Endovascular Therapy for PAD
Clinical Outcomes, Challenges and Potential for Disease Management

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Peripheral Arterial Disease Statistics Worldwide: 2008

Current Challenges for Medical/Non-invasive Therapy for Symptomatic PAD

Supervised Exercise Programs

- Trial comparisons limited in study size and number of trials
- Sedentary, unmotivated population often inherent, limiting practicality of exercise
- Cause or symptom effect
- Reimbursement and availability of supervised programs variable
- Concurrent comorbidity (eg, cardiac) may be limiting, and resistance training ineffective
- Most comparisons with EVT not representative of contemporary practice patterns

Current Challenges for Medical/Non-invasive Therapy for Symptomatic PAD

Secondary prevention for CV risk essential, but for medications specific to PAD symptom improvement…

- Trial comparisons with revascularization limited in number, trial design and/or suboptimal medical therapy
- Expense and intolerance
- Most pharmacologic therapies intended to reduce cardiovascular risk rather than alleviate symptoms
- Therapies intended to reduce symptoms do not alter disease progression
  - Cilostazol: concerns in heart failure/advanced cardiomyopathy
  - ‘Crossover’ to revascularization common due to persistent/refractory symptoms

Peripheral Arterial Disease Statistics Worldwide: 2008

Current Challenges for Medical/Non-invasive Therapy for Symptomatic PAD

Estimated Number of Endovascular Procedures Worldwide

Peripheral Stent Procedures in Medicare* by Specialty

* (CPT Code 37205)
Current Challenges for Endovascular Therapy for Symptomatic PAD

- Many trials, few approved indications
  - Potential for indication-specific reimbursement
  - Inability to promote products/educate clinicians regarding "off-label" use
- Evolving regulatory process to raise threshold requirements for approval
- Variability in trial endpoints and design permits broad interpretation of safety and efficacy
- Technologies, technique and outcomes are specific to vascular territory

Risk of Symptom Progression By Revascularization Option (Adjusted): 15 month Follow-up

Evolving regulatory process to raise threshold requirements for approval

Variability in trial endpoints and design permits broad interpretation of safety and efficacy

Technologies, technique and outcomes are specific to vascular territory

Risk-adjusted Medical Services Costs

Index Quarter

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>Cost per Patient</th>
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<tbody>
<tr>
<td>Angioplasty</td>
<td>$0 - $60,000</td>
</tr>
<tr>
<td>Stents</td>
<td>$10,000 - $60,000</td>
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</tr>
<tr>
<td>Bypass</td>
<td>$0 - $30,000</td>
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<tr>
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<td>$10,000 - $60,000</td>
</tr>
<tr>
<td>Surg + wound care</td>
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</tr>
<tr>
<td>Endo + wound care</td>
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Risk-adjusted Medical Services Costs

4 Quarters Following Index Quarter

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Endovascular Therapies for PAD

- Carotid Stent Revascularization
- Renal Revascularization
- Lower Extremity Revascularization
  - Superficial Femoral Artery Disease
  - Below Knee Disease/Critical Limb Ischemia
- New Technologies and Indications
SAPPHIRE Trial: Randomized CAS to CEA in High-Surgical Risk Patients

Cas is a durable procedure with similar long-term risk of stroke as CEA (8.0% vs. 6.7%, p=0.799), respectively.

Between 30 days and 3 years the incremental annual risk of ipsilateral stroke for all randomized patients was 1.5% with stenting which was similar to CEA (1.2%).


Cumulative MAE at 1080 Days

Post-market Surveillance High-Risk Registries

Clinical outcomes approximate the 3% and 6% benchmarked rates in recent trials in High-Risk Patients


Ongoing RCTs with Standard Risk Patients

CREST Trial
- CAS vs. CEA in standard-risk symptomatic patients with stenosis >50%
- Lead-in phase completed (n=1479)
- 30-day mortality and morbidity with CAS
  - (Symptomatic 6.1%, Asymptomatic 3.9%)

ACT 1
- CAS vs. CEA in standard-risk asymptomatic patients with >70 to ≤ 99% stenosis, no octogenarians included
- Lead-in patients completed (n=118)
- 30-day mortality and morbidity with CAS (1.7%)

Carotid Stent Revascularization

Renal Revascularization

Lower Extremity Revascularization
  - Superficial Femoral Artery Disease
  - Below Knee Disease/Critical Limb Ischemia

New Technologies and Indications

Endovascular Therapies for PAD

Renal Artery Stenting Trials

2-Year Follow-up

<table>
<thead>
<tr>
<th></th>
<th>ASPIRE-2 1</th>
<th>RENAISSANCE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Patients with Follow-up</td>
<td>104 (79%)</td>
<td>85 (88%)</td>
</tr>
<tr>
<td>Death (%)</td>
<td>0.5</td>
<td>5.3</td>
</tr>
<tr>
<td>QMI (%)</td>
<td>1.1</td>
<td>12.2</td>
</tr>
<tr>
<td>TLR (%)</td>
<td>14.4</td>
<td>18.1</td>
</tr>
<tr>
<td>Major Embolic Event (%)</td>
<td>6.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Overall MAE (%)</td>
<td>18.3</td>
<td>16.9</td>
</tr>
<tr>
<td>Systolic BP (Baseline)</td>
<td>168</td>
<td>157</td>
</tr>
<tr>
<td>Systolic BP (Follow-up)</td>
<td>149</td>
<td>144</td>
</tr>
<tr>
<td>Diastolic BP (Baseline)</td>
<td>82</td>
<td>75</td>
</tr>
<tr>
<td>Diastolic BP (Follow-up)</td>
<td>77</td>
<td>73</td>
</tr>
<tr>
<td>Serum Creatinine (Baseline)</td>
<td>1.34</td>
<td>1.27</td>
</tr>
<tr>
<td>Serum Creatinine (Follow-up)</td>
<td>1.40</td>
<td>1.43</td>
</tr>
</tbody>
</table>

1MAE defined as device or procedure related death, QMI, TLR, and significant embolic event causing and organ damage
2MAE defined as device or procedure related death, TLR, and significant embolic event causing and organ damage

ASTRAL Trial
(Angioplasty and Stent for Renal Artery Lesions)

Plot of SCr Over Time

- No evidence of differences in treatment effect across the various subgroups – for renal functional endpoint only

P. Katar et al., ACC 2008 Presentation.
CORAL Trial
Cardiovascular Outcomes in Renal Atherosclerotic Lesions

1000 pts with ≥ 60% RAS, SBP ≥ 155 mm Hg and ≥ 2 antiHTN meds

Stent w/EDP+medical therapy
Follow-up 3.5-5 years
Medical therapy alone

1° Endpoint: cardiovascular or renal death, stroke, MI, CHF hospitalization, decline in renal function, need for dialysis

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Endovascular Stent Treatment of Lower Extremities

<table>
<thead>
<tr>
<th>FAST 1</th>
<th>VIENNA 2</th>
<th>RESILIENT 3</th>
<th>PREVENT III 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTA n=121</td>
<td>Stent n=123</td>
<td>PTA n=53</td>
<td>Stent n=51</td>
</tr>
<tr>
<td>Lesion length (cm)</td>
<td>4.5</td>
<td>9.3</td>
<td>12.2</td>
</tr>
<tr>
<td>Occlusions (%)</td>
<td>25</td>
<td>37</td>
<td>31</td>
</tr>
<tr>
<td>Crossover (%)</td>
<td>11</td>
<td>32</td>
<td>41</td>
</tr>
<tr>
<td>12-month Primary Patency (%)</td>
<td>61</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>No. of Fractured Stents (n)</td>
<td>–</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
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Critical Limb Ischemia (CLI)
Background and Rationale

- Aggressive revascularization measures have become fundamental in contemporary treatment strategies for pts with lower limb CLI
- Despite initial treatment, most pts experience not only abbreviated survival but impaired functional status, characterized by rest pain and inability to ambulate
- In part due to failed prior revascularization attempts and comorbidity or extensive tissue loss that may preclude revascularization in CLI, major lower extremity amputation remains a commonly performed procedure
  - >100,000/year attributed to PAD
  - Overall amputation rates have not declined
  - Still <1/3 ambulate with a prosthesis following amputation

Critical Limb Ischemia
Advances in Limb Salvage and Wound Healing

12 weeks
Endovascular Therapies for PAD

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Novel Endovascular Therapies for PAD

**Perspective**

Rapid evolution in device technology against background of increasing disease recognition, constant medical therapy

- Self-expanding and drug-eluting stents
- Drug-eluting balloons
- Plaque excision/atherectomy
- Excimer laser
- Cryoplasty
- Cutting balloon angioplasty
- Distal embolic protection
- Chronic total occlusion and re-entry technologies

Alternative Therapies for Lower Limb Ischemia

**Claudication**

- Atherectomy
- Laser
- Cryo

**Critical Limb Ischemia (CLI)**

- Atherectomy
- Laser
- Cryo

**Study**

<table>
<thead>
<tr>
<th>Zeller</th>
<th>CELLO</th>
<th>CHILL</th>
<th>Zeller</th>
<th>LACI</th>
<th>BTK CHILL</th>
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<tbody>
<tr>
<td>Single</td>
<td>20</td>
<td>Single</td>
<td>16</td>
<td>Single</td>
<td>14</td>
</tr>
<tr>
<td>84</td>
<td>85</td>
<td>102</td>
<td>36</td>
<td>145</td>
<td>108</td>
</tr>
<tr>
<td>16.0</td>
<td>14.7</td>
<td>N/A</td>
<td>91.0</td>
<td>33.9</td>
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<tr>
<td>9.0 ± 10.6</td>
<td>5.6 ± 4.7</td>
<td>4.7 ± 2.6</td>
<td>4.8 ± 2.8</td>
<td>4.0</td>
<td>4.1 ± 3.0</td>
</tr>
<tr>
<td>&gt;60%</td>
<td>N/A</td>
<td>8.8</td>
<td>~40%</td>
<td>&gt;95%</td>
<td>N/A</td>
</tr>
<tr>
<td>12 mo.</td>
<td>6 mo.</td>
<td>9 mo.</td>
<td>12 mo.</td>
<td>6 mo.</td>
<td>12 mo.</td>
</tr>
<tr>
<td>84.0</td>
<td>84.0</td>
<td>82.2</td>
<td>76.0</td>
<td>N/A</td>
<td>84.3</td>
</tr>
<tr>
<td>5%</td>
<td>42%</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BASIL Trial**

**Angioplasty Attempts/Immediate Failures**

- Of the 224 patients allocated to angioplasty, 216 underwent attempted angioplasty
- Of these, 43 (20%) were considered immediate failures:
  - Lumen could not be crossed with guidewire
  - Lesion crossed subintimally, but could not be re-entered
  - Perforation
  - Patient could not tolerate procedure
  - No lesion upon angiography
  - Lytic/Aspiration Resistant Thrombosis

Novel ‘Enabling’ Technologies

**Chronic Total Occlusions**


Drug-Eluting Stents & Drug-Coated Balloons in SFA Disease

**SIROCCO II**

- TLR to 2-Years

**THUNDER Trial**

- TLR to 2-Years

**SIROCCO II: TLR to 2-Years**

- Uncropped Balloon vs. Uncropped Balloon Iopromid-Paclitaxel* vs. Paclitaxel-Coated Balloon**

- **~3 mg Paclitaxel/100 ml KM**

**THUNDER: TLR to 2-Years**

- Uncropped Balloon vs. Uncropped Balloon Iopromid-Paclitaxel* vs. Paclitaxel-Coated Balloon**

- **~3.5 µg/m²**

* - Sirolimus 90 µg/cm² (total 1 mg/stent)
** - Paclitaxel 1.5 mg/cm²

Drugs and Devices: Silicone, stainless steel, polyurethane, paclitaxel, paclitaxel-eluting, sirolimus-eluting.
Pharmacologic Inhibition of Restenosis
Cilostazol

Pharmacologic Prevention of Restenosis
Cilostazol

Feasibility of Percutaneous Revascularization with DES for Erectile Dysfunction

Evolution of novel endovascular therapies has broadened treatment to pts previously without options

- Improvements in procedural safety and efficacy have lowered interventional threshold for complex PAD, CLI
- "Enabling" technologies and techniques have revolutionized treatment paradigm of PAD

Issue is to focus on not what can be done, but what should be done, with emphasis on modifying cardiovascular risk