Bypass Surgery for the Patient with Critical Limb Ischemia: Where are we in 2016?

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CLI Prevalence

- Most severe form of Peripheral Arterial Disease (PAD)
- Over 100,000 lower extremity amputations are performed in the United States (US) every year for CLI
- In the United States, the amputation rate has increased from 19 to 30 per 100,000 persons years over the last two decades primarily due to an increase in diabetes and advancing age.
Critical Limb Ischemia

• Prognosis of CLI is poor
  – Diffuse nature of the arterial obstructions
  – Concurrent cardiac, cerebrovascular, renal & pulmonary co-morbidities
  – 25% mortality rate in first year
    • (less than the survival rate of breast & colon cancers)\textsuperscript{4,5,6}
  – 25% amputation rate in first year
  – 50% of all below the knee amputation patients do not survive beyond 5 years

Variation in Amputation Rates for CLI

Variation in the Use of Lower Extremity Vascular Procedures for Critical Limb Ischemia

Philip P. Goodney, MD, MS; Lori L. Travis, MS; Brahmajee K. Nallamothu, MD, MPH; Kerianne Holman, MD, MPH; Bjoern Suckow, MD; Peter K. Henke, MD; F. Lee Lucas, PhD; David C. Goodman, MS, MD; John D. Birkmeyer, MD; Elliott S. Fisher, MD, MPH

Figure 3. Map of revascularization rates, by hospital referral region, from 2003 to 2006.
% of Patients with CLI and Infrainguinal PAD treated using Surgical Bypass (vs. Endovascular Therapy)

All VQI Centers Mean = 31%

Procedure Selection Variation

100% Bypass

0% Bypass
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 Sreekanth Venulpalli, MD, a,b Sumeet Subherwal, MD, a Kristine Schmit, MD, a,c Brooke Heidenfelder, PhD, a,c and Manesh R. Patel, MD a,b Durham, NC

Background For patients with critical limb ischemia (CLI), the optimal treatment to enhance limb preservation, prevent death, and improve functional status is unknown. We performed a systematic review and meta-analysis to assess the comparative effectiveness of endovascular revascularization and surgical revascularization in patients with CLI.

Methods We systematically searched PubMed, Embase, and the Cochrane Database of Systematic Reviews for relevant English-language studies published from January 1995 to August 2012. Two investigators screened each abstract and full-text article for inclusion, abstracted the data, and performed quality ratings and evidence grading. Random-effects models were used to compute summary estimates of effects, with endovascular treatment as the control group.

Results We identified a total of 23 studies, including 1 randomized controlled trial, which reported no difference in amputation-free survival at 3 years (odds ratio [OR] 1.22, 95% CI 0.84-1.77) and all-cause mortality (OR 1.07, 0.73-1.56) between the 2 treatments. Meta-analysis of the observational studies showed a statistically nonsignificant reduction in all-cause mortality at 6 months (11 studies, OR 0.85, 0.57-1.27) and amputation-free survival at 1 year (2 studies, OR 0.76, 0.48-1.21) in patients treated with endovascular revascularization. There was no difference in overall death, amputation, or amputation-free survival at ≥2 years.

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.)

...There is paucity of high-quality data available to guide clinical decision making....
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
- Poorly powered
- Suboptimal endpoints
  - Amputation free survival
  - Target lesion revascularization
  - Target vessel revascularization
- Sponsor bias
- Operator bias
- Inclusion of claudicants
- Short or incomplete follow up
Inpatient sample shows reduced amputations and mortality seen with increased use of endovascular therapy and decreases in bypass surgery.
BASIL
Bypass versus Angioplasty in Severe Ischaemia of the Leg

- Multicenter, randomized controlled trial
- Inclusion: Rest pain, ulceration or gangrene infrainguinal disease
- Study design: Surgery first versus balloon angioplasty first strategy
- Primary endpoint: amputation free survival
- Secondary endpoints:
  - all-cause mortality,
  - 30 day morbidity and mortality,
  - health related quality of life,
  - use of hospital resources,
  - need for re-intervention.
The BASIL trial clearly indicates that, almost irrespective of what treatment is received, many patients with severe limb ischemia have an extremely poor prognosis.

Amputation free survival        All cause mortality

**Figure 2:** Amputation-free survival after bypass surgery and balloon angioplasty
Bars show 95% CIs for survival up to 1, 2, 3, and 4 years of follow-up, which were calculated from the cumulative hazards.

**Figure 3:** All-cause mortality after bypass surgery and balloon angioplasty
Bars show 95% CIs for survival up to 1, 2, 3, and 4 years of follow-up, which were calculated from the cumulative hazards.

**APPROXIMATELY 40% Amputation-free survival**
### BASIL trial

<table>
<thead>
<tr>
<th></th>
<th>Surgery (n=228)</th>
<th></th>
<th>Angioplasty (n=224)</th>
<th></th>
<th>p*</th>
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<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Range</td>
<td>Mean (SD)</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Number of admissions to hospital</td>
<td>2.14 (1.30)</td>
<td>(1–8)</td>
<td>2.06 (1.50)</td>
<td>(0–10)</td>
<td>0.286</td>
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<tr>
<td>Total days spent in hospital</td>
<td>46.14 (53.87)</td>
<td>(0–365)</td>
<td>36.35 (51.39)</td>
<td>(0–334)</td>
<td>&lt;0.0001</td>
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<td>Days spent in intensive therapy unit</td>
<td>0.13 (0.94)</td>
<td>(0–12)</td>
<td>0.04 (0.60)</td>
<td>(0–9)</td>
<td>0.012</td>
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<td>Days spent in high dependency unit</td>
<td>0.65 (1.60)</td>
<td>(0–11)</td>
<td>0.18 (1.17)</td>
<td>(0–16)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Number of surgical procedures</td>
<td>0.95 (0.50)</td>
<td>(0–4)</td>
<td>0.26 (0.52)</td>
<td>(0–3)</td>
<td>..</td>
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<tr>
<td>Number of angioplasty procedures</td>
<td>0.25 (0.54)</td>
<td>(0–3)</td>
<td>1.05 (0.36)</td>
<td>(0–3)</td>
<td>..</td>
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</table>

Decreased economic expense due to shorter hospital stay and short or no ICU stay for Angioplasty group.
BASIL Trial

**Analysis by Intention to Treat**

- 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 (70% of cohort)

**Analysis by Treatment received**

1. Prosthetic bypass (25%) performed poorly compared with vein

2. Patients who underwent bypass after initial failed PTA did significantly worse than those treated with initial bypass

Bradbury A. J Vasc Surg 2010; 51(5 Suppl)S5-17S
Limitations

• Endovascular arm was largely limited to plain balloon angioplasty

• 43 out of 224 (19%) endovascular cases were technical failures due to:
  ✓ inability to cross
  ✓ inability to re-enter
  ✓ vessel perforation
  ✓ vessel thrombosis
  ✓ distal embolization

• New technology and experience would certainly improve these results
Prior failed ipsilateral percutaneous endovascular intervention in patients with critical limb ischemia predicts poor outcome after lower extremity bypass

Brian W. Nolan, MD, MS,* Randall R. De Martino, MD,† David H. Stone, MD,§ Andres Schanzer, MD,‖ Philip P. Goodney, MD, MS,* Daniel W. Walsh, MD,* and Jack L. Cronenwett, MD,* for the Vascular Study Group of New England, Lebanon, NH, and Worcester, Mass

• Retrospective analysis 10 centers Vascular Study Group of New England
• 1880 underwent LEB, 603 had prior revascularization:
  • ipsilateral PVI or P Bypass
  • contralateral PVI or Bypass

Fig 1. One-year major amputation rates in patients undergoing lower extremity bypass who have undergone prior revascularization procedure. P values compared with patients with no prior revascularization procedure. PVI, Peripheral vascular intervention.

One year major amputation rate AND graft occlusion rate significantly higher in patients who had prior iPVI or bypass


http://dx.doi.org/10.1016/j.jvs.2011.03.236
Fig 3. Freedom from major adverse limb events after lower extremity bypass. Major adverse limb event includes amputation, graft occlusion, or reintervention. PVI, Peripheral vascular intervention.
• Retrospective review
• 213 lower extremity bypass procedures
  Group 1: No prior Endovascular Procedure
  Group 2: failed elective EV
• Primary Endpoints: early and 1 year major amputations and graft occlusions
Fig. 3. Limb salvage of the groups, standard error <10%; P > 0.02. Kaplan–Meier survival tables reporting limb salvage of the groups.

1 year Limb salvage rate was significantly higher in group 1
Growing Impact of Restenosis on the Surgical Treatment of Peripheral Arterial Disease

Douglas W. Jones, MD; Andres Schanzer, MD; Yuanyuan Zhao, MA; Todd A. MacKenzie, PhD; Brian W. Nolan, MD; Michael S. Conte, MD; Philip P. Goodney, MD, MS; for the Vascular Study Group of New England

26 centers
Primary outcome measures: short term efficacy, 1 year
Reintervention or amputation (RAO)
Major adverse limb events (MALE)
Crude (unweighted) analysis of RAO-free survival and MALE-free survival in primary versus secondary LEB. LEB indicates lower extremity bypass; MALE, major adverse limb event; PVI, peripheral endovascular intervention; RAO, reintervention or amputation.
Subgroup analysis of RAO-free survival and MALE-free survival, stratified by prior intervention type.

Impact of Endo-first Paradigm

- Bypass procedures have worse long term results
- Inflow may be compromised by prior interventions
- Distal target vessels more distal
- Patient may be subjected to multiple procedures at very real cost

- THE SIMPLE BYPASS CASES ARE GONE
BEST-CLI
Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia
Prospective, randomized, multicenter, pragmatic open label superiority trial

- 2,100 patients at 140 clinical sites in United States and Canada
- Each patient will have at least 2 year follow-up
- Funded by the National Heart Lung and Blood Institute
To compare **treatment efficacy, functional outcomes** and **cost** in patients with CLI undergoing best **open surgical** or best **endovascular** revascularization
Patient Population

Patients with **CLI and infrainguinal PAD** who are candidates for both infrainguinal bypass and endovascular therapy, in the eyes of the **individual investigator CLI Team**.
BEST-CLI is a Pragmatic Trial

- Definition of “Best Treatment” is left to the investigator
- All commercially available endovascular therapies allowed as long as accepted as standard of care
- All surgical bypass techniques and conduits allowed
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
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

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

**Freedom from hemodynamic failure**
- Major amputation or any re-intervention to maintain patency in the index limb
- Failure to increase ABI by at least .15 post-procedure
- Decrease of ABI by .15 or greater during follow-up
- Duplex diagnosed treated artery/graft occlusion or critical graft stenosis (PSV > 300 cm/sec and velocity ratio > 3.0)
- Angio diagnosed treated artery/graft occlusion or stenosis >50% with recurrent clinical symptoms

**Freedom from clinical failure**
- Death, MALE, non-healing or recurrence of index limb wound, worsening of Rutherford category, recurrence of ischemic rest pain that resolved after rx

**Freedom from critical limb ischemia**
Robust Cost-Effectiveness Analysis

- 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
Collaboration within BEST-CLI

Inclusive of everyone who treats CLI:

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

If our trial is going to define practice it has to involve everyone
CLI Team: Strategies

- Establishment of site-specific collaborative processes for conduct of trial
- Engaging the most experienced investigators for optimal surgical and endovascular treatment
- Communication between 2 PIs before patient randomization and re-intervention
- Regular meetings between members of the CLI-Team
Enrollment Status
BEST-CLI Investigators

- 574 Vascular Surgeons
- 141 Cardiologists
- 126 Radiologists
- 6 Vascular Medicine Specialists
BEST-CLI Investigators

• 574 Vascular Surgeons
• 141 Cardiologists
• 126 Radiologists

78% sites are multi-disciplinary
Enrollment Update

- 1<sup>st</sup> patient randomized 28/Aug/2014

As of 4/28/2016

- 120 sites open for enrollment
- 543 subjects randomized
NIHR HTA funded RCTs comparing vein bypass and different endovascular revascularisation strategies for SLI

**BASIL-2** – open and recruiting since September 2014

**BASIL-3** – funded since 1 August 2015

Andrew W. Bradbury

Chief Investigator & Sampson Gamgee Professor of Vascular Surgery

University of Birmingham, UK

[Logos and affiliations]
Why B-2?

“Why do we need BASIL-2 when it is obvious that endovascular revascularisation is the best strategy for almost all patients requiring infra-popliteal intervention for SLI?”

(i.e. reserve surgery for “endo-impossibles” and “endo-failures”)
Reason 1: in BASIL-1 bypass after “endo-failure” was much less successful than primary bypass. So, endovascular is not a “free shot.”

Amputation free survival

Overall survival
Reason 2: In BASIL-1, IP vein bypass (VB) and IP plain balloon angioplasty (PBA) were similar in terms of amputation free survival (AFS)

Amputation free survival

P = 0.3

Vein bypass

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<th>No. Patients</th>
<th>No. Events</th>
<th>Exp.</th>
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<td>33</td>
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<tr>
<td>Surgery</td>
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<td>32</td>
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At risk:

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<td>Endovascular</td>
<td>48</td>
<td>31</td>
<td>27</td>
<td>22</td>
<td>13</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>55</td>
<td>38</td>
<td>34</td>
<td>32</td>
<td>22</td>
<td>12</td>
<td></td>
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But, in BASIL-1, IP VB was much better than IP PBA in terms of overall survival.

Overall survival:
- Vein bypass: 57%, 35%
- PBA: 22%

What about new technology?

<table>
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<th>Intervention</th>
<th>No. of Patients</th>
<th>No. Events Obs.</th>
<th>No. Events Exp.</th>
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<tbody>
<tr>
<td>Endovascular surgery</td>
<td>48</td>
<td>23</td>
<td>21.6</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>28</td>
<td>29.4</td>
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P = 0.07

At risk:
- Endovascular surgery: 48, 37, 33, 28, 18, 6
- Surgery: 55, 47, 43, 40, 29, 16

Years from Intervention
BASIL 3

**Balloon vs Stenting in Severe Ischaemia of the Leg-3**

Multi-centre RCT of clinical and cost-effectiveness of plain and drug coated balloon angioplasty (both +/- ‘bail-out’ bare metal stent) and primary drug eluting stent revascularisation strategies for SLI due to femoro-popliteal +/- infra-popliteal disease
Randomisation (n = 861) (FP only)

- PBA +/- BMS (n = 287)
- DCB +/- BMS (n = 287)
- DES (n = 287)

Follow-up
Minimum 24 months
Mean 39 months (3.3 years)
Maximum 60 months
Who benefits from bypass

• My practice
  – Individualized approach
    • Average medical risk, young patient
    • More severe limb threat (based on objective criteria, WIFI)
    • Anatomy: multilevel severe disease
      – Long occlusions, heavy calcifications
      – Severe CFA disease, severe popliteal/trifurcation disease
    • Adequate vein conduit
    • Runoff to foot intact

• Bypass options discussed with the patient
• Team approach
In summary

• The future has never been brighter for scientific research related to surgical bypass for critical limb ischemia
• Enroll all patients with CLI into the BEST-CLI randomized study and the registry
• We await the results of BASIL 2 and Basil 3.
• Individualize treatment options for these complex patients