Emerging Treatments for Peripheral Arterial Disease (PAD)

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Disclosures

- None

What is Peripheral Arterial Disease?
Peripheral Arterial Disease: PAD

- Atherosclerosis
- Atherosclerotic lesions cause arterial blockages (stenosis & occlusion)
- Affects blood flow to critical arteries that supply brain, vital organs, and limbs
- Frequently affects lower extremities
- Associated with smoking, high blood pressure, diabetes, age, and hypercholesterolemia

Prevalence of PAD

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnosis</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>ABI &lt; 0.9</td>
<td>&gt;50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-6 million</td>
</tr>
<tr>
<td>Claudication</td>
<td>Muscle pain, ache, cramps, fatigue</td>
<td>30%-35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-4 million</td>
</tr>
<tr>
<td>Critical Limb Ischemia</td>
<td>Pain at rest, ulceration, gangrene</td>
<td>&lt;10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400,000-1 million</td>
</tr>
</tbody>
</table>

Hiatt WR, NEJM 2001

Prevalence of PAD

In a primary care population defined by age and common risk factors, the prevalence of PAD was approximately one in three patients.
Prevalence of PAD Increases With Age

Risk Factors for PAD

Atherosclerosis is the Biggest “Killer”
Ankle-Brachial Index (ABI)

- Independent predictor of cardiovascular and all-cause mortality
- ABI < 0.9
  - 3.8 increased risk of all cause mortality

Feringa, Arch Int Med, 2006

Peripheral Arterial Disease

- Intermittent claudication
  - "claudico" – to limp
  - Pain with walking
  - Relieved by rest

- Critical Limb Ischemia
  - Pain at rest, ulcers, or gangrene

Peripheral Arterial Disease

- Intermittent claudication
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  - Pain with walking
  - Relieved by rest

- Critical Limb Ischemia
  - Pain at rest, ulcers, or gangrene
Natural History of Claudication

5 Year Outcomes

- Non-fatal CV events: 20%
- Mortality: 15%-30% (~CV causes 75%)

Limb Morbidity

- Stable Claudication: 70%-80%
- Worsening Claudication: 10%-20%
- Critical Limb Ischemia: 1%-2%

Treatment:
- Risk factor modification
- Exercise
- Pharmacologic
- Revascularization for refractory or disabling symptoms

Weitz JI, Circulation 1996

Natural History of CLI

1 Year Outcomes

- Critical Limb Ischemia: 1%-2%
- Rest Pain
- Ulceration
- Gangrene

- Alive with both limbs: 50%
- Amputation: 25%
- Dead: 25%

Weitz JI, Circulation 1996

PAD and Diabetes Mellitus

- 24 million Americans (8% of total population) have diabetes
- For every 1% increase in HbA1c there is a 26% increased risk of PAD
- Claudication is 2X as common in diabetics
- 10-fold increased risk of progression to CLI
- 10% of patients with diabetes over age 75 have ulceration

Norgren L et al. TASC II. J Vasc Surg. 2007
Evaluation of Diabetic Foot Ulcer
- Patients with diabetes and ulceration with absent pedal pulses need arterial imaging.
- Noninvasive testing can be misleading.
- A severely neuropathic foot requires more perfusion than a normal foot to clear infection and heal ulceration.

CLI: Scope of the Problem in the US
- 67% of patients with CLI receive major amputation as primary therapy
  - Approximately 200,000 major amputations performed annually
  - < 50% have any vascular evaluation prior to amputation (ABI or angiography)
  - < 50% of all amputees will achieve mobility
  - Within 1 year > 50% of amputees are dead

We Can Do Better Than That!
- Patients with CLI should undergo expedited evaluation for possible revascularization with the goal of limb salvage
Bypass Surgery Remains the “Gold Standard”

5-Year Results

<table>
<thead>
<tr>
<th>Distal Anastomosis</th>
<th>Secondary Patency</th>
<th>Limb Salvage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popliteal¹</td>
<td>79%</td>
<td>89%</td>
</tr>
<tr>
<td>Tibial¹</td>
<td>67%</td>
<td>79%</td>
</tr>
<tr>
<td>Pedal²</td>
<td>63%</td>
<td>78%</td>
</tr>
</tbody>
</table>


Patency is good, however ...

Morbidity of open surgery often compromises functional outcomes:
- < 50% patients report a return to “normal” by 6 months postoperatively
- 20% lose independent living and ambulatory status at 1 year
- 25% have not healed wounds at 1 year

Abou-Zamzam JVS 1997; Chung JVS 2006

Measures of Success

Critical Analysis of Clinical Success after Surgical Bypass for Lower-Extremity Ischemic Tissue Loss Using a Standardized Definition Combining Multiple Parameters: A New Paradigm of Outcomes Assessment

- Retrospective review of 331 patients with CLI and infragenual bypass
- Endpoints:
  - Graft patency to wound healing
  - Limb salvage at 1-year
  - Maintenance of ambulatory status at 1-year
  - Survival at 6-months
### Critical Analysis of Clinical Success after Surgical Bypass for Lower-Extremity Ischemic Tissue Loss Using a Standardized Definition Combining Multiple Parameters: A New Paradigm of Outcomes Assessment

**Success** | **Failure**
--- | ---
Patency to wound healing | 76% 25%
Limb Salvage at 1-year | 81% 19%
Maintenance of ambulatory status at 1-year | 87% 13%
Survival (6-months) | 90% 10%
All parameters | 44% 56%

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### Endovascular Therapy?

> “Will unblock the clogged artery by inserting a balloon.”

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### Benefits of Endovascular Approaches

- Avoid general anesthetic
- Percutaneous - no wounds
- Short hospital stay
- Lower morbidity and mortality
- Excellent technical success
- Durability remains issue
- Technology driven and rapidly evolving

> **> 80%**

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Limb Salvage in CLI

- 67 yo man
- s/p liver and kidney transplant
- Rest pain for > 1yr
- “No options for revascularization”
- Admitted with gangrene & cellulitis
Many Endovascular Treatment Options…

Very Little
Randomized Data
Short Follow-Up

PTA vs. Stent: 1 Year Patency

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Mean Lesion Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSOLUTE Trial</td>
<td>104</td>
<td>9.5 cm</td>
</tr>
<tr>
<td>FAST Trial</td>
<td>244</td>
<td>6.5 cm</td>
</tr>
<tr>
<td>RESILIENT Trial</td>
<td>206</td>
<td>6.5 cm</td>
</tr>
</tbody>
</table>

- Schillinger NEJM 2006
- Krankenberg Circulation 2007
- Katzen ISET 2008
Prospective, randomized clinical trial of patients with critical limb ischemia

452 patients

Randomized to surgery-first or angioplasty first

Intention to treat analysis

Outcome variables:
- Amputation Free survival
- Mortality
- Quality of life
- Mean cost of first 12 months

BASIL: Bypass Vs. Angioplasty

No Difference

No Difference

37% 2yr Mortality

Decreased morbidity in PTA group

Shorter hospital stay

PTA less expensive

More reinterventions in PTA group

PTA preferred for “high risk” patients
Endovascular Treatment of Tibial Disease

- No prospective randomized trials comparing endovascular treatment of tibial arteries with surgery
- Technical success rate: 78-100%
- Limb salvage rate: 77-89% at one year
- Approximately 20% will need re-intervention
- Improved equipment and technique
- Viable (preferred) alternative in elderly patient, multiple co-morbidities, high surgical risk with CLI

In the Future

- We need better quality data
- Which patients are better treated with bypass surgery or endovascular approaches?
  - Wound size, location
  - Diabetes, ESRD
  - Type of vascular lesion
- Prospective trials are needed

In the Future

- Better device technology
  - Absorbable stents, new materials, nanotechnology
- Drug eluting stents and local drug delivery
- Molecular and cell-based therapies
  - Angiogenesis/arteriogenesis
  - Tissue regeneration
Final Thoughts

• PAD is common and remains underdiagnosed and undertreated
• Patients with claudication have significant risk of cardiovascular death (CAD and stroke) and thus need aggressive medical management as well as revascularization
• Patients with CLI require urgent vascular evaluation and treatment to maximize chances for limb salvage and to maintain independent living and ambulatory function

Final Thoughts

• New endovascular approaches provide additional treatment options, especially for higher-risk surgical patients
• Bypass surgery remains important for younger patients and patients who cannot be managed by endovascular approaches
• Multidisciplinary approaches to treat CLI (vascular specialists, podiatrist, wound specialists, plastic surgeons) are the key to achieve the best outcomes!