Critical Limb Ischemia: When Outcomes Matter, Design Matters

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Typical randomized device trial design

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%

• R4:	MAmp 0%	Death: 0%
• R5:	MAmp11%	Death: 0%
• R6:	MAmp 40%	Death: 32%
• +DM:	MAmp 20%	Death: 9%
• -DM:	MAmp 4%	Death: 11%

J Endovasc Ther. 2009 Apr;16(2 Suppl 2):II19-30.

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

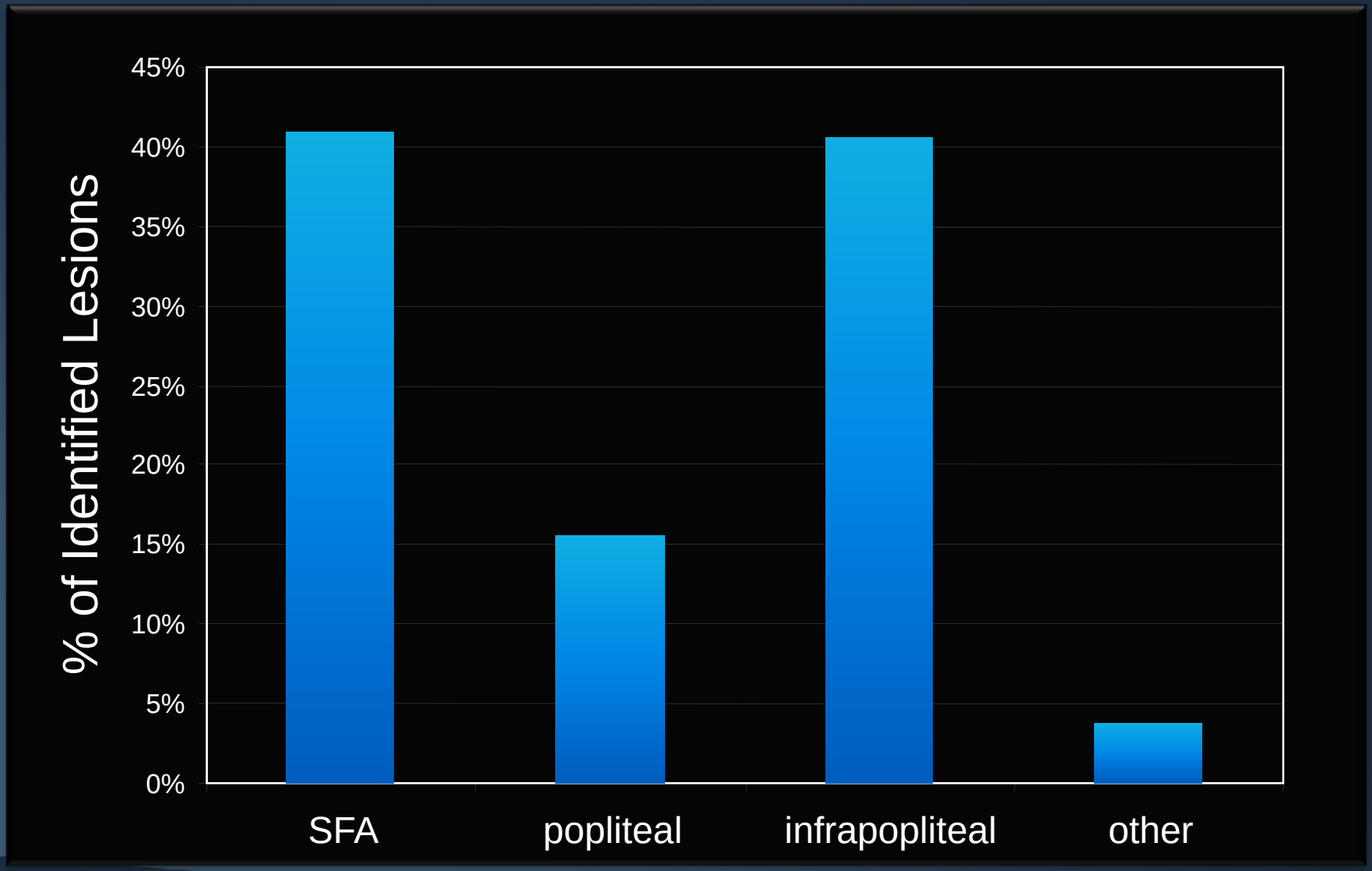
- Prospective, multi-center study
- Patients with CLI
  - Rutherford Category 4-6
- Treatment:
  - ELA of SFA, popliteal and/or infrapopliteal arteries
  - Optional adjunctive PTA and stenting
- Primary Endpoint:
  - limb salvage (freedom from amputation at or above the ankle) at 6 months

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



LACI 2 - Procedure Results

Guidewire crossing success		92%
Laser treatment delivered		99%
Adjunctive balloon		96%
Stent Placement		45%
Procedure Success <50% residual stenosis at final		85%
Straight line flow to foot established		89%
Hospital stay (days):	mean	3.0
	median	1.0

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LACI 2: 6-Month Results

Total enrollment	155
death	17 (11%)
lost to follow-up	11 (7%)
Reached 6-month follow-up	127
Major amputation	9 (7%)
Survival with limb salvage	118/127 = 93%

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

BASIL Results: AFS

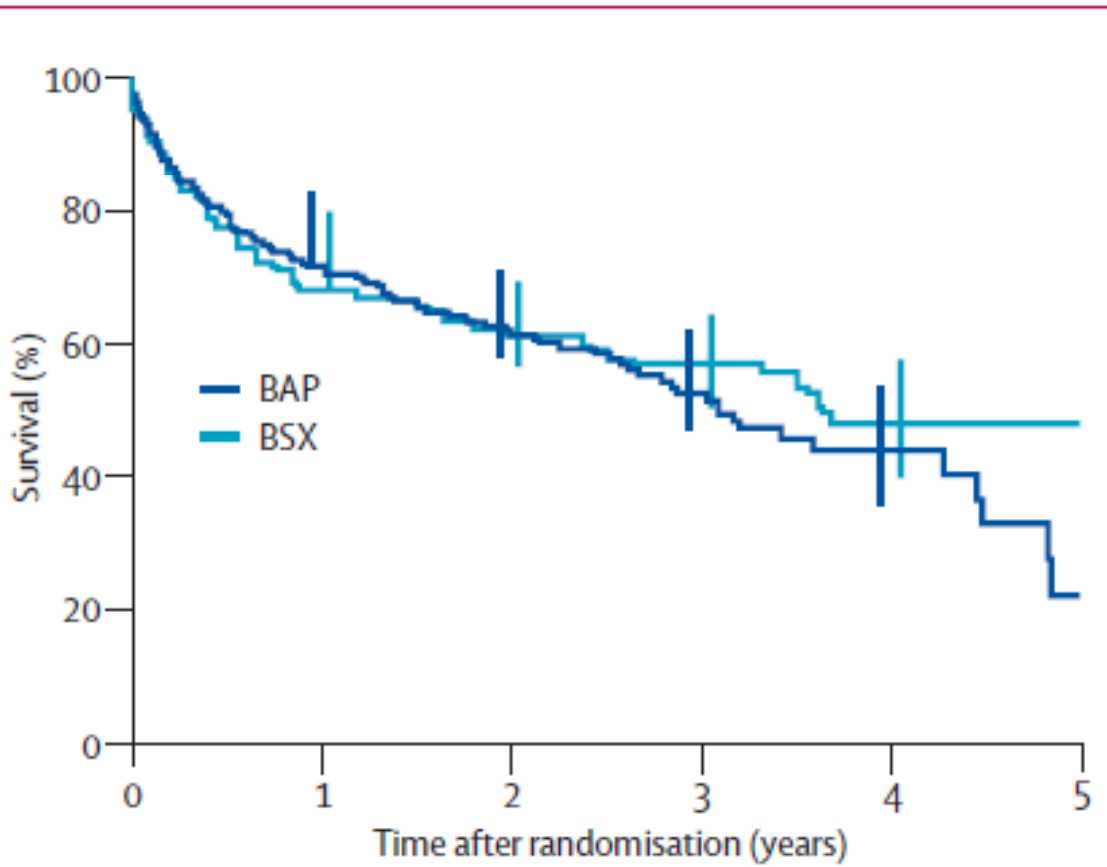
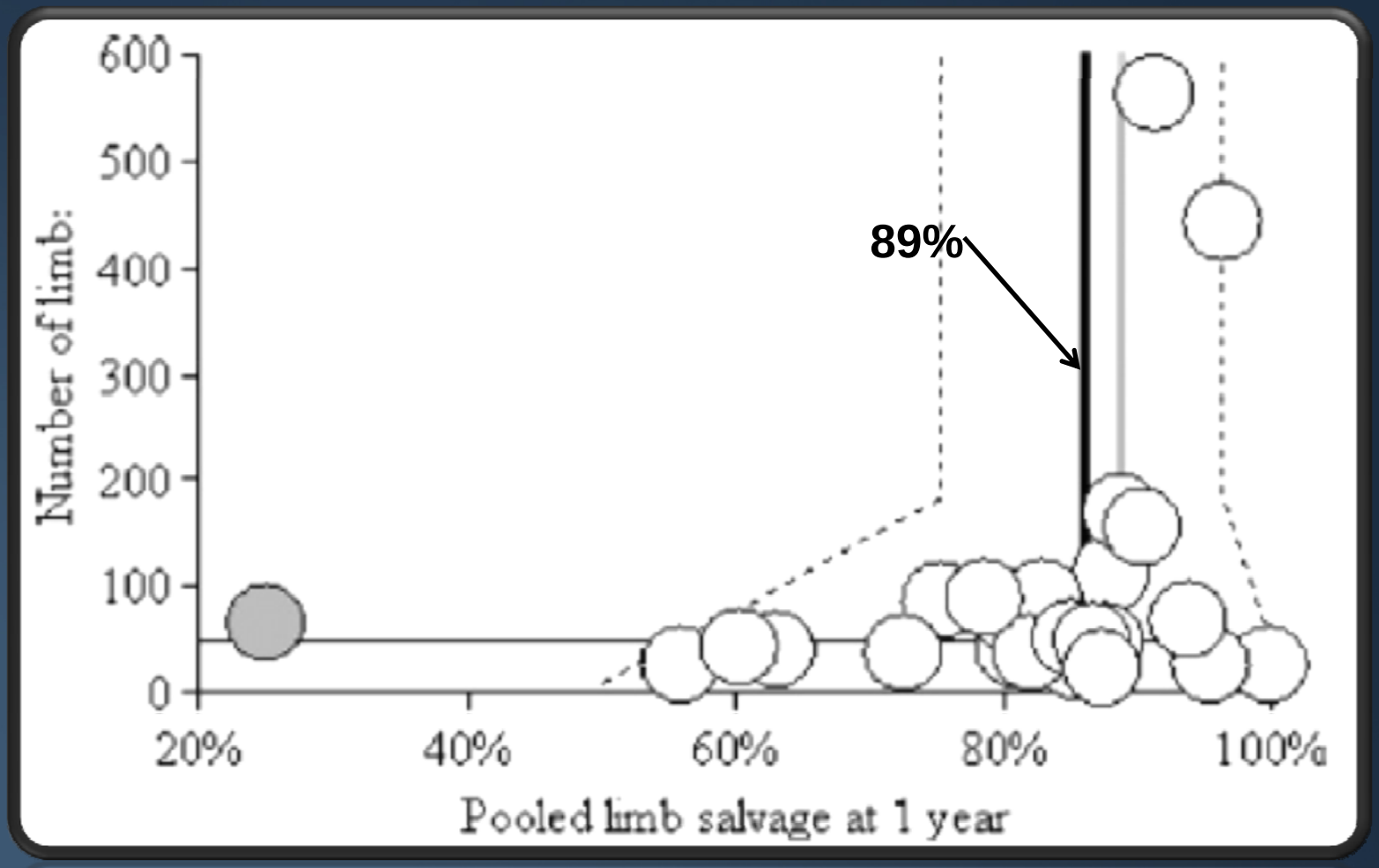


Figure 2: Amputation-free survival after bypass surgery and balloon angioplasty

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[a]

Result	*1 month*	*6 months*	*1 year*	*2 years*	*3 years*
Primary patency					
PTA	77.4 ± 4.1	65.0 ± 7.0	58.1 ± 4.6	51.3 ± 6.6	48.6 ± 8.0
Bypass	93.3 ± 1.1	85.8 ± 2.1	81.5 ± 2.0	76.8 ± 2.3	72.3 ± 2.7
P	<.05	<.05	<.05	<.05	<.05
Secondary patency					
PTA	83.3 ± 1.4	73.8 ± 7.1	68.2 ± 5.9	63.5 ± 8.1	62.9 ± 11.0
Bypass	94.9 ± 1.0	89.3 ± 1.6	85.9 ± 1.9	81.6 ± 2.3	76.7 ± 2.9
P	<.05	<.05	<.05		
Limb salvage					
PTA	93.4 ± 2.3	88.2 ± 4.4	86.0 ± 2.7	83.8 ± 3.3	82.4 ± 3.4
Bypass	95.1 ± 1.2	90.9 ± 1.9	88.5 ± 2.2	85.2 ± 2.5	82.3 ± 3.0
Patient survival					
PTA	98.3 ± 0.7	92.3 ± 5.5	87.0 ± 2.1	74.3 ± 3.7	68.4 ± 5.5
Bypass	NA	NA	NA	NA	NA

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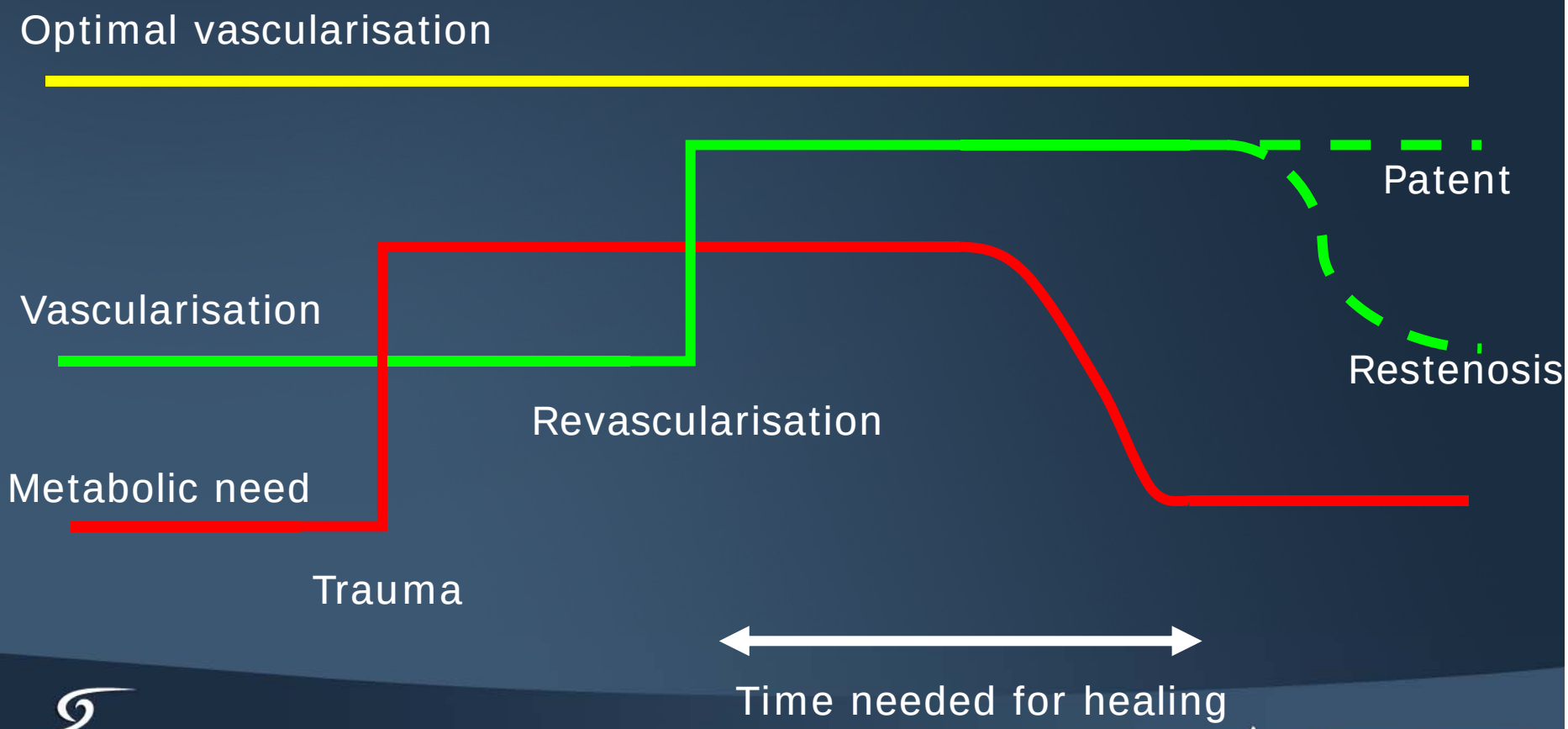
Is long term patency needed for ulcer healing ?



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Vermassen F 2010

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Back to the trial design…

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

Taylor LM et al. J Vasc Surg 1990; 11:193-206
Taylor LM et al. Am J Surg 1987;153:505-10
Holzenbein TJ et al. J Vasc Surg 1996;23:130-40

Vascular Surgical Trends: A Changing Standard of Care

Revascularization Procedures by Vascular Surgery 2002-4

	2002	2003	2004	% change
Endo	82	123	207	+152%
Bypass	218	219	144	-34%

Geraghty et al MVSS 2005

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2. 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

3. 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 *delta* between them is chosen. The statistics around these assumptions will drive trial size

- Problem #1: Endovascular *limb-salvage* rates are not significantly differentiated between therapies thus far
- Problem #2: Endovascular *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

Thank you

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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

Rutherford 5

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

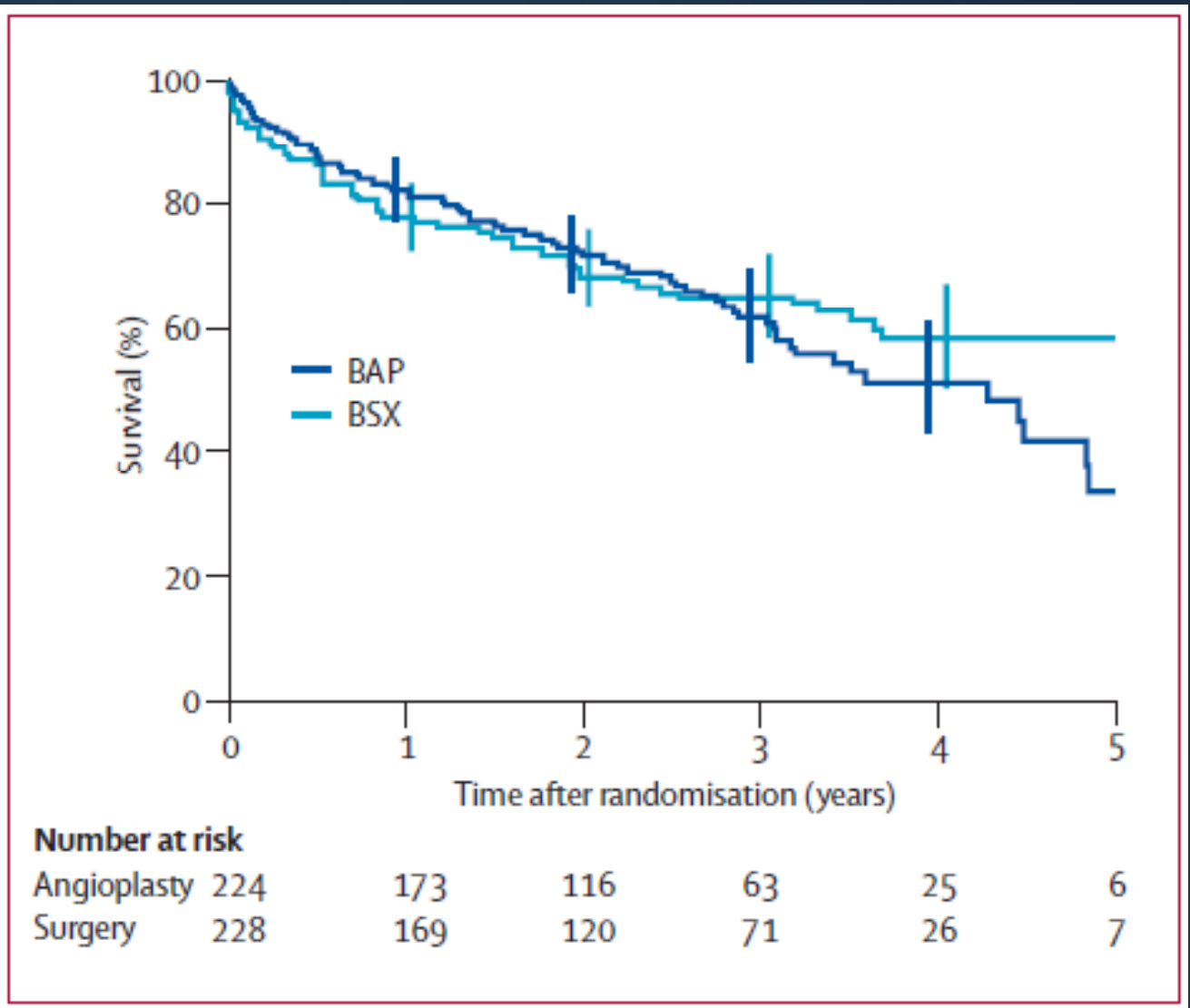

Figure 3: All-cause mortality after bypass surgery and balloon angioplasty

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