BEST-CLI Updates

SouthEastern Vascular Quality Initiative Spring Meeting
Clearwater, FL       March 21, 2019

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National Data Curtesy of Alik Farber, Matt Menard. National Co-Pis
BEST-CLI Clinical Trial
Disclosures

National Trial Manager

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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

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Durham, NC

Background For patients with critical limb ischemia (CLI), the optimal treatment to enhance limb salvage, prevent amputation-free survival at 3 years (odds ratio [OR] 1.22, 95% CI 0.92-1.58) and the mortality rate between the 2 treatments. Meta-analysis of the observational studies showed a statistically between 0.76, 0.48-1.21) in patients treated with endovascular revascularization. There was 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.)
Trends in PAD Therapy

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

Goodney et al. JAMA Surg 2015;150:84-86
% of Patients with CLI and Infrainguinal PAD treated using Surgical Bypass (vs. Endovascular Therapy)

All VQI Centers Mean = 31%

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

- Prospective, randomized, pragmatic, multicenter, international, multispecialty open-label superiority trial
- 2,100 patients at 160 clinical sites

**Goal:** to compare clinical outcomes, quality of life, cost and *value* of open and endovascular strategy in patients with Chronic Limb Threatening Ischemia
BEST-CLI Study Design

Patients with CLI (n=2,100)

Cohort # 1 SSGV (n=1,620)

Cohort # 2 Alternative Conduit (n=480)

Screening (Vein mapping, diagnostic imaging)

Consented

Follow-up Median = ~ 2.1 years

BEST Endovascular Revascularization

BEST Surgical Revascularization

Primary Endpoint:
  - MALE (Major Adverse Limb Event) - Free Survival

Secondary Endpoint (Clinical, Functional, Cost-effectiveness)
  - RAFS (Re-intervention and amputation-free survival);
  - MALE-POD Freedom (MALE or death within 30 days of index procedure); QoL, VascuQoL
  - Treatment associated costs (in- and out-patient)

Safety Endpoint:
  - MACE (Major Adverse Cardiovascular Events) through 30 days post index procedure
5 Active Sites Overseas
New Zealand
- Wellington Hospital
- Waikato Hospital
- Auckland City Hospital
Finland
- Helsinki University Hospital
Italy
- San Giovanni di Dio Hospital

Onboarding
Germany
- St. Franziskus Hospital – Muenster

133 Open Sites
Enrollment Update

As of March 17, 2019

- 1649 subjects randomized (79% complete)
Goal 2,100 Patients

- **Florida Sites**
  - Baptist Hospital of Miami
  - Mount Sinai Miami
  - Tampa General Hospital
  - Florida Hospital Ocala
  - University of Florida (Gainesville)

- **Alabama Sites**
  - University of Alabama

- **Georgia Sites**
  - Emory
Goal 2,100 Patients

- Florida Sites
  - Baptist Hospital of Miami 11
  - Mount Sinai Miami
  - Tampa General Hospital
  - Florida Hospital Ocala
  - University of Florida (Gainesville) 31

- Alabama Sites
  - University of Alabama

- Georgia Sites
  - Emory 11

**LEADERBOARD!!**  
Kudos
Goal 2,100 Patients

Florida Sites
- Baptist Hospital of Miami
- Mount Sinai Miami 1
- Tampa General Hospital 6
- Florida Hospital Ocala 4
- University of Florida (Gainesville)

Alabama Sites
- University of Alabama 4

Georgia Sites
- Emory
What are your center challenges???

▪ Are you multidisciplinary?
Results: Multidisciplinary Site Comparison

AVERAGE MONTHLY ENROLLMENT

No significant difference in monthly enrollment rates  \( P=0.72 \)

<table>
<thead>
<tr>
<th></th>
<th>Single-disciplinary</th>
<th>Multi-disciplinary</th>
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</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.30</td>
<td>0.27</td>
</tr>
<tr>
<td>Median</td>
<td>0.24</td>
<td>0.24</td>
</tr>
<tr>
<td>Range</td>
<td>0 - 1.77</td>
<td>0 - 1.30</td>
</tr>
</tbody>
</table>
What are your center challenges???

- Are you multidisciplinary?
- How many “engaged” co-investigators at your center?
Results: Multidisciplinary Site Comparison

Monthly site enrollment rate positively correlated with number of investigators

$R=0.0169 \ (95\% \ CI \ 0.00 - 0.03), \ p=0.0497$
What are your center challenges???

- Are you multidisciplinary?
- How many “engaged” co-investigators at your center?
- Are patients supportive of trials?
What are your center challenges???

- Are you multidisciplinary?
- How many “engaged” co-investigators at your center?
- Are patients supportive of trials?
- Are you just not seeing the anatomy?
Randomized to...

Good saphenous vein

OPEN
Randomized to... Endo

No vein
Randomized to...

OPEN
Prosthetic conduit arm

Short arm vein only
Key Inclusion Criteria

- Infrainguinal PAD
- CLI -- gangrene, non-healing ischemic ulcer, or rest pain
- Candidate for both open and endovascular infrainguinal revascularization as judged by the treating investigators
- Adequate popliteal, tibial or pedal revascularization target
- Adequate aortoiliac inflow
Aortoiliac Inflow Criteria

- Patients must have adequate inflow to the common femoral artery, as defined by presence of one of the following:
  - normal ipsilateral femoral pulse
  - biphasic or triphasic Doppler waveform in the ipsilateral common femoral artery
  - normal radiographic appearance of ipsilateral iliac artery
  - if radiographic evidence of ipsilateral common and external iliac artery occlusive disease, all lesions are of <50% severity
  - if radiographic evidence of ipsilateral common and external iliac artery occlusive disease, there is ≤ 10 mmHg aortic to femoral mean pressure gradient

- Rest pain (Rutherford 4) vs. Tissue Loss (Rutherford 5,6)
Key Exclusion Criteria

- Popliteal aneurysm (> 2cm) in the index limb
- Excessive risk for surgical bypass
- Active vasculitis, Buerger’s disease or acute limb ischemia
- Prior index limb infrainguinal stenting or stent grafting with restenosis or occlusion within intended treatment zone
- Any infrainguinal procedure performed on index limb within 3 months prior to enrollment, including:
  - Balloon angioplasty, atherectomy, stent or stent graft
  - Bypass with either venous or prosthetic conduit
- Current chemotherapy or radiation
- Open surgical inflow procedure within 6 weeks prior to enrollment
What are your center challenges???

- Are you multidisciplinary?
- How many “engaged” co-investigators at your center?
- Are patients supportive of trials?
- Are you just not seeing the anatomy?
- Endangers throughput at hospital
What challenges have we seen?

- Throughput... motivation to intervene during angio to get the patient dealt with
- Need to have information prior to angiogram:
  - Vein mapping, ?ECHO, patient willingness for trial
- Femoral and iliac disease
  - This is NOT a contraindication to enrollment. Can treat
  - Protocol addendum ratified to make this more acceptable
- Tibial disease- can treat during index procedure
What efforts to increase enrollment?

- Practice dynamics
  - High focus at our shared case conferences
  - Emails to faculty, fellows, extenders
  - Frequent review of patient lists for potential candidates
  - Bring up the concept of equipoise and the trial to the patient early
What efforts to increase enrollment?

- **Procedure dynamic**
  - Acknowledge treatment bias and consider alternatives
  - Increased pedal access approach
  - Flexibility...be willing to sacrifice throughput for consideration of BEST (i.e. diagnostic angiogram)
  - Consider on table randomization.

- **Novel approaches**
  - Recruit new faculty who trained under BEST PIs in Boston
    - Dean Arnaoutakis, Michol Cooper, Samir Shah
  - Bribe with a division fish taco party
Trends in PAD Endovascular Market-share

In Many Hospitals there is Inter-specialty Conflict
Multidisciplinary Challenges

- Randomization into trial is difficult
  - Personal treatment bias despite community equipoise

- Not everyone has bought in
  - A number of high profile resistors
  - Some fear that trial outcomes unfavorable to endo may lead to loss of professional stature and income

- There are financial disincentives
  - In a fee-for-service world enrolling a patient into trial may mean losing revenue
  - Sites with outpatient interventional labs have incentives not to participate in trial

- Difficult to overcome institutional politics
Course of Events for BEST-CLI Infancy

June 2010: Submitted R01 application

Proposal: --RCT comparing Bypass and Endo in CLI patients who are candidates for both
--performed by vascular surgeons

Rationale: --They can do both leg bypass and leg endo
--They have equipoise (confirmed by 2 surveys)
Response from NHLBI
Key Concerns from Summary Statement

1. Insufficient engagement of interventional cardiology and radiology
2. Insufficient description of a tight plan for medical therapy
3. Lack of inclusion of non-peripheral vascular endpoints such as stroke and non-fatal MI in the primary composite endpoint
4. Complex variability of clinical presentation and management of CLI patient population not considered in enough detail
5. Lack of presentation of mechanistic sub-studies that would provide insight into mechanisms of intervention failure
6. Estimate of prevalence of adequate saphenous vein was too optimistic
7. Trial leadership experience
8. Establishment of registry
9. Insufficient description of cost-effectiveness protocol
10. Inadequate per-patient reimbursement
Results

DISTRIBUTION OF BEST-CLI PARTICIPATING SITES

Total 132
Single-disciplinary 42
Multi-disciplinary 90

Single-disciplinary 31%
Multi-disciplinary 69%
Results

DISTRIBUTION BY SPECIALTY GROUPS

- VS alone: 31%
- VS + IR: 23%
- VS + IC: 33%
- VS + IC + IR: 33%
Results

BEST-CLI INVESTIGATORS BY SPECIALTY ROLE

<table>
<thead>
<tr>
<th>Role</th>
<th>Count</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>VS</td>
<td>690</td>
<td>74%</td>
</tr>
<tr>
<td>IC</td>
<td>114</td>
<td>12%</td>
</tr>
<tr>
<td>IR</td>
<td>111</td>
<td>12%</td>
</tr>
<tr>
<td>VM</td>
<td>3</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>1%</td>
</tr>
</tbody>
</table>

Total: 930
Results

Monthly site enrollment rate positively correlated with number of investigators

R=0.0169 (95% CI 0.00 - 0.03), p=0.0497
Results

DISTRIBUTION OF ENROLLMENTS BY SPECIALTY

- VS: 74%
- IC: 8%
- IR: 4%
- Others: 1%
Conclusion

- No significant relationship between multi-disciplinary status and monthly enrollment rates
- Monthly enrollment rates positively correlated with number of site investigators
- Enrollment is driven by Vascular Surgeons
- Continuing evaluation of factors that impact enrollment is crucial
Thank You