Stratifying Management Options for Patients with Critical Limb Ischemia:
When Should Open Surgery Be the Initial Option for CLI?

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## Chronic Lower Extremity Ischemia Classification

<table>
<thead>
<tr>
<th>Rutherford Category</th>
<th>Clinical Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>1</td>
<td>Mild claudication</td>
</tr>
<tr>
<td>2</td>
<td>Moderate claudication</td>
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<tr>
<td>3</td>
<td>Severe claudication</td>
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<tr>
<td>4</td>
<td>Rest pain</td>
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<tr>
<td>5</td>
<td>Minor tissue loss/non-healing ulcer/focal gangrene</td>
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<tr>
<td>6</td>
<td>Major tissue loss or gangrene, extending above the transmetatarsal level</td>
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Definition of Critical Limb Ischemia
Rutherford 5

• “Inadequate blood flow to accommodate resting metabolic needs”
• Will result in limb loss unless perfusion is improved
• Includes ischemic rest pain, nonhealing ischemic, an gangrene
Hemodynamics and Probability of Healing of a Diabetic Foot Ulcer - No Threshold

Healing unlikely if toe pressure < 55 mmHg
The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk stratification based on Wound, Ischemia, and Foot Infection (WIFI)

Joseph L. Mills, Sr, MD, a Michael S. Conte, MD, b David G. Armstrong, DPM, MD, PhD, a Frank B. Pomposelli, MD, c Andres Schanzer, MD, d Anton N. Sidawy, MD, MPH, e and George Andros, MD, f on behalf of the Society for Vascular Surgery Lower Extremity Guidelines Committee, Tucson, Ariz; San Francisco and Van Nuys, Calif; Brighton and Worcester, Mass; and Washington, D.C.
Alternatives for Revascularization and Treatment of CLI

- **Endovascular**
  - Angioplasty
  - Stent
  - Atherectomy
  - Lysis
- **Open surgery**
  - Bypass with vein/artery
  - Bypass with prosthetic graft
  - Endarterectomy
- **Non-operative**
  - Hyperbaric Rx
  - Arterial compression
  - DCS
  - Optimal wound care
Limitations of Current Data

- Retrospective, poorly controlled
- Suboptimal endpoints
  - Amputation free survival
  - Target lesion revascularization
  - Target vessel revascularization
  - Patency
- Sponsor/Operator bias
- Inclusion of claudicants
- Short or incomplete follow up
Comparison of Bypass vs. Angioplasty for CLI

Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial

BASIL trial participants

Summary

Background The treatment of rest pain, ulceration, and gangrene of the leg (severe limb ischaemia) remains controversial. We instigated the BASIL trial to compare the outcome of bypass surgery and balloon angioplasty in such patients.

Methods We randomly assigned 452 patients, who presented to 27 UK hospitals with severe limb ischaemia due to infra-inguinal disease, to receive a surgery-first (n=228) or an angioplasty-first (n=224) strategy. The primary endpoint was amputation (of trial leg) free survival. Analysis was by intention to treat. The BASIL trial is registered with the National Research Register (NRR) and as an International Standard Randomised Controlled Trial, number ISRCTN45398889.

Findings The trial ran for 5-5 years, and follow-up finished when patients reached an endpoint (amputation of trial leg above the ankle or death). Seven individuals were lost to follow-up after randomisation (three assigned angioplasty, two surgery); of these, three were lost (one angioplasty, two surgery) during the first year of follow-up. 195 (86%) of 228 patients assigned to bypass surgery and 216 (96%) of 224 to balloon angioplasty underwent an attempt at their allocated intervention at a median (IQR) of 6 (3-10) and 6 (2-20) days after randomisation, respectively. At the end of follow-up, 248 (55%) patients were alive without amputation (of trial leg), 38 (8%) alive with amputation, 36 (8%) dead after amputation, and 130 (29%) dead without amputation. After 6 months, the two strategies did not differ significantly in amputation-free survival (48 vs 60 patients; unadjusted hazard ratio 1.07, 95% CI 0.72-1.6; adjusted hazard ratio 0.73, 0.49-1.07). We saw no difference in health-related quality of life between the two strategies, but for the first year the hospital costs associated with a surgery-first strategy were about one third higher than those with an angioplasty-first strategy.

Interpretation In patients presenting with severe limb ischaemia due to infra-inguinal disease and who are suitable for surgery and angioplasty, a bypass-surgery-first and a balloon-angioplasty-first strategy are associated with broadly similar outcomes in terms of amputation-free survival, and in the short-term, surgery is more expensive than angioplasty.

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.

Lancet 2005; 366: 1925-34
TASC ll Guidelines (Only Anatomic!)

- Evidence based
- Stratifies Rx of arterial occlusive disease, based on location (iliac and femoral) and extent of disease
- Increasingly ignored by Cardiologists, IR, and Vascular Surgeons

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>Description</th>
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| A           | Single stenosis ≤10 cm in length  
              Single occlusion ≤5 cm in length |
| B           | Multiple lesions (stenoses or occlusions), each ≤5 cm  
              Single stenosis or occlusion ≤15 cm not involving the infrageniculate popliteal artery  
              Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass  
              Heavily calcified occlusion ≤5 cm in length  
              Single popliteal stenosis |
| C           | Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification  
              Recurrent stenoses or occlusions that need treatment after an endovascular intervention |
| D           | Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery)  
              Chronic total occlusion of popliteal artery and proximal trifurcation vessels |
Replacement of TASC Guidelines

- Multi-disciplinary
- International
- COI free
- Addresses non-anatomic indications, as well as anatomic
- Lead by Vascular Surgeons (Conte, White, Mills)
BEST-CLI
Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia
BEST Trial

- Prospective, randomized, multicenter, open label superiority trial

- 2,100 patients age 35+ at 120 clinical sites in the US and Canada

- 4-year trial extending from 2014-2017, with each patient having minimum of 2 years follow-up
BEST Trial Objective

To compare treatment efficacy, functional outcomes, and cost in patients with CLI undergoing best open surgical or best endovascular revascularization
Patient Population

• Patients with infrainguinal PAD and CLI who are candidates for BOTH, in the eyes of the investigator:
  
  – *Open* surgical revascularization, and
  
  – *Endovascular* treatment
Critical Limb Ischemia

Rutherford 4: Ischemic rest pain with AP < 40 mm Hg or TP < 30 mm Hg

Rutherford 5: Minor tissue loss, nonhealing ulcer, focal gangrene with diffuse pedal ischemia with AP < 60 mm Hg or TP < 40 mm Hg

Rutherford 6: Major tissue loss extending above TM level, functional foot no longer salvageable with AP < 60 mm Hg or TP < 40 mm Hg
Trial Design

- Definition of “Best Treatment” is determined by the investigator
- All endovascular therapies allowable, with the exception of cryoplasty
- All conduits allowed, including cryopreserved vein and prosthetic
- New and evolving therapies will be critically reviewed as trial progresses to determine if suitable for inclusion
Two Cohort Design

Cohort #1

- Patients with single segment great saphenous vein (N=1620)

Cohort #2

- Patients without single segment great saphenous vein (N=480)
BEST Primary Endpoint

- Primary
  - Major Adverse Limb Event (MALE) – free survival
  - MALE defined as:
    - Above ankle amputation of the index limb or major re-intervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis)
BEST: Secondary Endpoints

- Secondary
  - Re-intervention and Amputation (RAS) – free survival
  - RAS defined as:
    - MALE (Primary endpoint) or minor re-intervention (patch angioplasty, balloon angioplasty, atherectomy, stent/stent graft)
  - Amputation-free Survival
  - Post-Operative Death within 30 days of index procedure
BEST: Inclusion Criteria

- Age > 35 years
- Atherosclerotic, infrainguinal PAD
- CLI—gangrene, non-healing ischemic ulcer, or rest pain (Rutherford categories 4-6)
- Candidate for either open or endovascular infrainguinal revascularization, as judged by the investigator and consultant
- Adequate popliteal, tibial, or pedal revascularization target
- Adequate aortoiliac inflow
BEST: Key Exclusion Criteria

- Femoropopliteal TASC II A pattern disease
- Severe Common Femoral Artery Disease
- Popliteal aneurysm (>2cm) in the index limb
- Life expectancy < 2 years
- Planned above-ankle amputation on ipsilateral limb within 4 weeks of index procedure
- Hypercoagulable states
- Non-atherosclerotic occlusive disease or acute limb-threatening ischemia
Exclusion Criteria Continued

- Any of the following procedures performed in last 6 months:
  - Infrainguinal balloon angioplasty, atherectomy, stent, stent-graft
  - Common, superficial, or deep femoral endarterectomy
  - Infrainguinal bypass w/ venous or prosthetic conduit
  - Open surgical inflow procedure involving the index leg
- Current immune-suppressive meds, chemo/rad therapy
- Any prior index limb infrainguinal stenting or stent grafting associated with restenosis
Pre-Treatment Screening

CLI Patients

- Initial Screen for Eligibility
- Potentially Eligible
  - No Recent Angio
    - Vein Mapping
      - Potentially Eligible
        - Informed Consent
          - Eligibility unknown, Refused
            - Ineligible
          - Eligible, Refused
            - Eligible
          - Consenting
            - Angiography
              - Eligible
                - Eligible, Refused
                  - Ineligible
              - Ineligible
            - Consenting
              - Informed Consent
                - Eligible
                  - Eligible, Refused
                    - Ineligible
                - Eligible
                  - Eligible, Refused
                    - Ineligible
Randomization and Stratification

**COHORT #1**

**Factor A: CLINICAL CLASSIFICATION**

- Ischemic Rest Pain (Rutherford Class 4)
- Tissue Loss with or without Rest Pain (Rutherford Class 5,6)

**COHORT #2**

- Other Vein (N=480)

**ANATOMICAL CLASSIFICATION**

**Factor B:**

- Infrainguinal PAD without significant infrapopliteal occlusive disease
- Infrainguinal PAD with significant infrapopliteal occlusive disease

**Randomization** (Time 0)

- Best Endovascular Revascularization
  - (≤30 days post-rand.)
  - N=1050
  - Best Endo N=810
  - Best Endo N=240

**Post-Procedural Follow-Up Visit**
- 23 to 44 days

**FOLLOWING VISIT**
- 12, 18, 24, 30* mo, end study
- Enrolled pts: 36, 42*, 48 mo
  - *phone only
Debate at 2009 SVS VAM

Should endovascular or open surgery be the initial therapy for TASC D disease of the infrapopliteal arteries?

- Strong arguments made by Meier supporting endovascular first approach, and Conte, supporting open first approach
When Should Surgery Be Initial Therapy for CLI?

Bypass

Endovascular

Patient selection
Arguments For “Endo First” Procedures for CLI

- Better patient acceptance
- Lower initial morbidity and mortality with endo procedures
- Fewer wound complications
- More rapid return to activity in most patients
- “Adequate” improvement in perfusion with endo approach
- Limited life expectancy
- Better reimbursement per hour of work
Arguments for “Open First” Procedure for CLI

• Immediate complete revascularization
  — Greater increase in blood flow to the limb
• More durable than endovascular
• “Minimally invasive” open techniques are no more invasive than endovascular
• Cost is less than with repeated endo procedures
• Long-term survival is the same
Imaging Key to Decision Making in CLI

- Duplex arterial ultrasound
  - Localizes disease
  - Requires technical expertise
  - Does not give complete physiologic information
- CT angiogram
- MR angiogram
- Catheter angiogram
Severe Calf disease: 7 ml Gd
Survey of Rx for CLI
(>200 responses)

• Speakers and attendees at annual UCLA course for two years
  — Included program directors, division chiefs, and other speakers
  — Community based vascular surgeons re-certifying
  — Vascular fellows in training
• What is your initial approach to CLI
  — Open first
  — Endo first
• When do you use an “open first” approach to CLI?
Situations Where Open Surgery Should Be the First Option (Opinion of “Endovascular First” VS)

- **Anatomy**
  - Extensive disease of the common femoral artery which extends proximally under the inguinal ligament and distally into the profunda femoris artery
  - Long segment occlusions of the infrapopliteal arteries (TASC D)

- **Pathology**
  - Extrinsic compression of lower extremity arteries

- **Physiology**
  - Extensive foot sepsis or gangrene

- **Durability**
  - When combined with another bypass procedure
Situations Where Open Surgery Should Be the First Option

Anatomy

• Extensive disease of the common femoral artery
  — Stents ineffective
    • Calcified vessels difficult to dilate
    • Fracture with inguinal ligament compression
    • Self-expanding have inadequate radial strength
  — Atherectomy channel is too small
• Extensive disease of the infrapopliteal arteries
  — Restenosis rate high with endo
  — Difficult to establish durable pulsatile flow to the foot

Lawrence, et al; Eur J Vasc Surg 2010 When Should Open Surgery be the Initial Option for Critical Limb Ischemia?
Femoral Endarterectomy

- Extra-anatomic procedure
- Low risk
- Anesthesia with local or regional
Situations Where Open Surgery Should Be the First Option

Pathology

- Extrinsic compression
  - Popliteal entrapment
  - Adventitial cystic disease
  - Bony abnormalities (e.g. exostosis)
Popliteal Entrapment

- Posterior Approach to popliteal artery
- Division of aberrant muscle
- Release of artery or bypass
Situations Where Open Surgery Should Be the First Option

Durability

• Patients undergoing free tissue transfer
  — Need combination of durable bypass and tissue transfer
• Young patients with longer life expectancy
  — Unwilling to undergo multiple procedures for the same pathology
  — Infrapopliteal disease (extensive) in a young patient
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

Between 2003 and 2011, a total of 3504 patients underwent an index LEB procedure in the VSGNE database. Of these, 1154 (32.9%) were secondary LEBs, and 2350 (67.1%) were primary.

Secondary LEB following prior ipsilateral PVI in **552 of 1154 cases (48%)**, prior ipsilateral LEB in **437 of 1154 cases (38%)**, and both LEB and PVI in **165 of 1154 cases (14%)**.

Overall, the indication for LEB was claudication in 29.7% (1039/3504) and CLI in 70.3% (2465/3504). These indications...
Situations Where Open Surgery Should Be the First Option

**Physiology**

- Diabetic patients with:
  - Extensive tissue loss
  - Forefoot sepsis
  - Extensive forefoot gangrene

- Need immediate and maximum blood flow to foot—\textit{``pulsatile blood flow''}
Degree of complete healing

Type of Revascularization vs. Initial Size Wound

R Neville, et al Georgetown Diabetic Foot Center
In spite of current practice guidelines, most patients undergo an “endo first” approach for CLI. Imaging with MRA and/or CTA is critical in determining the extent of disease. CLI patients must be stratified; there are four situations in which an open first approach is preferable:

- Common femoral and extensive infra-popliteal disease
- Extrinsic arterial compression
- Young patients who need durability
- Extensive tissue loss and sepsis (e.g. ischemic, septic diabetic foot)

SVS international consortium will replace TASC for immediate future. BEST trial and European CLI trial will eventually help to answer this question for the CLI patient with typical atherosclerotic disease, but data will not be available for ~5 years.