Outcomes of BTK lesions and future directions

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Typical randomized device trial construct

1. The new device is compared to the existing standard of care device/surgery/medicine

2. A primary outcome endpoint is chosen not only to reflect the strengths of the new device, but also for clinical relevance

3. The endpoint will have a pre-specified time course
   a) Occasionally the time course will be driven by number of events and therefore be unspecified

4. An expected performance level of each therapy is determined, and then a clinically relevant *delta* between them is chosen. The statistics around these assumptions will drive trial size

5. Population heterogeneity, and confounding, is minimized
Prior relevant studies
CLI: Cutting Balloon PTA

- CTA of popliteal and infrapopliteal vessels in 73 pts with CLI
- Adjunctive stenting: 20%
- One year: no surgical bypass
- Limb salvage at 1 year: 89.5%

Ansel et al: CCI 2004
BTK Chill

- 115 limbs/108 patients Rutherford 4-6 treated with Cryoplasty
  - Infra-popliteal vessels between 2.5 and 5.0 mm
- Results:
  - 97% acute success
  - One-year TLR 21%
  - Overall 6 month and 1 year major amputation-free survival: 93% and 85%

<table>
<thead>
<tr>
<th></th>
<th>MAmp</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>R4:</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>R5:</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>R6:</td>
<td>40%</td>
<td>32%</td>
</tr>
<tr>
<td>+DM:</td>
<td>20%</td>
<td>9%</td>
</tr>
<tr>
<td>-DM:</td>
<td>4%</td>
<td>11%</td>
</tr>
</tbody>
</table>
BTK CHILL: Observations vis-à-vis trial design

- TLR rate acceptable, but likely restenosis rate ~40%
- Significant disparity in outcomes depending on Rutherford class, diabetes
LACI Phase 2 Registry

Laser Angioplasty for Critical Limb Ischemia

• Prospective, multi-center study

• Patients with CLI
  ▪ Rutherford Category 4-6

• Treatment:
  ▪ ELA of SFA, popliteal and/or infrapopliteal arteries
  ▪ Optional adjunctive PTA and stenting

• Primary Endpoint:
  ▪ limb salvage (freedom from amputation at or above the ankle) at 6 months
### LACI 2: Descriptors

| 155 limbs |
|-----------------|-
| **Rutherford Category** |    |
| 4                | 29% |
| 5 or 6           | 71% |
| **Reasons for poor surgical candidacy** |    |
| Absence of venous graft | 32% |
| Poor/no distal vessel | 68% |
| High surgical risk  | 46% |
| Only one reason    | 61% |
| Any two reasons    | 33% |
| All three reasons  | 6%  |
LACI 2: Vascular lesion locations

% of Identified Lesions

- SFA
- Popliteal
- Infrapopliteal
- Other
## LACI 2 - Procedure Results

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidewire crossing success</td>
<td>92%</td>
</tr>
<tr>
<td>Laser treatment delivered</td>
<td>99%</td>
</tr>
<tr>
<td>Adjunctive balloon</td>
<td>96%</td>
</tr>
<tr>
<td>Stent Placement</td>
<td>45%</td>
</tr>
<tr>
<td>Procedure Success</td>
<td>85%</td>
</tr>
<tr>
<td>&lt;50% residual stenosis at final</td>
<td></td>
</tr>
<tr>
<td>Straight line flow to foot</td>
<td>89%</td>
</tr>
<tr>
<td>established</td>
<td></td>
</tr>
<tr>
<td>Hospital stay (days):</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>3.0</td>
</tr>
<tr>
<td>median</td>
<td>1.0</td>
</tr>
</tbody>
</table>
## LACI 2: 6-Month Results

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total enrollment</td>
<td>155</td>
</tr>
<tr>
<td>Death</td>
<td>17 (11%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>11 (7%)</td>
</tr>
<tr>
<td>Reached 6-month follow-up</td>
<td>127</td>
</tr>
<tr>
<td>Major amputation</td>
<td>9 (7%)</td>
</tr>
<tr>
<td>Survival with limb salvage</td>
<td>118/127 = 93%</td>
</tr>
</tbody>
</table>
LACI 2: Observations vis-à-vis trial design

- Six month outcomes non-standard time course (12 months)
- CLI represents complex disease: multiple stenoses, heterogeneous vascular distribution and occlusions
- High risk patient population with high drop-out due to mortality
- Good limb salvage rate despite this high-risk patient cohort
- Incidence of surgical intervention is very low
BASIL trial
Bypass vs. angioplasty in Severe Ischemia of the Leg

- 452 patients with CLI due to infra-popliteal disease randomized to endovascular or surgical bypass (in patients with good vein)
  - 1999-2004
  - 30 day mortality low for both

  - Surgery with more infection and MI

  - Surgery with greater 1 year costs
    - PTA TVR: 28% v. 17% at 12 months
    - No differences at 2 year but trend favoring surgery at 5 years

Lancet 2005; 366: 1925–34
BASIL Results: AFS

Figure 2: Amputation-free survival after bypass surgery and balloon angioplasty

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number at risk</th>
<th>0 years</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
<th>4 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioplasty</td>
<td>224</td>
<td>149</td>
<td>100</td>
<td>51</td>
<td>19</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>228</td>
<td>148</td>
<td>108</td>
<td>64</td>
<td>23</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Survival (%) vs. Time after randomisation (years)
Observations from BASIL

- Comparing with a surgical standard, endovascular approach to CLI is a reasonable alternative for the endpoint of limb salvage
Mets-analysis: 12 month limb-salvage

J Vasc Surg 2008;47:975-81
Data from meta-analysis of infra-popliteal intervention for CLI

Table II. Meta-analysis results of crural percutaneous transluminal angioplasty and popliteal-to-distal bypass

<table>
<thead>
<tr>
<th>Result</th>
<th>1 month</th>
<th>6 months</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary patency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTA</td>
<td>77.4 ± 4.1</td>
<td>68.0 ± 7.0</td>
<td>58.1 ± 4.6</td>
<td>51.3 ± 6.6</td>
<td>48.6 ± 8.0</td>
</tr>
<tr>
<td>Bypass</td>
<td>93.3 ± 1.1</td>
<td>85.8 ± 2.1</td>
<td>81.5 ± 2.0</td>
<td>76.8 ± 2.3</td>
<td>72.3 ± 2.7</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Secondary patency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTA</td>
<td>83.3 ± 1.4</td>
<td>74.4 ± 1.1</td>
<td>68.2 ± 5.9</td>
<td>65.5 ± 8.1</td>
<td>62.9 ± 11.0</td>
</tr>
<tr>
<td>Bypass</td>
<td>94.9 ± 1.0</td>
<td>86.1 ± 1.6</td>
<td>85.9 ± 1.9</td>
<td>81.6 ± 2.2</td>
<td>76.7 ± 2.9</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Limb salvage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTA</td>
<td>93.4 ± 2.3</td>
<td>88.2 ± 4.4</td>
<td>86.0 ± 2.7</td>
<td>83.8 ± 3.3</td>
<td>82.4 ± 3.4</td>
</tr>
<tr>
<td>Bypass</td>
<td>95.1 ± 1.2</td>
<td>90.9 ± 1.9</td>
<td>88.5 ± 2.2</td>
<td>85.1 ± 2.5</td>
<td>82.3 ± 3.0</td>
</tr>
<tr>
<td>Patient survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTA</td>
<td>98.3 ± 0.7</td>
<td>92.3 ± 5.5</td>
<td>87.0 ± 2.1</td>
<td>74.3 ± 3.7</td>
<td>68.4 ± 5.5</td>
</tr>
<tr>
<td>Bypass</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Notes:
- NA: Not applicable
- P values are shown for significant differences.
1. The new device is compared to the existing standard of care device/surgery/medicine

- The standard of care in critical limb ischemia is bypass surgery, except when it isn’t:
  - Amputation is still prevalent
  - As many as 45% of patients with CLI do not have suitable ipsilateral GSV
  - The BASIL/LACI trial demonstrated both a mixed lesion location and “primitive” PTA
    - Majority of patients had SFA, 62% had infra-popliteal, PTA
    - 20% initial failure rate
  - BASIL demonstrated parity between the surgical standard, when it was available

## Vascular Surgical Trends: A Changing Standard of Care

Revascularization Procedures by Vascular Surgery 2002-4

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endo</td>
<td>82</td>
<td>123</td>
<td>207</td>
<td>+152%</td>
</tr>
<tr>
<td>Bypass</td>
<td>218</td>
<td>219</td>
<td>144</td>
<td>-34%</td>
</tr>
</tbody>
</table>

Geraghty et al MVSS 2005
3. A primary outcome endpoint is chosen not only to reflect the strengths of the new device, but also for clinical relevance.

The most relevant clinical endpoint is amputation-free survival/limb salvage, but does not highlight the strengths of a device which improves patency.

3a. The endpoint has a pre-specified time course.

A 1-year time course appears to be most appropriate.

• Although this may not be long enough to highlight a patency advantage.
4. An expected performance level of each therapy is determined, and then a clinically relevant \textit{delta} between them is chosen. The statistics around these assumptions will drive trial size.

- Problem #1: Endovascular \textit{limb-salvage} rates are not significantly differentiated between therapies thus far.
- Problem #2: Endovascular \textit{patency} data is limited, but suggests that the relationship to limb-salvage is only moderate.
5. Population heterogeneity, and confounding, is minimized

- Inclusion of Rutherford classes 4-6 leads to heterogeneity in outcomes
  - As demonstrated in LACI 2

- Both LACI and BASIL demonstrated significant lesion location heterogeneity

- Even assuming intervention is limited to infra-popliteal vessels, considerable variability in patterns of disease exist
Patterns of infra-popliteal anatomy in CLI: what to allow in studies?

- Stenosis/occlusion of the distal popliteal/TP trunk
- Stenosis of multiple vessels
- Occlusions of 1 or 2 vessels with diseased remaining vessel to foot
  - Last remaining vessel is the peroneal which incompletely collateralizes AT/PT at the ankle
- Patent single AT or PT to the foot, but incomplete plantar arch results in ischemic dermatomes
Summary of challenges

• Evolving standard of care away from surgery
• The established primary endpoint is not well defined, not well described according to patency, and not well differentiated
• Time course of follow-up may be too short to establish value of patency
  - Possible reformation of wounds is countered by subject deaths
• Marked heterogeneity in various aspects of CLI intervention
• Above combine to make statistical assumptions less well defined, thus requiring more patients, longer trials, and making success less certain
Possible solutions

- Combine limb-salvage with another meaningful endpoint (e.g., patency, wound healing)
- Be prescriptive regarding intervention to reduce heterogeneity
  - Vessel location
  - Number of vessels
  - Specify allowed anatomy
  - Limit Rutherford class inclusions
- These will increase time course of enrollment, but should allow proof of the value of patency
Overview

- Infra-popliteal anatomy and implications
- Critical limb ischemia definitions
- Importance of limb salvage
  - Consequences of amputation
- Prior interventional results
  - Laser
  - Cryoplasty
  - BASIL
- Randomized trial design challenges
Critical limb ischemia: definitions

- Rutherford classification
  - R4: Resting symptoms
  - R5: Minor tissue loss
  - R6: Major tissue loss

- Fontaine classification
  - FIII: Resting symptoms
  - FIV: tissue loss
Prognosis after amputation

• 2 year mortality rates 40%-50% following major amputation
Overview

• Define the typical trial design for new devices
• Present representative available data on infra-popliteal therapy
• Define unique regulatory challenges based on 3 characteristics of infra-popliteal disease
  - Variability in natural history among classifications
  - Anatomic variability
  - Clinically relevant endpoints
BASIL Results: Mortality

Figure 3: All-cause mortality after bypass surgery and balloon angioplasty