How to Interpret the Results of BEST-CLI?

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Disclosure

I have the following potential conflicts of interest to report:

Consultant: BD, Boston Scientific, Contego Medical, Cordis, Endologix, Inspire MD, Medtronic, Rapid Medical, Shockwave, Penumbra, Vivasure, W.L. Gore

Stock: Inspire MD and Centerline Biomedical

VIVA Physicians, Board Member

Research Studies: Abbott, Endologix, Surmodics, W.L. Gore, Terumo Aortic, NIH, Boston Scientific, Merit, Contego Medical, Inspire MD, Reva Medical, Penumbra, Medalliance, Nectero
Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia


ABSTRACT
BEST-C LI Study Design: Endpoints

• Primary Endpoint: Major Adverse Limb Event (MALE) or all-cause death
  • All-cause death
  • MALE
    • First Major Reintervention: new bypass, surgical interposition graft, thrombectomy thrombolysis

• Safety Endpoints: Major Adverse Cardiovascular Events (MACE)
  • All-cause death
  • MI
  • Stroke
Prospective, Randomized, Multicenter, Multispecialty Pragmatic Clinic Trial

**BEST-CLI Study Design: Two Parallel Trials**

- Duplex of GSV
- Imaging of index leg arteries
- Review by open and endo credentialed investigators

Patients with CLTI due to infrainguinal PAD
- not at excessive risk for surgery
- eligible for open and endo

- Cohort # 1
  - SSGSV
  - Stratification
  - 1:1
  - Endovascular
    - Surgical

- Cohort # 2
  - Alternative Conduit
  - Stratification
  - 1:1
  - Endovascular
    - Surgical

**Strata:**
- Ischemic Rest Pain Alone vs. Tissue Loss
- Significant Tibial Occlusive Disease vs. No Tibial Occlusive Disease
Cohort 1: Single Segment Great Saphenous Vein Available

1,434 patients with SSGSV (Cohort 1)

Crossovers:
- Surgery → Endo 3.5%
- Endo → Surgery 0.4%

Follow up:
- Median 2.7 years
- Maximum 7.0 years

Lost to Follow up:
- Surgery 9.5%
- Endo 8.9%

Withdrawn:
- Surgery 13.1%
- Endo 8.4%

Allocation:
- 718 Surgery
  - 662 randomized procedure initiated first
  - 25 other procedure initiated first
  - 31 no procedure initiated
- 716 Endovascular
  - 705 randomized procedure initiated first
  - 3 other procedure initiated first
  - 8 no procedure initiated

Analysis:
- Analyzed (n=718)
  - 718 included in ITT
  - 662 included in per-protocol
- Analyzed (n=716)
  - 716 included in ITT
  - 705 included in per-protocol

Disposition:
- 209 died
- 94 withdrew
- 68 lost to follow-up
- 37 consent limited to 48 month follow-up
- 27 followed to early site closure
- 283 followed to study closure
- 248 died
- 60 withdrew
- 64 lost to follow-up
- 39 consent limited to 48 month follow-up
- 28 followed to early site closure
- 277 followed to study closure
BEST-CLI Results

• In cohort 1, after a median follow-up of 2.7 years
  • Primary-outcome event occurred
  • 42.6% in the surgical group vs
  • 57.4% in the endovascular group
  • (hazard ratio, 0.68; 95% confidence interval [CI], 0.59 to 0.79; P<0.001).

• In cohort 2, after a median follow-up of 1.6 years
  • Primary-outcome event occurred
  • 42.8% in the surgical group
  • 47.7% in the endovascular group
  • (hazard ratio, 0.79; 95% CI, 0.58 to 1.06; P=0.12).

• The incidence of adverse events was similar in the two groups in the two cohorts.
Primary Endpoint

MALE (Major Re-intervention, or Above-Ankle Amputation) or All-cause Death (%)

- Event Rate: 52.9% (Surgery)
- Event Rate: 42.6% (Endovascular)

Cohort 1
P <0.001 by log-rank test

Median Follow-up: 2.7 Years

No. at Risk
Surg. 718 463 349 204 117 52 12 0
Endo. 716 404 304 175 102 46 14 0

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Primary Endpoint Component

Major Re-intervention (%)

Cohort 1
- Surgery
- Endovascular

P < 0.001 by log-rank test

No. at Risk
- Surg.: 718
- Endo.: 716

Years from Randomization
- Median Follow-up: 2.7 Years
- Event Rate: 24.8%
- Event Rate: 10.9%

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Primary Endpoint Component

Above-Ankle Amputation (%)

Cohort 1
- Surgery
- Endovascular

P = 0.02 by log-rank test

No. at Risk
- Surg.: 718, 502, 387, 229, 131, 58, 15, 0
- Endo.: 716, 501, 387, 239, 142, 64, 17, 1

Median Follow-up: 2.7 Years
Event Rate: 15.5%
Event Rate: 12.2%
Primary Endpoint Component

Death (%)

Cohort 1
- Surgery
- Endovascular

P = 0.26 by log-rank test

<table>
<thead>
<tr>
<th>Years from Randomization</th>
<th>No. at Risk Surg.</th>
<th>No. at Risk Endo.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>718</td>
<td>716</td>
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<tr>
<td>0</td>
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<tr>
<td>1</td>
<td>577</td>
<td>586</td>
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<tr>
<td>2</td>
<td>457</td>
<td>462</td>
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<tr>
<td>3</td>
<td>282</td>
<td>298</td>
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<tr>
<td>4</td>
<td>168</td>
<td>182</td>
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<td>5</td>
<td>80</td>
<td>85</td>
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<td>6</td>
<td>20</td>
<td>23</td>
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<tr>
<td>7</td>
<td>0</td>
<td>1</td>
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</table>
The BEST-CLI Trial Reaffirmed

• Both therapies work; acceptably low rate of major amputation.
• Both are safe; low rate of perioperative death and MACE.
• Value of teams.
• Bypass should be available as an option in **appropriate patients**.
• This is a vulnerable population: at 2.7 years
  • 33-38% are dead
  • 10-15% have lost the limb.
BEST-CLI Highlights

• First major RCT in CLTI
• Unequivocal result (in the population in which the hypothesis was tested)
• Most patients had wounds
• 2/3 of patients had tibial disease
• Included WIFI stage 4
• Included renal failure
• Hemodynamics were required for enrollment
• Experts doing revascularization the way they think is best
• Opportunity for improved medical management
### Table 2. Efficacy and Safety Outcomes in Cohort 1.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Surgery</th>
<th>Endovascular Therapy</th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
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<tr>
<td>Primary outcome: major adverse limb event or death from any cause — no./total no. (%)‡</td>
<td>302/709 (42.6)</td>
<td>408/711 (57.4)</td>
<td>0.68 (0.59–0.79)</td>
<td>&lt;0.001</td>
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<td>Secondary outcomes — no./total no. (%)</td>
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<tr>
<td>Death from any cause</td>
<td>234/709 (33.0)</td>
<td>267/711 (37.6)</td>
<td>0.98 (0.82–1.17)</td>
<td></td>
</tr>
<tr>
<td>Above-ankle amputation of the index limb</td>
<td>74/709 (10.4)</td>
<td>106/711 (14.9)</td>
<td>0.73 (0.54–0.98)</td>
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<tr>
<td>Intervention in index limb</td>
<td></td>
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<tr>
<td>Major</td>
<td>65/709 (9.2)</td>
<td>167/711 (23.5)</td>
<td>0.35 (0.27–0.47)</td>
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<tr>
<td>Minor</td>
<td>205/718 (28.6)</td>
<td>237/716 (33.1)</td>
<td>0.85 (0.70–1.02)</td>
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</tr>
<tr>
<td>Perioperative death§</td>
<td>12/687 (1.7)</td>
<td>9/708 (1.3)</td>
<td>1.54 (0.64–3.68)</td>
<td></td>
</tr>
<tr>
<td><strong>Major adverse limb event or perioperative death</strong></td>
<td>139/687 (20.2)</td>
<td>246/708 (34.7)</td>
<td>0.53 (0.43–0.65)</td>
<td></td>
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<tr>
<td><strong>Safety</strong></td>
<td></td>
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<tr>
<td>Major adverse cardiovascular event — no. of patients with ≥1 event/total no. of patients (%)</td>
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<tr>
<td>Event ≤30 days after procedure¶</td>
<td>33/718 (4.6)</td>
<td>23/716 (3.2)</td>
<td>1.46 (0.86–2.50)</td>
<td>0.16</td>
</tr>
<tr>
<td>Event during follow-up</td>
<td>269/718 (37.5)</td>
<td>309/716 (43.2)</td>
<td>0.94 (0.80–1.11)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Serious adverse event</strong></td>
<td></td>
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<tr>
<td>Event occurred ≤30 days after index procedure — no. of patients with ≥1 event/total no. of patients (%)</td>
<td>244/718 (34.0)</td>
<td>226/716 (31.6)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>No. of events ≤30 days after index procedure</td>
<td>427</td>
<td>379</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>No. of patients with ≥1 event/total no. of patients (%)</td>
<td>590/718 (82.2)</td>
<td>614/716 (85.8)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>No. of events during follow-up</td>
<td>3141</td>
<td>3468</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Technical success of index procedure — no./total no. (%)</strong>**</td>
<td>651/662 (98.3)</td>
<td>596/704 (84.7)</td>
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<tr>
<td><strong>Length of hospital stay after index procedure††</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of days</td>
<td>7.5±6.2</td>
<td>5.9±7.3</td>
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<tr>
<td>Median no. of days (IQR)</td>
<td>6 (4–9)</td>
<td>3 (1–8)</td>
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</tbody>
</table>


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35% still smoking
30% not on statins
28% not on antiplatelet
There is a lot more to learn from BEST-CLI

- NEJM Supplement-61 pages
- WIFI and GLASS sub-segmentation
- Angiographic evaluation of disease morphology-TAP
- Wound healing assessment
- Complications/readmissions/surgical site infection
- QOL
- Cost
- Technical failure of endovascular
Every Major RCTs Faces Two Key Challenges

• Appropriateness of endpoint
  • Is the endpoint meaningful as an outcome of care in the context of the disease process, to the patient, to the healthcare team?

• Generalizability
  • To which population can the conclusion be applied?
Appropriateness of Endpoint

• Death or MALE (above-ankle amputation, new bypass, thrombectomy/thrombolysis, open graft revision)
• AFS not sensitive enough
• Substantial data on MALE collected in the literature
technical success of the index procedure was 98% in the surgical group and 85% in the endovascular group. Of the 108 cases of early technical failure in the endovascular group, 66 were treated with a bypass operation within 30 days. The need for and timing of the reintervention was determined by the trial site investigator on the basis of clinical assessment. All first major reinterventions were adjudicated by an independent, multidisciplinary clinical-events committee. A
Technical Success/Failure and Evolving Technology

Definition of Technical Failure

Technical failure in the setting of a surgical bypass is defined as occlusion of the bypass graft or failure to achieve a patent bypass graft at the completion of the procedure. Abortion of the procedure prior to successful completion due to non-technical reasons (e.g. due to hemodynamic instability following a myocardial infarction) will still be considered a technical failure of bypass surgery.

Technical failure in the setting of endovascular therapy is defined as the inability to cross a stenosis or occlusion or a residual obstruction of >50% in the superficial femoral artery, popliteal and/or all tibial arteries (from recoil, dissection, thrombosis, embolization or other complication) such that there is no in-line flow to the foot.

- Evolving technology: Enrollment: 8/14-10/19
- Retrograde access for crossing (antegrade has a 15-20% failure rate).
- Paclitaxel usage lower than expected.
- Are there varying adoption rates of new technologies among specialties?
- Could some of the endo failures be treated with more aggressive endo?
BEST-CLI Generalizability
The Challenge of Clinical Equipoise

• Did all sites have clinical equipoise?
• Selection bias of team
• What if easy for endo?
• What if unfit for surgery?
• When is primary amputation the option?
• Who was not enrolled?

• Companion Registry
BEST-CLI Challenges

• Imaging data not collected prospectively
• No hemodynamics beyond trial entry
• No patency information
• Withdrawn or Lost to Follow up: Endovascular 26.7%, Surgery 31.5%
• Patient preference

Additional analyses regarding anatomical patterns of vascular disease, predictors of technical failure, effect on quality of life, cost, and role of patient preference will further elucidate subgroups of patients who are most likely to benefit from each approach.
BEST-CLI: Conclusion

• Endovascular first is not appropriate for ALL patients
• Cohort 1: In the studied population, bypass had an advantage.
  • Additional analyses will give us more direction about which population is best for each treatment strategy.
  • Key unknowns: severity of disease morphology, medical risk of the enrolled patients.
• Cohort 2: No advantage for bypass, even when fit for surgery.
• Saphenous vein map and surgical risk assessment applied more liberally.
  • Every CLTI program should ensure it has bypass capability.
BEST-CLI: Big Picture

• A real CLTI trial.
• Immense undertaking that has enriched our field.
• Highlighted the vulnerability of the CLTI population.
• Future trials will include MALE.
• Future trials will be designed with BEST-CLI as a benchmark.
• We have a workflow and a resource problem.

Unanswered:
• When the first plan fails, have we done damage?
• What are the hemodynamic needs of a given patient?