or diabetes. (Level of Evidence: B)

- 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)
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)  
  * = NEW RECOMMENDATION

- 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)*
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)
2011 Focused Update
Recommendations:

**Class 2b**

- Antiplatelet Therapy
  - 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).
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)
# 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>
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%/47%

- 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

Popliteal access

Retrograde Pedal Punctures
Endovascular Lesion Crossing Devices
Endovascular Lesion Modification Devices

2.1 mm

3.0 mm
Endovascular Devices to Increase Patency
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.

doi:10.1016/j.jacc.2009.11.072
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 × 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 GANGRENE: POPLITEAL AND TIBIAL DISEASE

POPLITEAL

ANTERIOR TIBIAL

POSTERIOR TIBIAL?

PERONEAL

POSTERIOR TIBIAL?

ANTERIOR TIBIAL?

PERONEAL
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.
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

2012
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

Non-DEB treatment

DEB treatment (IN.PACT Pacific™)

DEB 6x60  Post DEB

6m fu

Post PTA  PTA 6x60

6m fu

baseline
* DEB overlapping zones

- baseline
- DEB 5x60s and 5x80s
- Post DEB
- 6m fu

Case Study # 2
PACIFIER - Conclusions

- IN.PACT PACIFIC™ confirms to effectively reduce neointima hyperplasia in SFA with a significant decrease in LLL at 6 months vs standard PTA (Primary Endpoint)
- Clinical Events (Secondary Endpoints) trend / are in favor of DEB
- Efficacy reached with a low stent rate
- Promising results with DEB in complex / long lesions
- No coating related adverse events noted
## Drug Eluting Balloon Technology

**Table 1: Key players active in developing DEB technologies**

<table>
<thead>
<tr>
<th>Company</th>
<th>DCB Name</th>
<th>Drug formulation</th>
</tr>
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<tbody>
<tr>
<td>Aachen Resonance GmbH</td>
<td>ELUTAX®</td>
<td>Formulated with a matrix of pure Paclitaxel</td>
</tr>
<tr>
<td>B. Braun Melsungen AG</td>
<td>SeQuent® Please</td>
<td>Paclitaxel with iopromide formulation (Paccocath® technology)</td>
</tr>
<tr>
<td>Bayer AG (MEDRAD, Inc.)</td>
<td>CotavanceTM with Paccocath® coating technology</td>
<td>Paclitaxel with iopromide formulation (Paccocath® technology)</td>
</tr>
<tr>
<td>Caliber Therapeutics, Inc.</td>
<td>TADD (Targeted Angioplasty Drug Delivery)</td>
<td>Rapalog-based with unknown formulation</td>
</tr>
<tr>
<td>Cook Group, Inc.</td>
<td>Advance® 18PTX®</td>
<td>Paclitaxel with unknown additive-based formulation</td>
</tr>
<tr>
<td>Eurocor AG</td>
<td>DIOR®</td>
<td>Paclitaxel without any formulation. (Opto Circuits Ltd. also developing rapamycin-based technology)</td>
</tr>
<tr>
<td>Invatec s.r.l.</td>
<td>IN.PACT™ Amphirion</td>
<td>Paclitaxel with FreePac™ hydrophilic formulation</td>
</tr>
<tr>
<td>Lutonix, Inc.</td>
<td>Unknown</td>
<td>Paclitaxel with unknown formulation</td>
</tr>
</tbody>
</table>
Summary

- 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
- Newer endovascular technology may offer better outcomes, but clinical trials are needed
Questions?