Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischemia

Sponsored by the National Heart Lung and Blood Institute
Disclosures

• Trial Co-Chair
  ✯ Supported by NHLBI: 1U01HL107407-01A1

• Merck (Consultant, < $10,000)
• Proteon (Consultant, < $10,000)
BEST-CLI Trial Leadership

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Critical Limb Ischemia (CLI) - Impact

- In the absence of revascularization, limb amputation rate in patients with CLI approaches 40%

- CLI – associated annual mortality exceeds 20%

Hirsch AT et al. J Am Coll Cardiol 2006;47:1239-1312
Trends in PAD Therapy

- Endovascular Interventions
  RR = 3.3;
  95% CI 2.9-3.8

- Lower Extremity Bypass Surgery
  RR = 0.58;
  95% CI 0.5-0.7

Figure 2. Trends in Diagnostic Angiography, Therapeutic Endovascular Interventions, and Lower Extremity Bypass Surgery, 1996-2010

- No. of diagnostic lower extremity angiographic procedures (RR, 1.65 [95% CI, 1.56-1.73])
- No. of endovascular interventions (RR, 4.23 [95% CI, 4.17-4.28])
- No. of lower extremity bypass surgical procedures (RR, 0.39 [95% CI, 0.38-0.41])
One-year and cumulative 2-year costs ($) associated with hospitalizations for vascular reasons, per patient, by baseline PAD class:

*1-year costs based on patients with available 1-year data (N=2137)
Cumulative 2-year costs on patients with available 2 year data (N=1677)
Revascularization Options in CLI
Which is best?
Large RCT’s for Vascular Disease

- **Carotid Endarterectomy**
  - NASCET, ACAS, ACST, VA Trial, ECST, GALA

- **CEA vs Carotid Stent**
  - ACT I, CREST, CASANOVA, EVA 3s, ICSS, SAPPHIRE, SPACE, CAVATAS

- **AAA**
  - ADAM, UK Small AAA

- **AAA vs EVAR**
  - DREAM I and II, EVAR I and II, OVER, ACE, Numerous IDE studies.

- **CLI: Bypass vs Endo**
  - BASIL
Limitations of Current Data

- Retrospective
- Poorly controlled
- Suboptimal endpoints
  - Amputation free survival
  - Target lesion revascularization
  - Target vessel revascularization
  - Patency
- Sponsor bias
- Operator bias
- Inclusion of claudicants
- Short or incomplete follow up
**BASIL Trial**

- **Aim:** To compare outcomes of surgery-first strategy with angioplasty first strategy in patients with CLI

- **Results:**
  - No significant difference in amputation-free survival at >5 year follow-up
  - Trend toward benefit for surgery noted in those patents who survived more than 2 years

- **Limitations:**
  - Underpowered
  - Endovascular therapy limited to angioplasty
  - Lack of lesion standardization
  - Suboptimal primary endpoint

Bradbury A. J Vasc Surg 2010; 51(5 Suppl)5S-17S
THE USE OF ANGIOPLASTY, BYPASS SURGERY, AND AMPUTATION IN THE MANAGEMENT OF PERIPHERAL VASCULAR DISEASE


Abstract. Background. Percutaneous transluminal angioplasty has been adopted widely as a treatment for patients with peripheral vascular disease of the lower extremities. However, the effect of this procedure on the overall management of peripheral vascular disease and on the outcomes of patients has not been clearly delineated. In particular, it is not known whether angioplasty has replaced other treatments for peripheral vascular disease.

Methods. To assess the extent to which angioplasty is used and the associated changes in the surgical management of peripheral vascular disease of the lower extremities, we used data on hospital discharges in Maryland to identify all angioplasty procedures, peripheral bypass operations, and lower-extremity amputations performed for peripheral vascular disease in Maryland hospitals between 1979 and 1989.

Results. We estimate that from 1979 to 1989 the annual rate of percutaneous transluminal angioplasty for peripheral vascular disease of the lower extremities, adjusted for age and sex, rose from 1 to 24 per 100,000 Maryland residents (P<0.0001 by linear regression). Despite this increase in the use of angioplasty, the adjusted annual rate of peripheral bypass surgery also rose substantially, from 32 to 65 per 100,000 (P<0.001), whereas the adjusted annual rate of lower-extremity amputation remained stable at about 30 per 100,000. Total charges for hospitalizations during which a peripheral revascularization procedure was performed increased from $14.7 million in 1979 (in 1989 dollars) to $30.5 million in 1989.

Conclusions. In Maryland, the adoption of percutaneous transluminal angioplasty for peripheral vascular disease of the lower extremities has been associated with an increase in the use of peripheral bypass surgery and with no decline in lower-extremity amputations. These results could be due to increased diagnosis of peripheral vascular disease, expanded indications for procedural interventions, or an increased number of repeat procedures performed in patients with peripheral vascular disease of the lower extremities. (N Engl J Med 1991; 325:556-62.)
Definition of Clinical Equipoise

“A state of honest, professional disagreement amongst the community of experts about the preferred treatment”


- Individual Equipoise: Personal declaration that equipoise exists
- Community Equipoise: Offsetting discordance in choice of competing therapies
69 yo F, plantar heel ulcer, L TBI .25, “good vein”
69 yo F, plantar heel ulcer, L TBI .25, “good vein”
75 yo F with non-healing ulcer
75 year old diabetic woman

- Right toe gangrene
- Absent distal pulses
- R ABI: 0.3
Critical Limb Ischemia: % Treated by Bypass (vs. PVI)

All VQI Centers Mean = 31%

Procedure Selection Variation

0% Bypass

100% Bypass
Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia
To compare treatment efficacy, functional outcomes and cost in patients with CLI undergoing best open surgical or best endovascular revascularization.
BEST-CLI Trial: Overview

- Prospective, randomized, multicenter, open label superiority trial

- **2100 patients** at **120 clinical sites** in United States and Canada

- Multi-year trial with each patient having minimum of 2 year follow-up

- Funded by National Heart Lung and Blood Institute at level of $24,990,000
Two Cohort Design

- **Cohort #1** Patients with single segment great saphenous vein (SSGSV) N=1620
  
  Open surgery vs. Endovascular treatment

- **Cohort #2** Patients without SSGSV (if randomized to OPEN conduit may include arm vein, short saphenous vein, composite vein, cryopreserved vein, and prosthetic conduit) N=480
  
  Open surgery vs. Endovascular treatment
Stratification

- Clinical Presentation
  - ischemic rest pain vs. tissue loss

- Arterial Anatomy
  - presence or absence of significant tibial disease
Definition of “Best Treatment” is left to the investigator.

All commercially available endovascular therapies allowed as long as accepted as standard of care.
  • Investigational Device Exemption (IDE) granted by the FDA

All surgical bypass techniques and conduits allowed.

New and evolving therapies will be critically reviewed as trial progresses to determine if suitable for inclusion.
  • Technology Assessment Committee
MALE defined as:

- Above ankle amputation
- **Major** re-intervention
  - new bypass graft
  - jump/interposition graft revision
  - thrombectomy/thrombolysis

Major Adverse Limb Event (MALE) – free survival
РAS defined as:

Above ankle amputation

**Major** re-intervention

**Minor** re-intervention
- patch angioplasty
- balloon angioplasty
- atherectomy
- stent/stentgraft

Re-intervention and Amputation (RAS)-free Survival
Key Secondary Endpoints

- Amputation-free Survival
- MALE-POD (Post-Operative Death within 30 days of index procedure)
Selected Clinical Secondary Endpoints

- Freedom from hemodynamic failure
- Freedom from clinical failure
- Freedom from critical limb ischemia
Additional Clinical Secondary Endpoints

- Number of re-interventions per limb salvaged
- Freedom from secondary interventions (major and minor) in index leg
- Freedom from POD
- Freedom from all cause mortality
- Freedom from myocardial infarction
- Freedom from stroke
Safety Endpoints

- **Serious Adverse Events**
- MACE at 30 days post-procedure:
  - Death
  - Myocardial infarction
  - Stroke
- Non-serious adverse events – from randomization through 30 days post-procedure
- Perioperative complications
Comparative Effectiveness: BEST-CLI

Target Population

Randomize

Intervention

Control

Trial Completion

Lifetime

MEASUREMENT

MODELING
BEST-CLI aims to quantify:

- All financial costs of care
  - Hospital care (index admission and all f/u)
  - Outpatient care
  - Rehabilitation
- Functional status / quality of life measures
  - EQ5D as main measure; also SF-12
Cost-Effectiveness Endpoints

- Treatment-associated costs (in- and out-patient)
- Incremental CE measured in dollars per quality adjusted life years (QALY)
Functional and QOL Endpoints

- Numerical Rating Scale (NRS) for pain
- VascuQoL
- EuroQoL EQ-5D
- SF-12
- Six-minute walk test (subset of sites)
Collaboration

Inclusive of all specialists who treat CLI:

- Interventional Cardiologists
- Interventional Radiologists
- Vascular Medicine Specialists
- Vascular Surgeons
144 Interventional Cardiologists

93 of 120 sites are multi-disciplinary – 78%

2 Cardiothoracic Surgeons
BEST-CLI Investigators

- 144 Cardiologists
- 116 Radiologists
- 4 Vascular Medicine Specialists
- 510 Vascular Surgeons
- 2 Cardiothoracic Surgeons
Map of BEST-CLI Sites
Endorsements

- Society of Vascular Surgery (SVS)
- Society of Interventional Radiology (SIR)
- Society of Vascular Medicine (SVM)
- Vascular Disease Foundation (VDF)
- Society for Cardiovascular Angiography & Interventions (SCAI)
- Vascular Interventional Advances (VIVA)
- Food and Drug Administration (FDA)
Enrollment

- 1st patient randomized August 28, 2014
- 104 of 120 sites activated
- 185 subjects randomized
N = 27/64
Summary

The BEST-CLI Trial aims to:

- Assess the role of infrainguinal bypass with optimal conduit
- Assess the role of bypass when optimal conduit is not available
- Assess comparative QOL and cost effectiveness
- Assess outcomes of revascularization as it relates to presence of tibial disease, clinical presentation, gender, race, age, diabetes, heel ulcer, renal dysfunction
- Prospectively validate the SVS WIFI classification and OPG endpoints
- Relate comparative hemodynamic outcomes of revascularization to clinical outcomes
- in synergy with BASIL 2 and BASIL 3...

Define an evidence-based standard of care
Messaging: Collaboration

- Secondary goal:
  - Move beyond the rancor
  - Move beyond the suspicion
  - Raise the bar of CLI care – through interdisciplinary awareness-raising sharing of skill sets collaboration everyone wins – especially our patients!