The BEST-CLI Trial

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Disclosure

Speaker name: Matthew T. Menard

I do not have any potential conflict of interest
# BEST-CLI Trial Leadership

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Natural History of CLI

Critical Limb Ischemia
(Rest Pain, Ulceration or Gangrene)

1-Year Outcomes

Alive with 2 Limbs
45%

Amputation
30%

Mortality
25%

Continued CLI
20%

CLI Resolved
25%

Hirsh et al. JACC. 2006;47:1239-1312.
Trends in PAD Therapy

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])
Endovascular first strategy for de novo TransAtlantic Inter-Society Consensus C and D femoro-popliteal disease: Mid-term outcomes from a single tertiary referral center

Jeffrey Lorne Grenville¹, Kong Teng Tan², Hadas Moshonov² and Dheeraj Kumar Rajan²

Limb Salvage in Patients With Peripheral Arterial Disease Managed by Endovascular First Approach

Kyin Kyin May, MBBS¹,², Peter Ashley Robless, FRCS³, Harvinder Raj Singh Sidhu, FRCS³, Ben Soo Yeng and Pei Ho, FRCS¹,²

Long-term limb salvage and survival after endovascular and open revascularization for critical limb ischemia after adoption of endovascular-first approach by vascular surgeons

Hasan H. Dosluoglu, MD,⁴ Purandath Lall, MBBS,⁴ Linda M. Harris, MD,⁴ and Maciej L. Dryski, MD,⁴,⁵ Buffalo, NY

Endovascular-first approach is not associated with worse amputation-free survival in appropriately selected patients with critical limb ischemia

Karan Garg, MD, Patrick A. Kazubski, BS, Rameen Moridzadeh, BS, Caron B. Rockman, MD, Mark A. Adelman, MD, Thomas S. Maldonado, MD, Frank J. Veith, MD, and Firas F. Mussa, MS, MD, New York, NY

Endovascular first as "preliminary approach" for critical limb ischemia and diabetic foot

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 Treatment Strategy is Best?

Bypass Surgery

Endovascular Therapy
What is current state of evidence
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
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
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 patients 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
Why we need the BEST-CLI Trial!

Peripheral Vascular Disease

Comparative effectiveness of endovascular and surgical revascularization for patients with peripheral artery disease and critical limb ischemia: Systematic review of revascularization in critical limb ischemia

W. Schuyler Jones, MD, a,b Rowena J. Dolor, MD, a,c Vic Hasselblad, PhD, a Sreecanth Vemulapalli, MD, a,b Sumeet Subherwal, MD, a Kristine Schmit, MD, a,c Brooke Heidenfelder, PhD, a,c and Manesh R. Patel, MD a,b

...paucity of high-quality data available to guide clinical decision making....

Conclusions The currently available literature suggests that there is no difference in clinical outcomes for patients with CLI treated with endovascular or surgical revascularization. There is a paucity of high-quality data available to guide clinical decision making, especially as it pertains to patient subgroups or anatomical considerations. (Am Heart J 2014;167:489-498.e7.)
Variation in Amputation Rates Among Patients with CLI
Variation in LE Revascularization

Critical Limb Ischemia: % Treated by Bypass (vs. PVI)

All VQI Centers Mean = 31%

0% Bypass

Procedure Selection Variation

100% Bypass
Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischemia
BEST-CLI Trial: Overview

- Prospective, randomized, multicenter, open-label superiority trial
- **2100** patients at **150** clinical sites in United States and Canada
- Funded by National Institutes of Health

**Goal:** to assess outcomes, quality of life and cost in patients who are candidates for both open and endovascular therapy
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  \(N=480\)
  
  (arm vein, short saphenous vein, composite vein, cryopreserved vein, and prosthetic conduit)

  Open surgery vs. Endovascular treatment
Why is BEST-CLI Important?

 Positioned to answer questions BASIL I, registries and non-RCT data-sets cannot

- Real world pragmatic trial
- Multi-disciplinary – everyone involved
- Two cohort design – all conduits allowed

 Novel primary and secondary endpoints
  - Major Adverse Limb Event (MALE) - free survival
Key Secondary Endpoints

- Re-intervention and Amputation-free Survival (RAS)
- Amputation-free Survival
- MALE-POD

Additional Secondary Endpoints

- Freedom from hemodynamic failure
- Freedom from clinical failure
- Freedom from critical limb ischemia
- Number of re-interventions per limb salvaged
- Freedom from re-interventions (major and minor) in index limb
Design and Rationale of the Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia (BEST-CLI) Trial

Matthew T. Menard, MD; Alik Farber, MD; Susan F. Assmann, PhD; Niteesh K. Choudhry, MD, PhD; Michael S. Conte, MD; Mark A. Creager, MD; Michael D. Dake, MD; Michael R. Jaff, DO; John A. Kaufman, MD; Richard J. Powell, MD; Diane M. Reid, MD; Flora Sandra Siami, MPH; George Sopko, MD; Christopher J. White, MD; Kenneth Rosenfield, MD

**Background**—Critical limb ischemia (CLI) is increasing in prevalence, and remains a significant source of mortality and limb loss. The decision to recommend surgical or endovascular revascularization for patients who are candidates for both varies significantly among providers and is driven more by individual preference than scientific evidence.

**Methods and Results**—The Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia (BEST-CLI) Trial is a prospective, randomized, multidisciplinary, controlled, superiority trial designed to compare treatment efficacy, functional outcomes, quality of life, and cost in patients undergoing best endovascular or best open surgical revascularization. Approximately 140 clinical sites in the United States and Canada will enroll 2,100 patients with CLI who are candidates for both treatment options. A pragmatic trial design requires consensus on patient eligibility by at least 2 investigators, but leaves the choice of specific procedural strategy within the assigned revascularization approach to the individual treating investigator. Patients with suitable single-segment of saphenous vein available for potential bypass will be randomized within Cohort 1 (n=1620), while patients without will be randomized within Cohort 2 (n=480). The primary efficacy end point of the trial is Major Adverse Limb Event-Free Survival. Key secondary end points include Re-intervention and Amputation-Free-Survival and Amputation Free-Survival.

**Conclusions**—The BEST-CLI trial is the first randomized controlled trial comparing endovascular therapy to open surgical bypass in patients with CLI to be carried out in North America. This landmark comparative effectiveness trial aims to provide Level I data to clarify the appropriate role for both treatment strategies and help define an evidence-based standard of care for this challenging patient population.

**Clinical Trial Registration**—URL: https://www.clinicaltrials.gov/. Unique identifier: NCT02060630. (J Am Heart Assoc. 2016;5: e003219 doi: 10.1161/JAHA.116.003219)

**Key Words:** atherosclerosis • cost-effectiveness • critical limb ischemia • endovascular • outcome • quality • stent treatment • surgery
Clinical outcomes

A typical trial

- Target Population
- Randomize
  - Intervention
  - Control
- Clinical outcomes
- Trial Completion
CEA alongside a prospective study

Target Population

Randomize

Intervention

$\$$ $ $$ $$ $$ $$ $$ $$ $

Control

$\$$ $ $$ $$ $$ $$ $$ $$ $

Trial Completion
The approach we’re taking in BEST

Target Population

Randomize

Intervention

Control

Trial Completion

Lifetime

MEASUREMENT

MODELING
Collaboration

Inclusive of all specialists who treat CLI:

- Interventional Cardiologists
- Interventional Radiologists
- Vascular Medicine Specialists
- Vascular Surgeons
81% sites are multi-disciplinary
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 Update

• 1st patient randomized 28/Aug/2014

As of 1/22/2017

• 130 sites open for enrollment

• 832 subjects randomized
BEST-CLI Is Unique

- Positioned to

Define an evidence-based standard of care.

- Assess outcomes as they relate to:
  - tibial disease, clinical presentation, gender, race, age, diabetes, heel ulcer, renal dysfunction
- Prospectively validate the SVS WIFI classification and OPG endpoints
The BEST-CLI Trial

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