Update On The Best-CLI RCT Comparing Open And Endo Treatments Of CLTI: Recruitment To Date: Successes And Problems To Date: What Will It Tell Us And When

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Disclosures

- BEST-CLI Trial Co-Chair
- Supported by NHLBI: 1U01HL107407-01A1
- Janssen (SAB)

CLI: A Growing Worldwide Epidemic

Diabetes
Obesity
Metabolic Syndrome
Elderly
PAD/CLI

CDC Trends in 2 Major PAD Risk Factors


Beckman, JA Circ Res. 2016;118:1771-1785

Vorapaxar and MACE in Patients with PAD

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
**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)**
- **Inclusion criteria:**
  - 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.
- **Treatment Phase**
  - Placebo + ASA 100 mg od post-procedural concomitant thienopyridines allowed for a maximum period of 30 days
  - Placebo + ASA 100 mg od
  - Rivaroxaban 2.5 mg bid + ASA 100 mg od T0, Day 1
  - Rivaroxaban + Aspirin: HR: 0.59 (0.35 – 0.80) P=0.0038
  - Rivaroxaban vs. Aspirin: HR: 0.80 (0.61 – 1.02) P=0.08
- **Screening Phase**
  - Wash-out, Safety FU

**Initial revascularization for CLI**

- **Critisch Registry:** 45% bypass
- **Recent VQI Data:** 40% bypass (N=38,470)

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**COMPASS Trial PAD+CAD**

- 28% Reduction in MACE
- 70% Increase in Major Bleeding
- >90% with CAD, large subgroup with Concomitant PAD

**Summary of Effects of PCSK9i Evolocumab**

Bonaca et al. Circulation 2018


**COMPASS Trial PAD+CAD**

Day 1: Placebo + ASA 100 mg od

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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

Advantages and Disadvantages of Randomized Clinical Trial Design

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

Randomized controlled trials represent the most internally valid forms of evidence

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

How Often Do We Know What to Do for the Patient?
Cardiovascular Treatment Guidelines

Which FIRST Revascularization Option in CLI Has the BEST Value?

Bypass Surgery
Endovascular Therapy (Endo)
**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

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**Why Is BEST-CLI Important?**

*Uniquely positioned to provide level I data for CLI*

- Well-powered and designed
- Real-world pragmatic trial

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**Novel Primary Endpoint**

**Major Adverse Limb Event (MALE) – free survival**

**MALE defined as:**

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

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**Key Secondary Endpoints**

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

**Additional SecondaryEndpoints**

- 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

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**Optimal Medical Therapy**
Might be cleaner to include the flow chart in the protocol and just explain the process.
SVS Lower Extremity Threatened Limb Classification - WIfI Index

- Wound: extent and depth
- Ischemia: perfusion/flow
- Foot Infection: presence and extent

Risk of Amputation

<table>
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Impact of Diabetes Mellitus

- Patients with diabetes at 6X risk of amputation

Benefit of Revascularization

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Collaboration and CLI teams

TIDE Ancillary Study Update

Swim with (on) TIDE

Joshua Beckman, MD

Sponsored by the National Heart, Lung, and Blood Institute

Howard et al. Circulation 2015

N = 27/64
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...

Health Policy Value

Quality Adjusted Life Years (QALYs)

Quality of Life

Follow-up month

Open
Endo

Enrollment Obstacles

- Competing Trials
- Understanding the protocol
- “Hassle Factor”
- Restrictive inclusion/exclusion criteria
- Increasing awareness of BEST-CLI at your site
- Establishing flow of screening and randomization procedures
- Overcoming treatment bias
- Discussing trial with prospective patients and families
- Engaging investigators to participate in trial
Treatment Bias is the Biggest Obstacle

Enrollment Obstacles
- Competing Trials
- Understanding the protocol
- Increasing awareness of BEST-CLI at your site
- Establishing flow of screening and randomization procedures

Treatment Bias
- Engaging investigators to participate in trial

Collaboration is the antidote to treatment bias

Challenges
- Folks that have an idiopathic allergy to an attempt to obtain Level I evidence
- Goal is to clarify the role of both endo and open
  - Which are complementary, not mutually exclusive treatment strategies

BEST-CLI in North America
130 Active Sites

BEST-CLI Global Footprint

Overseas
- New Zealand
  - Wellington Hospital
  - Waikato Hospital
  - Auckland City Hospital
- Finland
  - Helsinki University Hospital

Europe
- Germany
  - St. Franziskus Hospital – Muenster
- Italy
  - San Giovanni di Dio Hospital

Investigators
- 930 Investigators
  - 114 Interventional Cardiologists
  - 111 Interventional Radiologists
  - 3 Vascular Medicine Specialists
  - 690 Vascular Surgeons
  - 12 Other
Enrollment Update

As of 11/13/2018

- 1,510 subjects randomized

Is the BEST-CLI Trial going to give us all the answers?
- No
Will it settle controversy?
- Unlikely
Will it give folks an opportunity to test their bias?
- Yes
Will it be better than what we have now?
- Absolutely

Conclusions

- There is an exceptional knowledge deficit in CLI management of 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, in synergy with BASIL-2 and BASIL-3, 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