BEST-CLI

Best **E**ndovascular vs. Best **S**urgical **T**herapy in Patients with **C**ritical **L**imb **I**schemia

Sponsored by the National Heart Lung and Blood Institute

BWH

BOSTON MEDICAL CENTER
EXCEPTIONAL CARE. WITHOUT EXCEPTION.

MGH 1811

neri
New England Research Institutes

Disclosures

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

- Merck (Consultant, < $10,000)
- Proteon (Consultant, < $10,000)

BEST-CLI Trial Leadership

Clinical Coordinating Center: Brigham and Women's Hospital

Alik Farber	Boston Medical Center
Matthew Menard	Brigham and Women's Hospital
Kenneth Rosenfield	Massachusetts General Hospital
Meaghan Dunn	

Date Coordinating Center: New England Research Institutes (NERI)

Sandra Siami
Susan Assmann

Cost Effectiveness Core: Brigham and Women's Hospital

Jerry Avorn
Niteesh Choudhry

Sponsor: National Heart Lung and Blood Institute (NHLBI)

Diane Reid
George Sopko

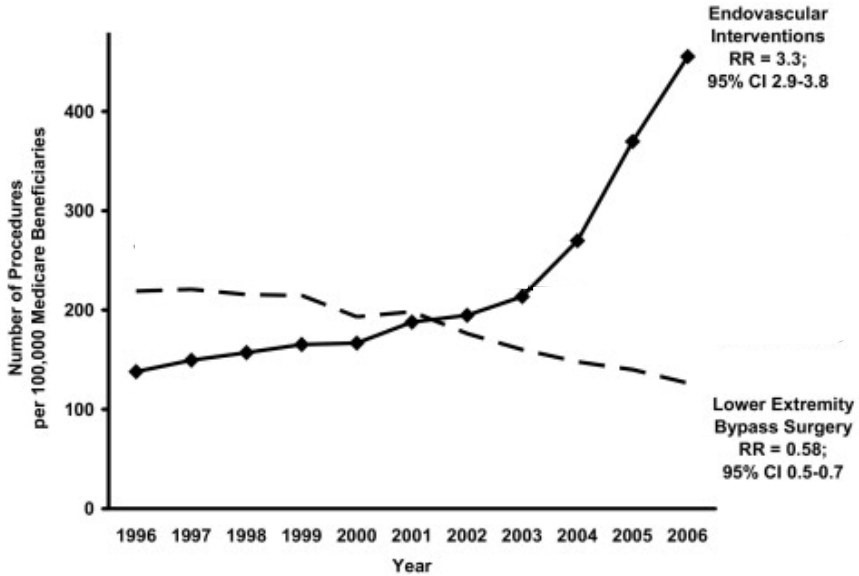
Critical Limb Ischemia (CLI) - Impact

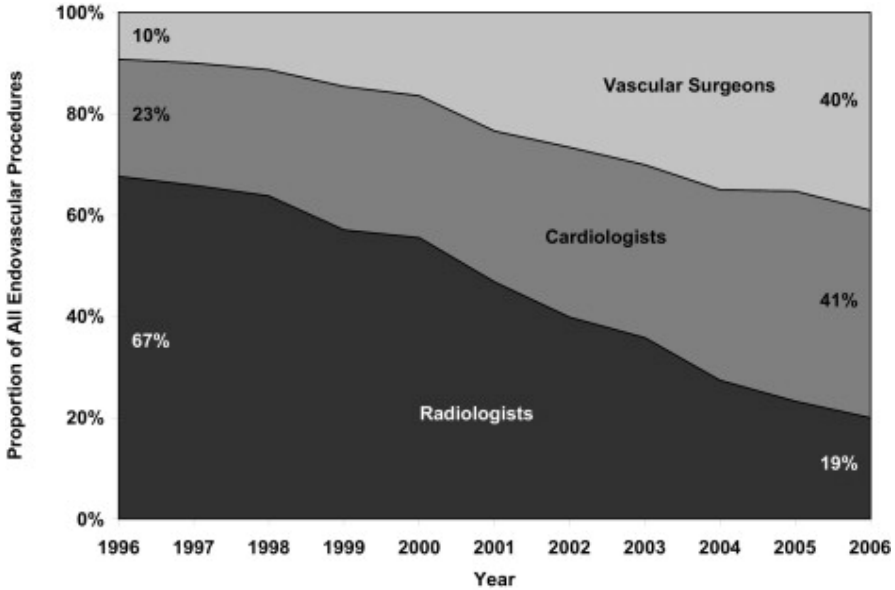
- In the absence of revascularization, limb amputation rate in patients with CLI approaches 40%

- CLI – associated annual mortality exceeds 20%

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

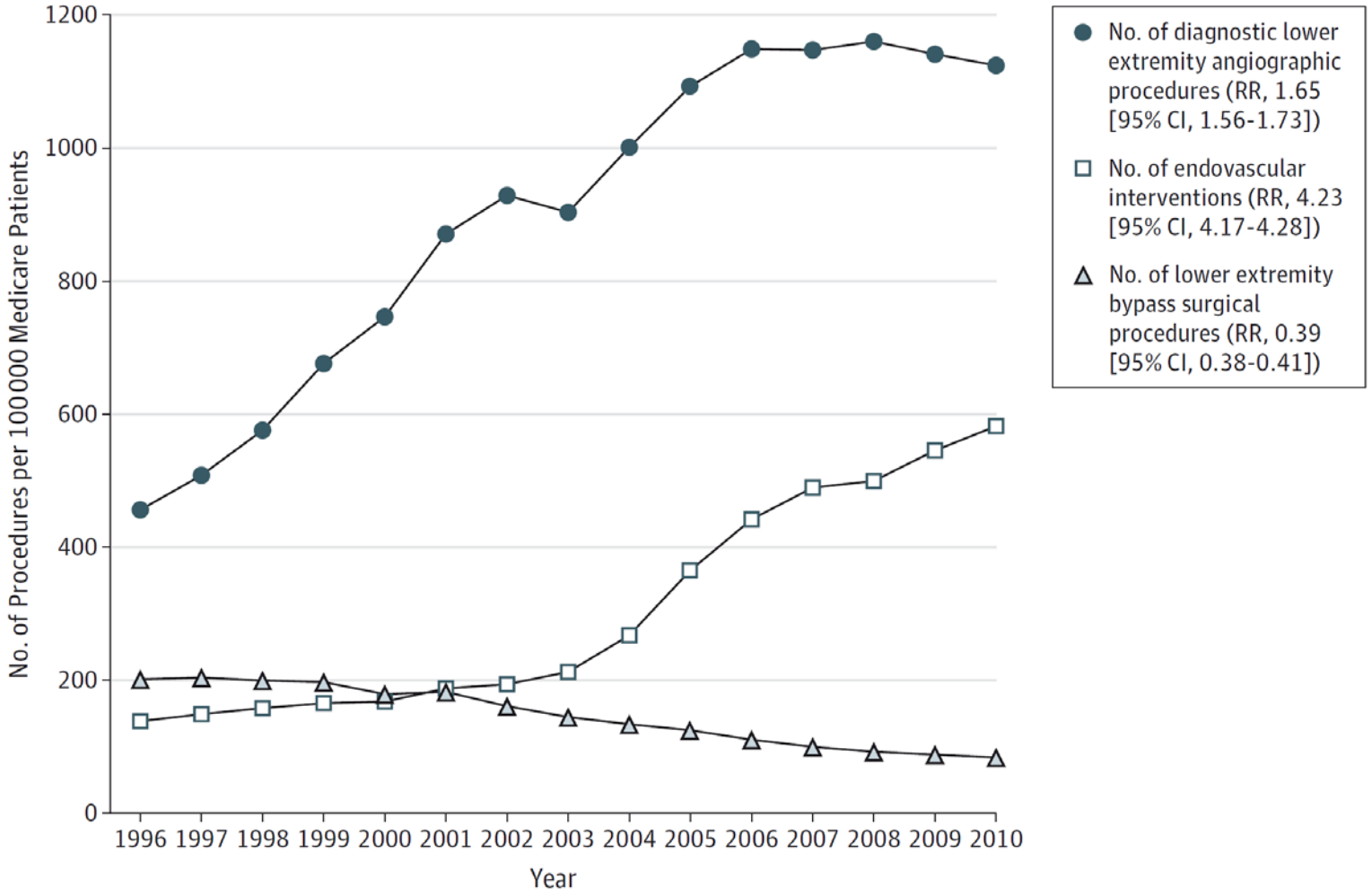
Trends in PAD Therapy





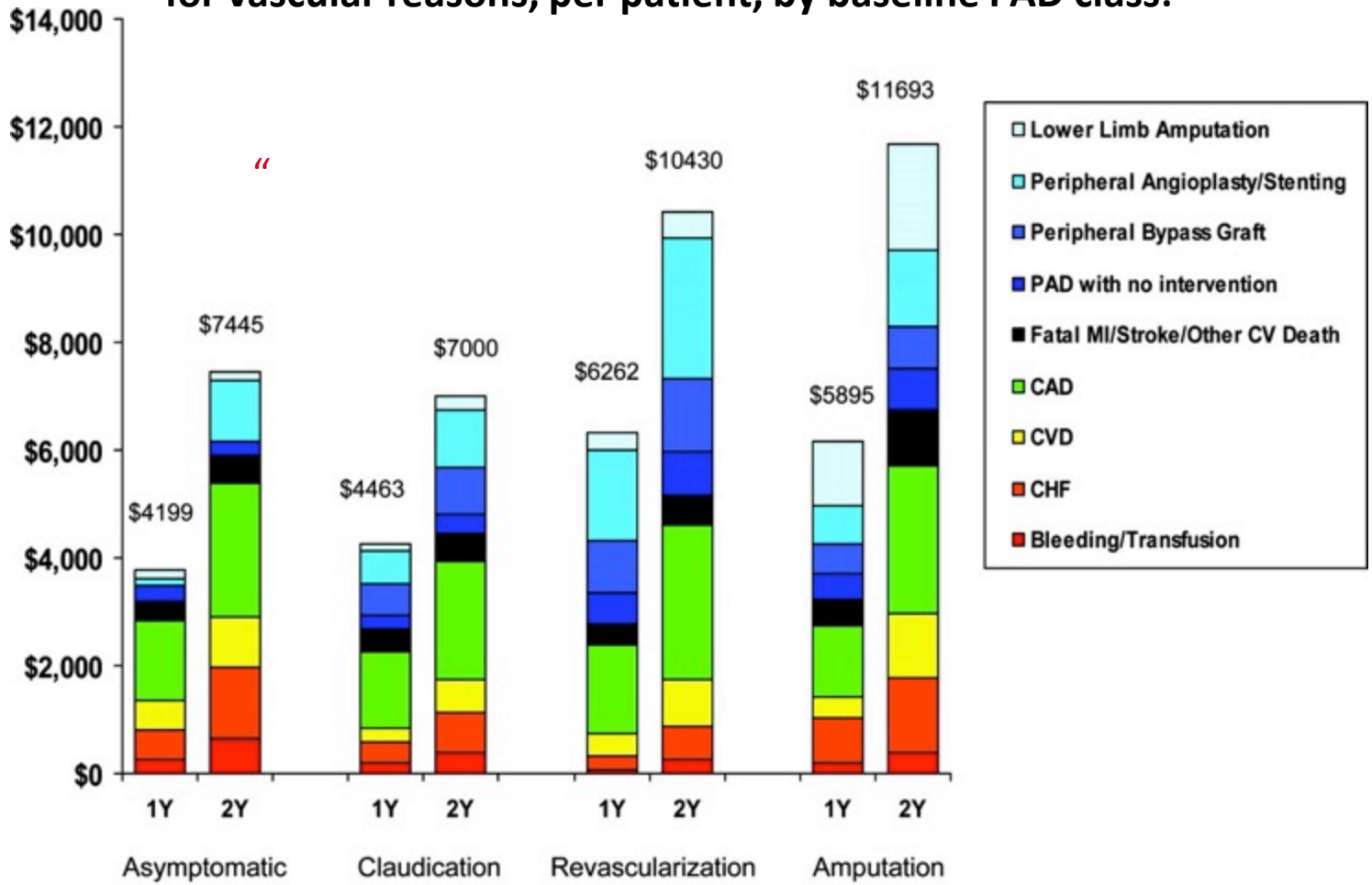
Goodney et al. J Vasc Surg 2009;50:54-60

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



Reach Registry

One-year and cumulative 2-year costs ($) associated with hospitalizations for vascular reasons, per patient, by baseline PAD class:

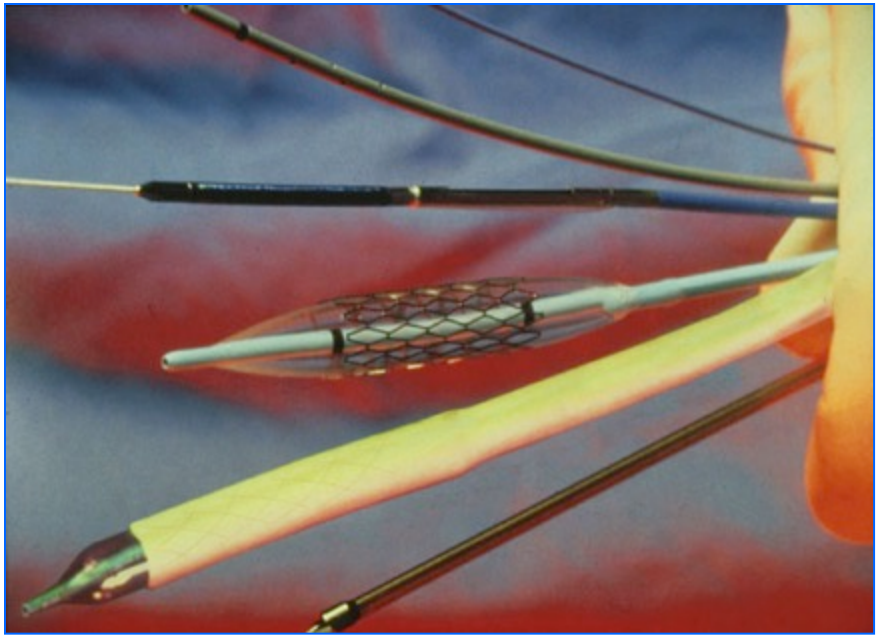


**1-year costs based on patients with available 1-year data (N=2137)*
Cumulative 2-year costs on patients with available 2 year data (N=1677)

Mahoney E M et al. Circ Cardiovasc Qual Outcomes 2010;3:642-651

American Heart Association
Learn and Live

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

Adam DJ. Lancet. Dec 3 2005;366(9501):1925-1934
Bradbury A. J Vasc Surg 2010; 51(5 Suppl)5S-17S

Tunis et al.

BEST-CLI

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

THE USE OF ANGIOPLASTY, BYPASS SURGERY, AND AMPUTATION IN THE MANAGEMENT OF PERIPHERAL VASCULAR DISEASE

SEAN R. TUNIS, M.D., M.SC., ERIC B. BASS, M.D., M.P.H., AND EARL P. STEINBERG, M.D., M.P.P.

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.)

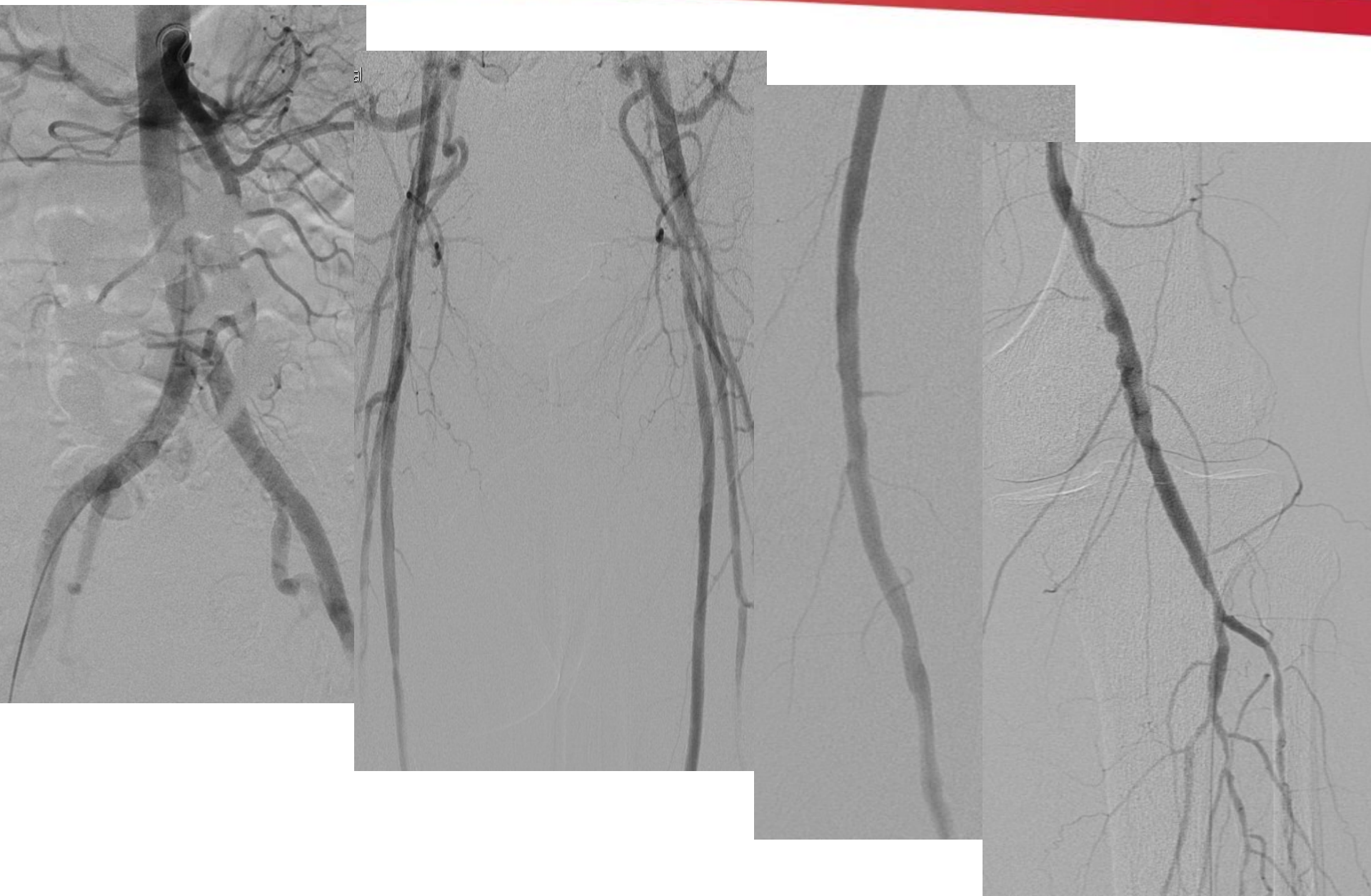
Definition of Clinical Equipoise

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

(Freedman B. Equipoise and the ethics of clinical research. *New England Journal of Medicine* 1987:317: 141-145)

- 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”



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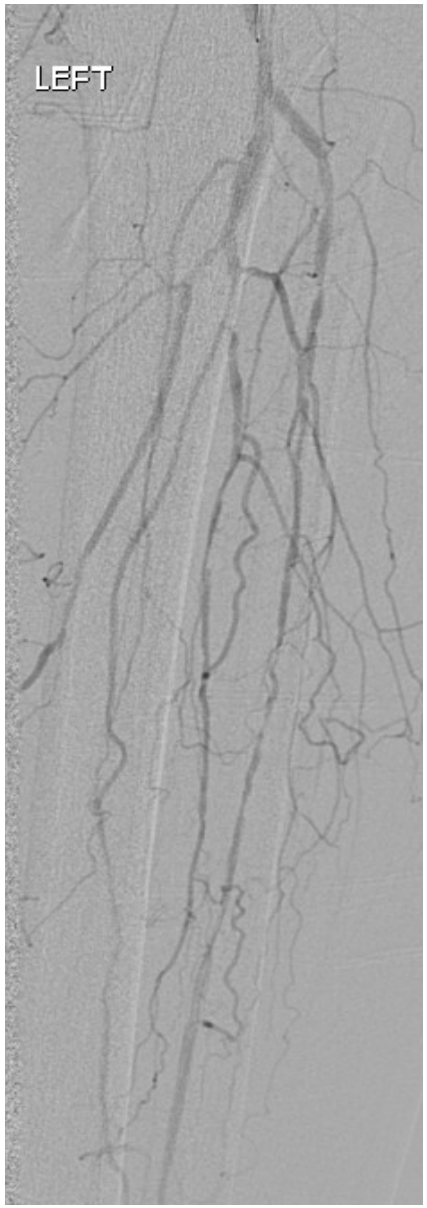
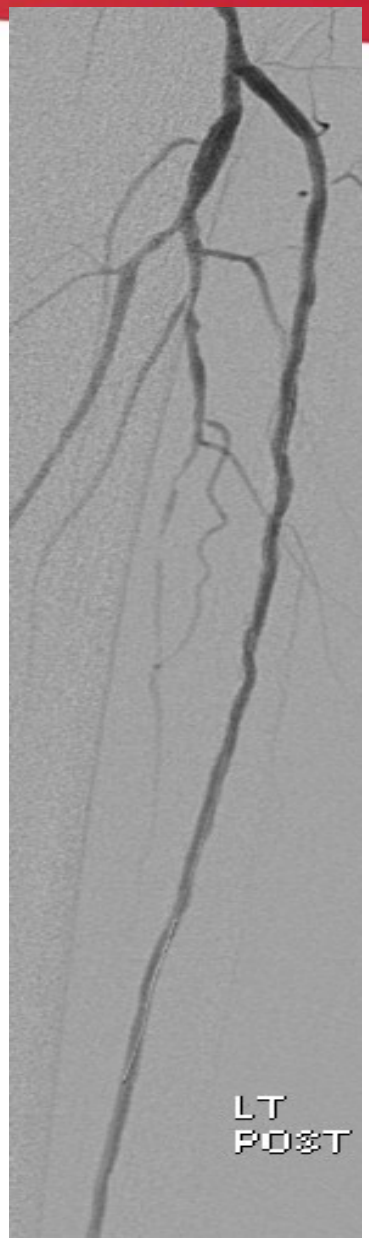
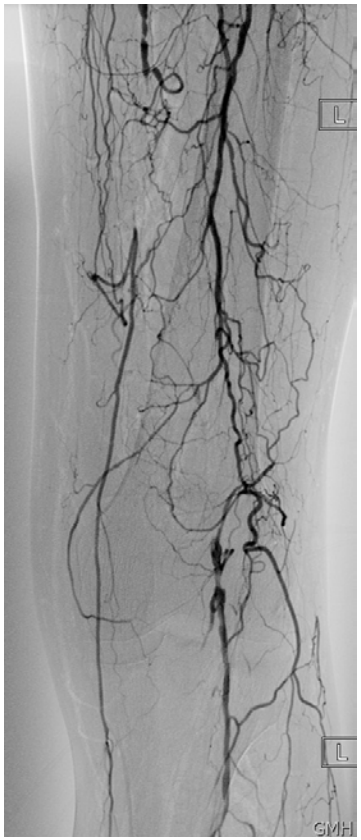
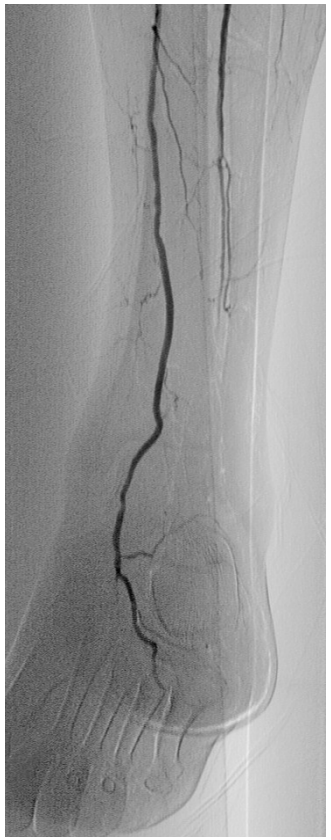




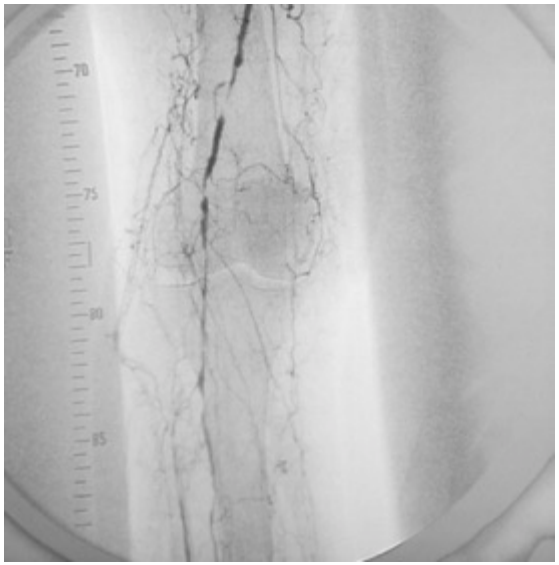
75 yo F with non-healing ulcer





75 year old diabetic woman

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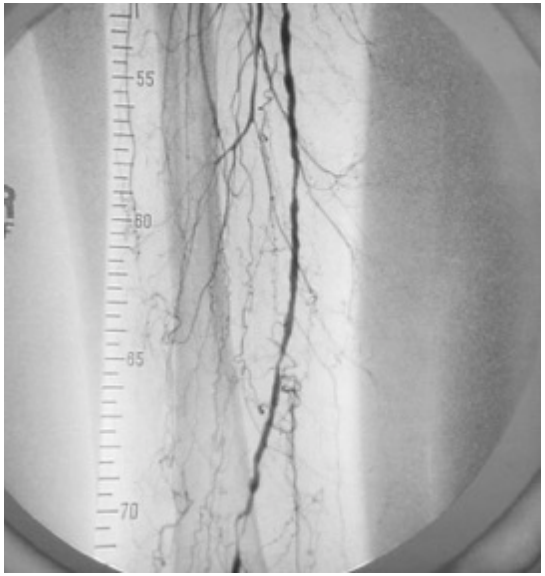
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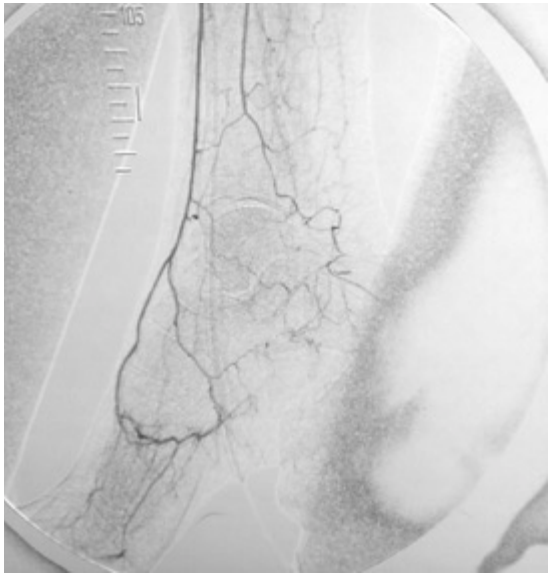
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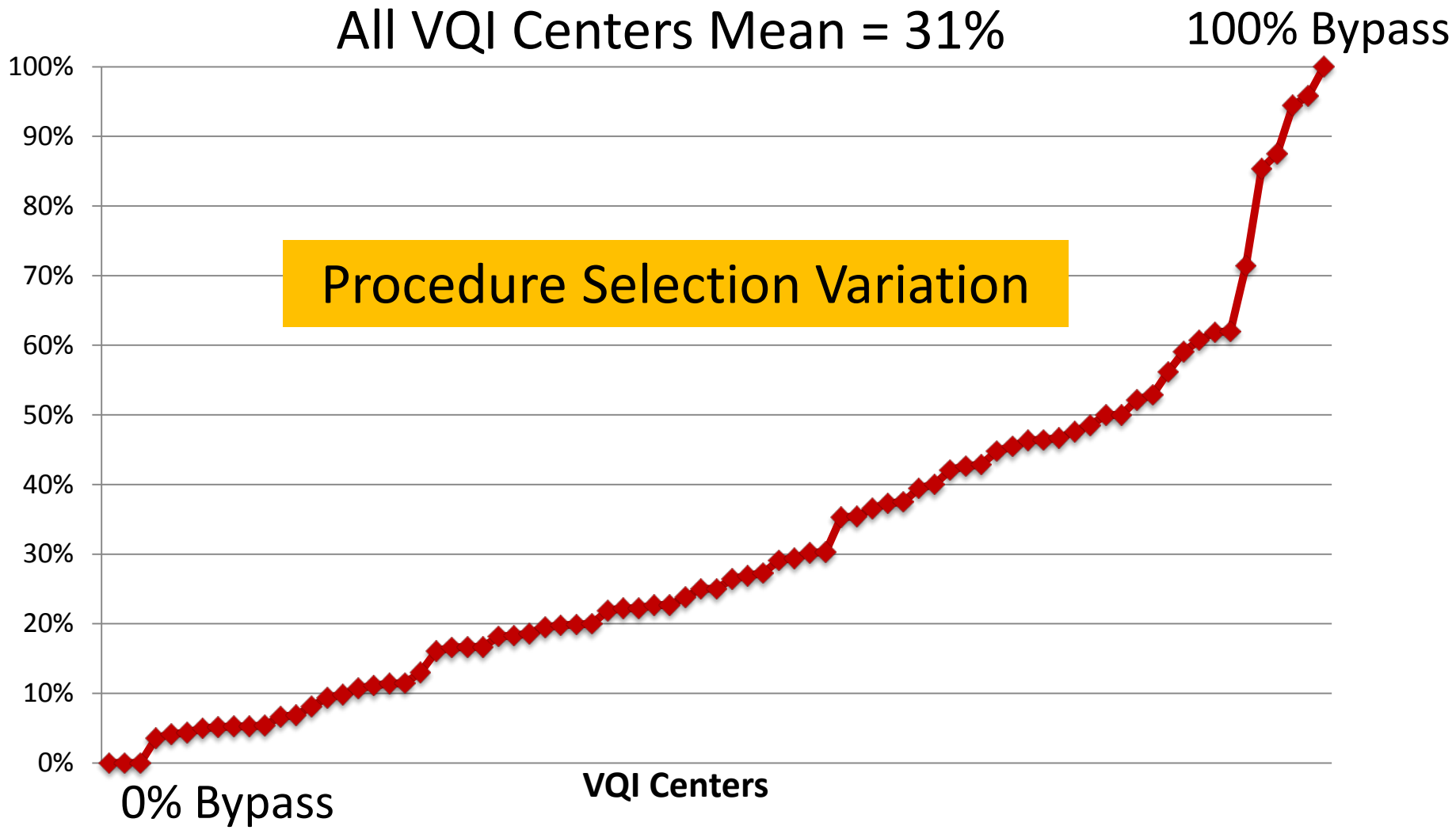
Critical Limb Ischemia: % Treated by Bypass (vs. PVI)



BEST-CLI

Best **E**ndovascular versus Best **S**urgical **T**herapy
in Patients with **C**ritical **L**imb **I**schemia

BEST Trial Objective

BEST-CLI

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 <u>with</u> single segment great saphenous vein (SSGSV) N=1620**

  Open surgery vs. Endovascular treatment

- **Cohort #2 Patients <u>without</u> 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

Pragmatic Trial

BEST-CLI

- **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

Novel Primary Endpoint

Major Adverse Limb Event (MALE) – free survival

MALE defined as:

Above ankle amputation

Major re-intervention

- new bypass graft
- jump/interposition graft revision
- thrombectomy/thrombolysis

Key Secondary Endpoints

Re-intervention and Amputation(RAS)-free Survival

RAS defined as:

Above ankle amputation

Major re-intervention

Minor re-intervention

- patch angioplasty
- balloon angioplasty
- atherectomy
- stent/stentgraft

Key Secondary Endpoints

BEST-CLI

- 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

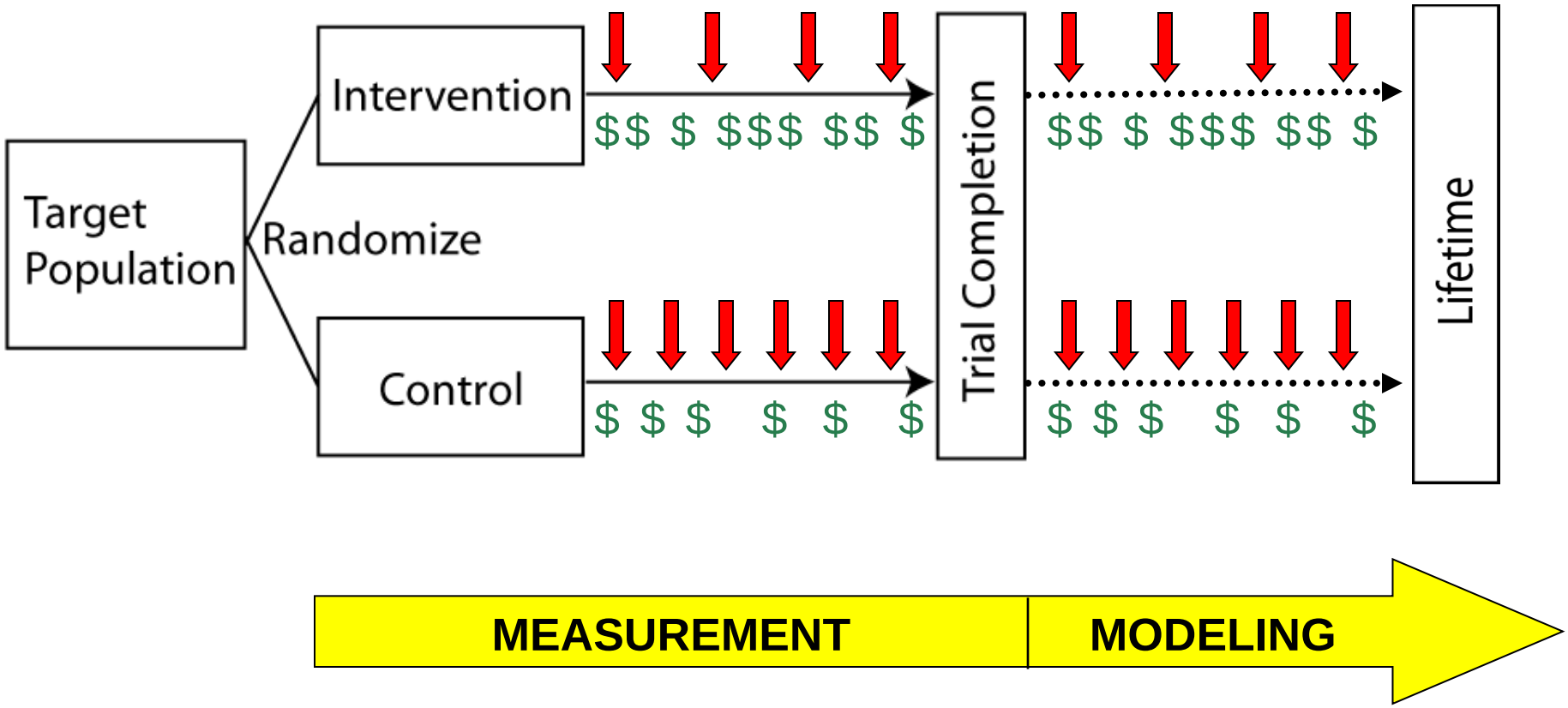
Additional Clinical Secondary Endpoints

- 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



Robust Cost-Effectiveness Analysis

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

BEST-CLI

- 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

BEST-CLI

Inclusive of all specialists who treat CLI:

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

BEST-CLI Investigators

- 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

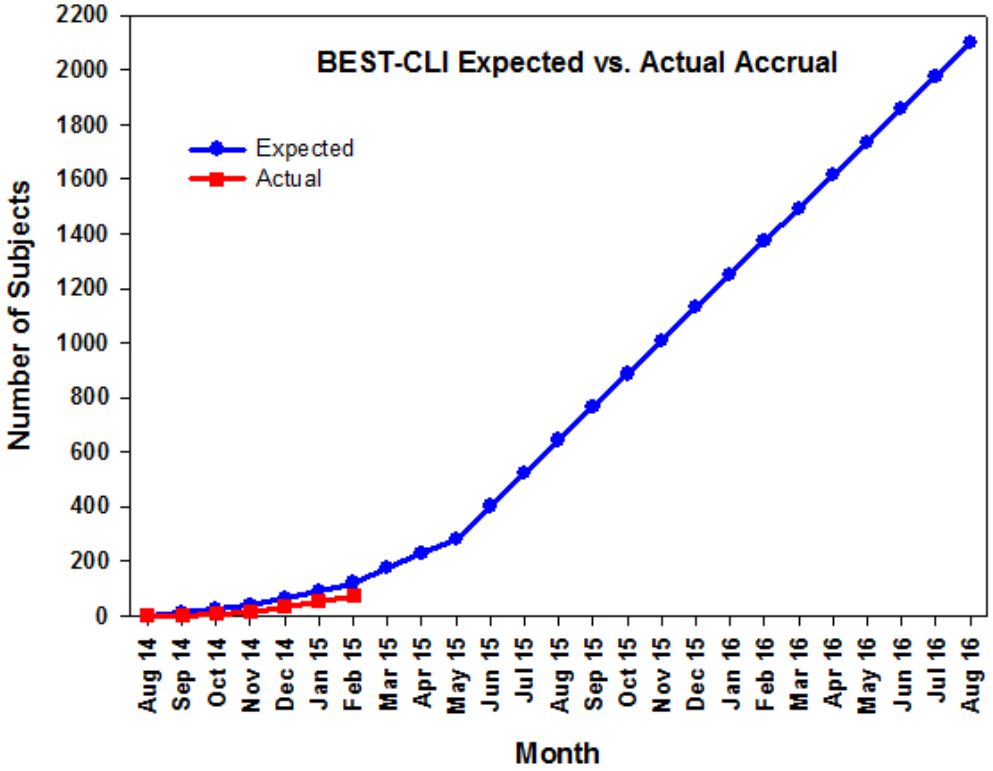
- Society of Vascular Surgery **(SVS)**
- Society of Interventional Radiology **(SIR)**
- Society of Vascular Medicine **(SVM)**
- Vascular Disease Foundation **(VDF)**
- Society for Cardiovascular Angiography & Interventions **(SCAI)**
- Vascular Interventional Advances **(VIVA)**

- Food and Drug Administration **(FDA)**

Enrollment

- 1st patient randomized August 28, 2014

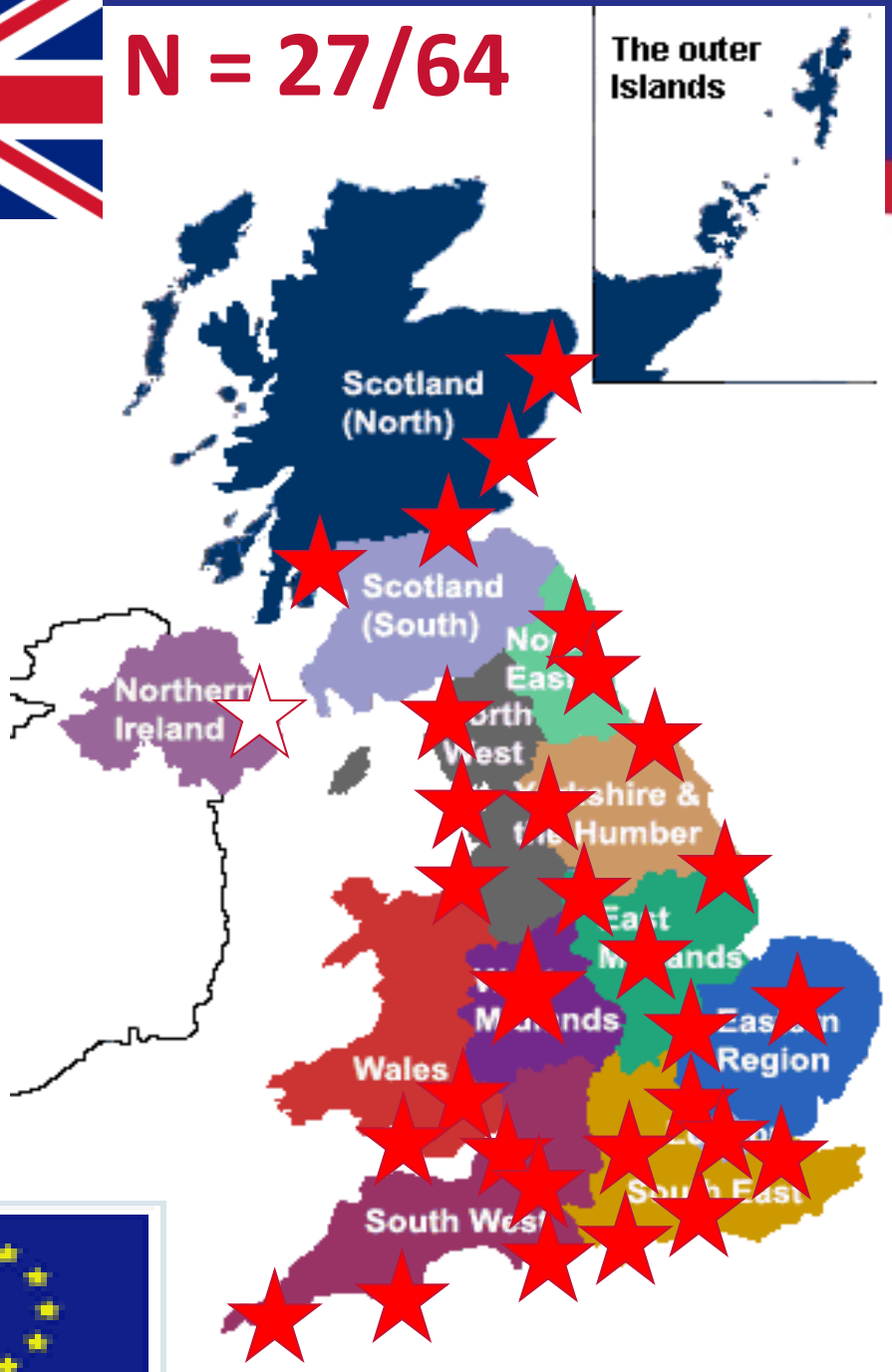
- 104 of 120 sites activated
- 185 subjects randomized

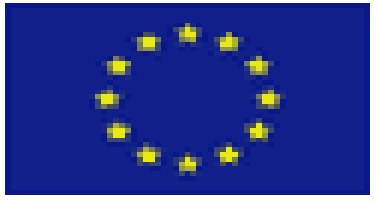


BASIL-2

BASIL-3

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

Define an evidence-based standard of care

- 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…*

Messaging: Collaboration

- Secondary goal:
  - Move beyond the rancor

Raise the bar of CLI care

  - sharing of skill sets
  - collaboration
  - everyone wins – especially our patients!