Update on the BEST-trial: How will it change our practice?

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Disclosure

Speaker name: Matthew Menard

I have the following potential conflicts of interest to report:

☐ Consulting

☐ Employment in industry

☐ Stockholder of a healthcare company

☐ Owner of a healthcare company

☒ Other(s) – Scientific Advisory Board: Janssen, Inc

☐ I do not have any potential conflict of interest
CLI: A Growing Worldwide Epidemic

- Diabetes
- Obesity
- Metabolic Syndrome
- Elderly
- PAD/CLI
CDC Trends in 2 Major PAD Risk Factors

Trends in Current Cigarette Smoking by High School Students* and Adults**—United States, 1965–2014

Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958–2015

Beckman, JA Circ Res. 2016;118:1771-1785
Vorapaxar and MACE in Patients with PAD

Days from Randomization

<table>
<thead>
<tr>
<th>Days from Randomization</th>
<th>Vorapaxar</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 0.85 (0.73-0.99)</td>
<td>12.5%</td>
</tr>
<tr>
<td></td>
<td>P=0.034</td>
<td>10.7%</td>
</tr>
<tr>
<td>3 Yr. KM Estimate</td>
<td>1.8% ARR</td>
<td>NNT 56</td>
</tr>
</tbody>
</table>

ISTH Major Bleeding HR 1.39, p<0.001
GUSTO Mod/Severe 1.62 p=0.001
No significant increase in ICH or Fatal Bleeding
MACE or MALE
In Patients with PAD and no MI or Stroke

Bonaca et al. Circulation 2018
COMPASS Trial PAD+CAD

>90% with CAD, large subgroup with Concomitant PAD
VOYAGER PAD: Study Design

Multicenter, randomized, double-blind, placebo-controlled, event-driven phase III study

Primary efficacy outcome: CV death, MI, ischemic stroke, acute limb ischemia, and major amputation

Principal safety outcome: TIMI Major Bleeding

Event driven (~1015 PEP)

Pts age ≥ 50 yo with:
- Documented moderate to severe PAD with ABI <0.90 and angiographic or imaging evidence of occlusive PAD
- Any vascular surgical bypass to the lower extremity including aorto-iliac, infra-inguinal, and extra-anatomic bypass for symptomatic PAD
- Clinical indication to treat symptomatic PAD with peripheral revascularization to restore limb perfusion

Exclusion criteria:
- Rutherford category 0, 1, & 6;
- Endovascular revascularization of the aorto-iliac segment without any additional revascularization below the inguinal ligament; general criteria based on known rivaroxaban contraindication such as allergy, known bleeding diathesis, etc.

Rivaroxaban 2.5 mg bid + ASA 100 mg od

T0, Day 1

1:1 randomization*

R

N = 6500

Placebo + ASA 100 mg od

1 month post study drug observation period

Capell W, Bonaca MP, …Hiatt WR et al. AHJ in Press
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])
Current practice of first-line treatment strategies in patients with critical limb ischemia

Theodosios Bisdas, MD, Matthias Borowski, PhD, and Giovanni Torsello, MD, for the First-Line Treatments in Patients With Critical Limb Ischemia (CRITISCH) Collaborators, Muenster, Germany

Critical limb ischemia lasting > 2 weeks
Rutherford stages 4 to 6

Excluded patients (n=59)
Reasons:
- Admission through ICU
- Inability to provide informed consent or dementia
- Denial of inclusion in the registry
- Admission to another ward

Informed consent
Eligibility for inclusion

n=1200 patients

CRITISCH Registry

Decision for type of treatment by the responsible physician (best treatment option)

Exclusion criteria:
1. Acute limb threatening ischemia
2. Isolated interventions at the aorto-iliac segment
3. Bone fractures in relevant areas
4. Non-atherosclerotic disease

Group I
Endovascular therapy
n=642 patients

Group II
Bypass surgery
n=284 patients

Group III
Patchplasty
n=126 patients

Group IV
Conservative treatment
n=118 patients

Group V
Primary amputation
n=50 patients

Initial revascularization for CLI:

- Critisch Registry: 45% bypass
- Recent VQI Data: 40% bypass (N= 38,470)
CLI is Expensive!

- Medicare expenditure on CLI > $4 billion
  (CHF = $3.9B, Cerebrovascular disease = $3.7B)

  - 90% inpatient care

  - $1,700 per patient (>2X avg beneficiary)

  - 3% of total Medicare budget (THR = 0.9%, TKR 1.7%)
We can’t afford every health intervention that is effective

NATIONAL HEALTH EXPENDITURES AS A SHARE OF GDP, 1987-2016

The share of GDP devoted to health was 17.9% in 2016

SOURCE: CMS
Randomized controlled trials represent the most internally valid forms of evidence

A WELL-DESIGNED TRIAL IDENTIFIES THE OPTIMAL COURSE OF ACTION IN RESEARCH SETTINGS

<table>
<thead>
<tr>
<th>Clinical Trial Design</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Randomized Clinical Trial | - eliminates confounding factors  
- minimizes treatment selection bias  
- reduces spurious causality  
- most reliable form of scientific evidence | - time intensive  
- expensive  
- generizability |

James, S. et al. (2015) Registry-based randomized clinical trials—a new clinical trial paradigm
*Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2015.33
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, SAPHIRE, SPACE, CAVATAS

- **AAA**
  - ADAM, UK Small AAA

- **AAA vs EVAR**
  - DREAM I and II, EVAR I and II, OVER, Numerous IDE studies.

- **CLI: Bypass vs Endo**
  - BASIL
How Often Do We Know What to Do for the Patient?
Cardiovascular Treatment Guidelines

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

JAMA. 2009;301(8):831-841

16 High impact cardiovascular guidelines used to power healthcare decisions by payers, healthcare providers and consumers

2,711 Recommendations within these guidelines

11% Were based upon enough evidence to warrant the recommendation.
The vast majority were based upon a single trial and expert opinion
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 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
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-

...There is paucity of high-quality data available to guide clinical decision making....
Of 134 recommendations from 5 guidelines for endovascular and surgical procedures... only 13% were supported by level A evidence.
The mandate for better evidence is compelling.
Which **FIRST** Revascularization Option in CLI Has the BEST **Value**?

VS

**Bypass Surgery**

VS

**Endovascular Therapy (Endo)**
BEST-CLI
Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia
BEST-CLI Trial Design: Two Cohorts

- **Cohort #1** Patients with adequate single segment great saphenous vein (SSGSV) \( N=1620 \)
  
  Open surgery vs. Endovascular treatment

- **Cohort #2** Patients without adequate 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
Why Is BEST-CLI Important?

Uniquely positioned to provide level I data for CLI

- Well-powered and designed
- Real-world pragmatic trial
MALE defined as:

- Above ankle amputation or
- **Major** re-intervention
  - new bypass graft
  - jump/interposition graft revision
  - thrombectomy/thrombolysis

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
### BEST-CLI Trial Optimal Medical Therapy (OMT) Report Cards

**Overview of Site 1005 Optimal Medical Therapy Performance Metrics**

<table>
<thead>
<tr>
<th>Site</th>
<th>Site Name</th>
<th>Date of Data Freeze</th>
<th># Randomized</th>
<th>HTN Control</th>
<th>DM Control</th>
<th>Statin Use</th>
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<tbody>
<tr>
<td>1005</td>
<td>Brigham and Women’s Hosp.</td>
<td>11/1/2017</td>
<td>17</td>
<td>✅</td>
<td>✅</td>
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</table>

*Summary of Performance Metrics on Page 3

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#### Explanation of Performance Metrics

<table>
<thead>
<tr>
<th>Metric</th>
<th>Grade</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (HTN) Control</td>
<td>✅</td>
<td>Excellent Greater than 80% of patient visits with subjects either meeting age-specific targets for both SBP and DBP or at least one anti-hypertensive medication reported</td>
</tr>
<tr>
<td></td>
<td>✅</td>
<td>Fair Between 60% and 80% of patient visits with subjects either meeting age-specific targets for both SBP and DBP or at least one anti-hypertensive medication reported</td>
</tr>
<tr>
<td></td>
<td>✅</td>
<td>Poor Less than 60% of patient visits with subjects either meeting age-specific targets for both SBP and DBP or at least one anti-hypertensive medication reported</td>
</tr>
<tr>
<td></td>
<td>✅</td>
<td>NA Your site did not have any patient visits with data available for this metric</td>
</tr>
<tr>
<td>Diabetes (DM) Control</td>
<td>✅</td>
<td>Excellent Greater than 80% of patient visits with Hemoglobin A1c &lt;8%</td>
</tr>
<tr>
<td></td>
<td>✅</td>
<td>Fair Between 60% and 80% of patient visits with Hemoglobin A1c &lt;8%</td>
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<td>Poor Less than 60% of patient visits with Hemoglobin A1c &lt;8%</td>
</tr>
<tr>
<td></td>
<td>✅</td>
<td>NA Your site did not have any patient visits with data available for this metric</td>
</tr>
<tr>
<td>Statin Use</td>
<td>✅</td>
<td>Excellent Greater than 80% of patient visits with statin use reported</td>
</tr>
<tr>
<td></td>
<td>✅</td>
<td>Fair Between 60% and 80% of patient visits with statin use reported</td>
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<td></td>
<td>✅</td>
<td>NA Your site did not have any patient visits with data available for this metric</td>
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</table>

- Based on percentage of post-baseline visits at which targets are met
- Baseline visits are not considered because they reflect care the subject received before the subject was enrolled in BEST
- One patient can contribute data at more than one visit
- Grades are based on accepted, defined standards and not on comparison with other trial sites
SVS Lower Extremity Threatened Limb Classification - **WIfI Index**

- **Wound**: extent and depth
- **Ischemia**: perfusion/flow
- **Foot Infection**: presence and extent
### Risk of Amputation

<table>
<thead>
<tr>
<th></th>
<th>Ischemia – 0</th>
<th>Ischemia – 1</th>
<th>Ischemia – 2</th>
<th>Ischemia – 3</th>
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<tr>
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<td>W-2</td>
<td>L</td>
<td>L</td>
<td>M</td>
<td>HH</td>
</tr>
<tr>
<td>W-3</td>
<td>M</td>
<td>M</td>
<td>H</td>
<td>HH</td>
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### Benefit of Revascularization

<table>
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<tr>
<th></th>
<th>Ischemia – 0</th>
<th>Ischemia – 1</th>
<th>Ischemia – 2</th>
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<tr>
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<td>W-3</td>
<td>VL</td>
<td>VL</td>
<td>M</td>
<td>HH</td>
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</tbody>
</table>
Impact of Diabetes Mellitus

- Patients with diabetes at 6X risk of amputation

Howard et al. Circulation 2015
TIDE Ancillary Study Update

Swim with (the) TIDE

Joshua Beckman, MD

Sponsored by the National Heart Lung and Blood Institute
Collaboration and CLI teams
Collaboration within BEST-CLI

Inclusive of everyone who treats CLI:

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

81% of Sites are multidisciplinary
Expectations of the NIH...
Quality Adjusted Life Years (QALYs)
BEST-CLI in North America

130 Active Sites

North America
Europe

New Zealand
- Wellington Hospital
- Waikato Hospital
- Auckland City Hospital

Finland
- Helsinki University Hospital

Italy
- San Giovanni di Dio Hospital

Germany
- St. Franziskus Hospital – Muenster

5 Active Sites

Onboarding
930 Investigators

- 114 Interventional Cardiologists
- 111 Interventional Radiologists
- 3 Vascular Medicine Specialists
- 690 Vascular Surgeons
Enrollment Update

As of 1/21/2019

• **1,581** subjects randomized
Conclusions

- There is an exceptional knowledge deficit in CLI management cf other areas of clinical therapy.
- Systematic data regarding outcomes will be necessary in order to change behaviors and practice patterns, and reduce cost.
- BEST CLI will provide powerful, Level I data that will help to shape a much-needed evidence based approach to CLI.
- And set the stage for the next generation of investigations.
Thank you
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