Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Impact of Bypass Conduit and Early Technical Failure on Revascularization for Chronic Limb-Threatening Ischemia

Michael S. Conte, MD; Alik Farber, MD, MBA; Andrew Barleben, MD; Emiliano Chisci, MD, PhD; Gheorghe Doros, PhD; Vikram S. Kashyap, MD; Ahmed Kayssi, MD; Philippe Kolh, MD, PhD; Carla C. Moreira, MD, PhD; Timothy Nypaver, MD; Kenneth Rosenfield, MD; Vincent L. Rowe, MD; Andres Schanzer, MD; Niten Singh, MD; Jeffrey J. Siracuse, MD, MBA; Michael B. Strong, MA; Matthew T. Menard, MD

BACKGROUND: The optimal strategy for lower extremity revascularization (surgical bypass versus endovascular intervention) in patients with chronic limb-threatening ischemia (CLTI) is unclear. We examined the effectiveness of open surgical bypass using single-segment great saphenous vein conduit (SSGSV), alternative conduits (AC), or endovascular interventions (ENDO) among patients with CLTI deemed acceptable for either open surgical bypass or ENDO treatment.

METHODS: This was a planned as-treated analysis of the multicenter BEST-CLI (Best Endovascular Versus Best Surgical Therapy in Patients With Critical Limb Ischemia) randomized controlled trial comparing open surgical bypass and ENDO for CLTI due to infrainguinal peripheral artery disease. Outcomes were tabulated based on the initial revascularization received: SSGSV bypass, AC bypass, and ENDO. Analyses were performed for all treated patients and then excluding those who experienced early technical failure. Multivariable Cox regression models were used. End points included the primary trial outcome (major adverse limb event [MALE] or all-cause death), major amputation, MALE at any time or perioperative (30-day) death, reintervention-amputation-death, and all-cause mortality.

RESULTS: Among 1780 patients with CLTI, treatments received included SSGSV bypass (n=621), AC bypass (n=236), and ENDO (n=923) procedures. There were no significant differences in 30-day mortality, major adverse cardiovascular events, or serious adverse events; subjects treated with ENDO experienced greater MALE within 30 days (13.1% versus 2.7%, 3% for SSGSV, AC; $P<0.001$). On risk-adjusted analysis, SSGSV bypass was associated with reduced MALE or all-cause death (hazard ratio, 0.65 [95% CI, 0.56–0.76]; $P<0.001$), major amputation (hazard ratio, 0.70 [95% CI, 0.52–0.94]; $P=0.017$), MALE or perioperative death (hazard ratio, 0.51 [0.41–0.62]; $P<0.001$), and reintervention-amputation-death (hazard ratio, 0.69 [95% CI, 0.61–0.79]; $P<0.001$). AC bypass was associated with reduced MALE or perioperative death and reintervention-amputation-death compared with ENDO. Significant benefits of SSGSV over ENDO remained when excluding patients who experienced early technical failure. There were no significant differences in long-term mortality by initial treatment received. When analyzed by the level of disease treated, the improved outcomes of SSGSV were greatest among patients who underwent femoropopliteal revascularization.

CONCLUSIONS: Analysis of as-treated outcomes from the BEST-CLI trial demonstrates the safety and clinical superiority of bypass with SSGSV among patients with CLTI who were deemed suitable for either open surgical bypass or ENDO revascularization. Assessment of great saphenous vein quality should be incorporated into the evaluation of patients with CLTI who are surgical candidates.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT02060630 and NCT02060630.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: amputation ■ chronic limb-threatening ischemia ■ endovascular procedures ■ limb salvage ■ saphenous vein ■ vascular grafting

Correspondence to: Michael S. Conte, MD, Division of Vascular and Endovascular Surgery, University of California, 400 Parnassus Ave, San Francisco, CA 94143.
Email michael.conte2@ucsf.edu

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCINTERVENTIONS.124.014716.
For Sources of Funding and Disclosures, see page 264.

Circulation: Cardiovascular Interventions is available at www.ahajournals.org/journal/circinterventions

WHAT IS KNOWN

- Effective revascularization is a cornerstone of treatment for chronic limb-threatening ischemia and may be accomplished by employing a range of endovascular and open surgical techniques.
- Baseline patient and anatomic factors strongly influence the technical success and clinical effectiveness of limb revascularization strategies in chronic limb-threatening ischemia.

WHAT THE STUDY ADDS

- Among patients with chronic limb-threatening ischemia who are deemed suitable for either open surgical bypass or endovascular intervention, both strategies are associated with similar short and long-term mortality.
- Open bypass using a single-segment great saphenous vein conduit provided greater limb salvage and reduced target limb reinterventions compared with endovascular intervention.
- Superior outcomes for single-segment great saphenous vein conduit bypass remained evident when early endovascular intervention technical failures were excluded.

Nonstandard Abbreviations and Acronyms

AC	alternative conduits
BASIL-2	Bypass Versus Angioplasty in Severe Ischemia of the Leg Trial-2
BEST-CLI	Best Endovascular Versus Best Surgical Therapy in Patients With Critical Limb Ischemia
CLTI	chronic limb-threatening ischemia
ENDO	endovascular intervention
GSV	great saphenous vein
HR	hazard ratio
ITT	intention-to-treat
KM	Kaplan-Meier
MALE	major adverse limb event
MALE-POD	MALE at any time or perioperative (30 day) death
OPEN	open surgical bypass
RAD	reintervention-amputation-death
SSGSV	single-segment great saphenous vein
TF	technical failure

Effective revascularization is a fundamental pillar of limb preservation for patients with chronic limb-threatening ischemia (CLTI). Clinical success in CLTI is largely dependent on patient risk, the severity of limb threat at presentation, and the anatomic complexity of arterial occlusive disease.[1] Open surgical bypass (OPEN) grafting is an established modality whose outcomes are strongly dependent on the quality of conduit used, among other factors. For infrainguinal bypass, a single-segment great saphenous vein conduit (SSGSV) of adequate caliber (ie, >3 or 3.5 mm) provides the optimal patency and limb salvage rates.[2,3] Alternative conduits (AC), which include spliced autologous vein grafts, prosthetic grafts, cryopreserved allografts, or composites of any of the above, may provide reasonable mid-term results in selected patients but are inferior to SSGSV in terms of patency and limb salvage.[4] Endovascular interventions (ENDO) have assumed a dominant role in the treatment of CLTI over the last 2 decades. ENDO techniques encompass a spectrum of plain balloon angioplasty, atherectomy, bare metal or covered stents, or drug-eluting devices (drug-coated balloons, drug-eluting stents). ENDO procedures are minimally invasive but may be limited by immediate technical failure (TF) as well as high rates of restenosis in complex patterns of disease. Although recent randomized controlled trials demonstrate that reinterventions are significantly reduced when drug-eluting devices are used versus plain balloon angioplasty for femoropopliteal artery disease, few patients with CLTI are represented in these trials.[5] In addition, patients with CLTI commonly present with infrapopliteal or multilevel disease[6] and only recently has any drug-eluting device for infrapopliteal disease gained regulatory approval in the United States (https://www.fda.gov/medical-devices/recently-approved-devices/esprit-btk-everolimus-eluting-resorbable-scaffold-system-p230036; no patient in the BEST-CLI trial [Best Endovascular Versus Best Surgical Therapy in Patients With Critical Limb Ischemia] was treated with that device). Thus, in contrast to open surgery, the optimal ENDO strategy for clinical success in CLTI remains highly variable and operator-dependent.

The BEST-CLI trial was a large, multicenter, pragmatic, randomized, controlled trial designed to compare the effectiveness of OPEN versus ENDO revascularization among patients with CLTI due to infrainguinal peripheral artery disease, who were deemed acceptable candidates for either treatment.[7,8] The trial was designed as 2 parallel randomized controlled trial, based on a-priori hypotheses related to the differential performance of bypass conduits. Specifically, cohort 1 included patients deemed to have an acceptable SSGSV based on preoperative evaluation, with the hypothesis that bypass with SSGSV would be superior to ENDO. In contrast, the hypothesis for cohort 2 (patients lacking adequate SSGSV) was that ENDO would outperform AC bypass. The specific strategy for the best OPEN or ENDO approach for each patient was left to the treating investigator. Randomization in the trial was stratified by clinical indication (ischemic rest pain versus tissue loss) and by the presence of significant infrapopliteal disease.

The primary end point was freedom from a major adverse limb event (MALE) or death from any cause.

Secondary end points included components of the primary end point, major (above the ankle) limb amputation, all-cause mortality, and the composite outcome of target limb reintervention-amputation-death (RAD). The primary trial results analyzed by intention-to-treat (ITT) have been reported, demonstrating the superiority of OPEN over ENDO in cohort 1, and no significant difference in cohort 2. Immediate TF was higher in the ENDO arms of both cohorts (15.1% and 18.6%, respectively), leading some to question whether the selection of patients and expertise or bias of the trial investigators may reduce the applicability of the findings.

Here, we report a planned analysis of the key clinical outcomes in BEST-CLI, based on the initial treatment received. We hypothesized that open bypass using a SSGSV graft would provide superior clinical effectiveness to ENDO in all limb-related end points, regardless of the immediate technical outcome. We examined the outcomes of all patients as-treated (both cohorts) across the 3 groups—SSGSV bypass, AC bypass, and ENDO—and then excluded subjects who experienced immediate TF.

METHODS

The design and primary outcomes of BEST-CLI are reported elsewhere. Trial oversight committees were selected to represent multiple specialties and stakeholders and included attention to diversity in recruitment and retention of study participants.[7,8]

Deidentified BEST-CLI data and materials have been made publicly available by the National Heart, Lung, and Blood Institute and are available under accession HLB02932424a through this National Heart, Lung and Blood Institutes BIOLINCC (Biologic Specimen and Data Repository Information Coordinating Center; website: https://biolincc.nhlbi.nih.gov/studies/best_cli/).

Study Population

BEST-CLI was conducted at 150 sites in the United States, Canada, Finland, Italy, and New Zealand. The study protocol was approved by the appropriate ethics committee at each site, and all patients provided written informed consent. The disposition of patients enrolled in the trial and the treatments received are summarized in the modified CONSORT diagram (Figure S1; Table S1). Enrolled patients were placed into either cohort 1 or 2 based on assessment of the great saphenous vein (GSV); they were further stratified by the limb status at presentation (rest pain or tissue loss) and the presence of significant infrapopliteal artery disease to ensure balance in these factors. Following randomization (N=1830), a total of 50 patients did not undergo any revascularization procedure; the remaining 1780 are included in the as-treated analysis and received ENDO (n=923), SSGSV bypass (n=621), or AC bypass (n=236). This includes 34 patients who crossed over from their randomized (OPEN versus ENDO) treatment assignment. Of the 718 patients randomized to OPEN in cohort 1, 662 received an open operation as the first procedure per protocol, and 581 (88%) of these received an SSGSV bypass; 81 (12%) received an AC bypass. Of the 197 patients randomized to OPEN in cohort 2, 188 received an open operation as their first procedure per protocol and 151 (80%) of these received an AC bypass; 37 (20%) had their bypass completed using SSGSV.

TF in the trial was defined as failure to achieve a patent bypass graft or abandonment of the surgical bypass procedure for any cause in the OPEN arm; for ENDO, it was defined as inability to cross a target lesion, occlusion, or persistent obstruction (>50%) of the target artery path such that in-line flow to the foot was not achieved or a complication (vessel rupture, dissection or embolization) that could not be managed via an endovascular approach. Of note, investigators were permitted to execute a planned second stage ENDO within 4 days of the initial procedure without penalty if this was deemed clinically appropriate. Further details of the BEST-CLI trial design and procedures are reported elsewhere.[7,8]

Study End Points

All end points were measured as time to event, except for total number of target limb reinterventions over time. MALE were defined in accordance with the Society for Vascular Surgery Objective Performance Goals[9] as either a major limb amputation or a major reintervention (new open bypass graft, major open surgical revision [jump or interposition graft], or thrombectomy/thrombolysis of the target limb). Minor reinterventions included repeat percutaneous angioplasty, stenting, or atherectomy or a surgical patch angioplasty.

The primary composite end point was MALE or all-cause mortality at any time. Secondary end points included MALE at any time or perioperative (30 day) death (MALE-POD), major amputation, all-cause mortality, any target limb reintervention, and the composite end point of RAD.

Statistical Analysis

All BEST-CLI patients who underwent a revascularization procedure (N=1780) were included in this analysis. The outcome analyses were performed according to the as-treated principle. Time-to-event outcomes were described with the use of Kaplan-Meier (KM) methods, and treatment groups were compared with the use of log-rank test statistics; KM event rates are reported at 1 and 3 years. Multivariable Cox proportional hazards models were created for each of the end points, adjusting for prespecified baseline variables including randomization strata, prior infrainguinal revascularization in the target limb, end-stage renal disease, diabetes, and smoking. Additional baseline covariates identified as being associated with study end points on univariate screen ($P<0.2$) were also included in these models. Hazard ratios (HRs) and 95% CIs are reported with ENDO as the referent group. The outcome of major limb amputation was also analyzed with death as a competing risk using the Fine-Gray subdistribution hazard model.[10]

We used the sensitivity index of the KM estimate, defined as $D(t)=100\times[1-KM(t)]/n(t)$, where $KM(t)$ is the incidence rate at time t and $n(t)$ is the number of subjects at risk, to determine the time beyond which the estimates are less meaningful. Based on Gebski et al,[11] this threshold was determined to be 5 years; thus, in our presentation, the KM curves were truncated at 5 years.

In computing the number of target limb reinterventions/person-year, the follow-up time was determined by either major limb amputation or study termination for each subject. The widths of the CIs have not been adjusted for multiplicity, so CIs should not be used for hypothesis testing. All the analyses were performed with the use of SAS version 9.4 (SAS Institute) and R software, version 4.30.

RESULTS

Baseline Characteristics of the As-Treated Subgroups

Baseline patient characteristics, limb status, and procedural details are summarized in Tables 1 and 2. In general, patient characteristics were well balanced across the 3 as-treated groups with the exceptions of prior coronary artery bypass grafting (37.5% SSGSV, 68.8% AC, 49.6% ENDO; $P<0.001$), prior coronary artery bypass grafting or percutaneous coronary intervention (66.8% SSGSV, 85.7% AC, 76.2% ENDO; $P<0.001$), prior transient ischemic attack or stroke (13.9% SSGSV, 20.8% AC, 17.3% ENDO; $P=0.037$), and baseline antiplatelet use (dual therapy: 13.4% SSGSV, 20.3% AC, 20.6% ENDO; $P<0.001$). There were no significant differences in prior index limb revascularization, wound, ischemia, and foot infection staging system stage, or baseline hemodynamics in the affected limb. Bypass targets differed across the 2 OPEN subgroups with SSGSV targets more commonly being infrapopliteal (56%, versus 44% for AC; $P<0.001$). Levels of disease treated (femoropopliteal only, infrapopliteal only, or combined femoropopliteal+infrapopliteal) were significantly different ($P=0.003$) with notably few (9.5%) isolated infrapopliteal bypasses using AC conduits. Among the ENDO subgroup, 41% underwent multilevel interventions, 46% were treated with a drug-eluting device (drug-coated balloon or drug-eluting stent), stents were used in 39.8%, and atherectomy was infrequently used (14.3%). In the SSGSV subgroup, 39% of bypasses were multilevel (femoropopliteal+infrapopliteal), 42.5% were femoropopliteal only, and 18.5% were infrapopliteal only.

Overall, immediate TF occurred in 157 subjects, the majority in the ENDO subgroup (16.3% ENDO versus 0.3% SSGSV, 3.9% AC; $P<0.001$). Examination of the baseline patient and limb characteristics across the 3 subgroups with technical success (not shown) demonstrated similar findings to the overall population.

Summary of Outcomes by Treatment Received (All Subjects)

Periprocedural (30-day) outcomes across the 3 as-treated groups are summarized in Table 3. Mortality (1.3% SSGSV, 2.5% AC, 0.9% ENDO; $P=0.114$) was not different by treatment received. There were a greater number of major adverse cardiovascular events in both OPEN subgroups, but the difference was not significant (4.5% SSGSV, 4.7% AC, 2.6% ENDO; $P=0.084$). There was no difference in the proportion of patients experiencing at least 1 serious adverse event. MALE was significantly greater in the ENDO subgroup (2.7% SSGSV, 3% AC, 13.1% ENDO; $P<0.001$).

In comparison to ENDO-treated patients, those treated with SSGSV bypass experienced significantly reduced rates of the primary end point MALE or all-cause death (HR, 0.65 [95% CI, 0.56–0.76]; $P<0.001$), as well as major amputation (HR, 0.7 [95% CI, 0.52–0.94]; $P=0.016$), MALE-POD (HR, 0.51 [95% CI, 0.41–0.62]; $P<0.001$), RAD (HR, 0.69 [95% CI, 0.61–0.79]; $P<0.001$), and any target limb reintervention (HR, 0.64 [95% CI, 0.55–0.76]; $P<0.001$). In comparison to ENDO, those treated with AC bypass experienced reduced rates of MALE-POD (HR, 0.69 [95% CI, 0.52–0.92]; $P=0.01$), RAD (HR, 0.79 [95% CI, 0.66–0.95]; $P=0.014$), and any reintervention (HR, 0.73 [95% CI, 0.57–0.93]; $P=0.011$). Unadjusted time-to-event curves are illustrated in Figure (A) through (F). The estimated KM outcome rates at 3 years for each of the as-treated subgroups are summarized in Table 4. Table S2 provides 1-year KM estimates for all as-treated patients. Table S3 provides 3-year KM estimates separately for the 2 ITT cohort subpopulations.

To examine the impact of anatomic levels of disease treated, we repeated the Cox regression models separately within the 3 subgroups of femoropopliteal only, infrapopliteal only, and femoropopliteal+infrapopliteal. These results (Figure S2) demonstrate that the improved outcomes associated with SSGSV bypass versus ENDO were greatest in the patients who underwent femoropopliteal-only procedures. In this subgroup, SSGSV bypass was associated with reduced incidences of major amputation (HR, 0.54; $P=0.025$), MALE or death (HR, 0.63; $P<0.001$), MALE or postoperative death (MALE-POD: HR, 0.5; $P<0.001$), reintervention-amputation or death (RAD; HR, 0.7; $P<0.001$), and any reintervention (HR, 0.66; $P=0.002$) versus ENDO. AC bypass in the femoropopliteal-only subgroup was also superior to Endo in the end points of MALE-POD (HR, 0.59; $P=0.027$) and any reintervention (HR, 0.63; $P=0.012$). Although outcome trends were similar in the femoropopliteal+infrapopliteal and infrapopliteal-only subgroups, they did not achieve significance with the exception of RAD (HR, 0.81; $P=0.046$) for SSGSV versus Endo in the combined femoropopliteal+infrapopliteal patients.

We also examined the total number of target limb reinterventions experienced by patients over follow-up in the trial. Among the 621 patients treated with SSGSV bypass, a total of 344 reinterventions were performed, yielding a rate of 23.8 reinterventions per 100 person-years. In the 236 patients treated with AC bypass, 147 reinterventions were performed for a rate of 34.8 per

Table 1. Summary of Baseline Demographics, Comorbidities, and Limb Status at Presentation by As-Treated Subgroups

Characteristics	Overall (N=1780)	SSGSV (n=621)	AC (n=236)	ENDO (n=923)	*P* value
Demographics and comorbidities					
Age, y					
Mean±SD	67.2±9.7 (1780)	66.8±9.7 (621)	67.9±8.9 (236)	67.3±10.0 (923)	0.295
Sex					0.159
Male	71.7% (1276/1780)	74.1% (460/621)	67.8% (160/236)	71.1% (656/923)	
Female	28.3% (504/1780)	25.9% (161/621)	32.2% (76/236)	28.9% (267/923)	
Hispanic	13.3% (236/1779)	12.6% (78/620)	11.9% (28/236)	14.1% (130/923)	0.551
Race					0.610
White	72.0% (1269/1763)	72.0% (443/615)	70.7% (164/232)	72.3% (662/916)	
Black	20.2% (357/1763)	21.3% (131/615)	21.6% (50/232)	19.2% (176/916)	
Other	7.8% (137/1763)	6.7% (41/615)	7.8% (18/232)	8.5% (78/916)	
BMI, kg/m^2, mean±SD	27.9±6.0 (1708)	27.9±6.2 (595)	27.4±5.8 (227)	28.1±5.9 (886)	0.359
Hypertension	87.1% (1548/1778)	85.9% (532/619)	88.1% (208/236)	87.5% (808/923)	0.573
Previous MI	50.1% (398/795)	50.4% (130/258)	50.0% (56/112)	49.9% (212/425)	0.992
Prior CABG	46.7% (373/798)	37.5% (97/259)	68.8% (77/112)	46.6% (199/427)	<0.001
Prior PCI	41.2% (329/799)	38.2% (99/259)	37.5% (42/112)	43.9% (188/428)	0.235
Prior CABG/PCI	74.5% (595/799)	66.8% (173/259)	85.7% (96/112)	76.2% (326/428)	<0.001
Congestive heart failure	5.6% (100/1776)	4.5% (28/618)	7.2% (17/236)	6.0% (55/922)	0.259
Chronic obstructive pulmonary disease	15.2% (271/1778)	13.9% (86/619)	16.9% (40/236)	15.7% (145/923)	0.458
History of TIA/stroke	16.6% (295/1778)	13.9% (86/619)	20.8% (49/236)	17.3% (160/923)	0.037
CKD grade					0.474
No CKD or stage <3	73.2% (1300/1777)	74.5% (461/619)	75.0% (177/236)	71.8% (662/922)	
Stage 3	12.1% (215/1777)	12.8% (79/619)	9.3% (22/236)	12.4% (114/922)	
Stage 4	2.4% (42/1777)	2.6% (16/619)	1.7% (4/236)	2.4% (22/922)	
Stage 5	0.6% (10/1777)	0.2% (1/619)	1.3% (3/236)	0.7% (6/922)	
Dialysis dependent	10.6% (189/1777)	8.9% (55/619)	11.4% (27/236)	11.6% (107/922)	
Functional renal transplant	1.2% (21/1777)	1.1% (7/619)	1.3% (3/236)	1.2% (11/922)	
ESRD	10.6% (189/1777)	8.9% (55/619)	11.4% (27/236)	11.6% (107/922)	0.216
Smoking status					0.728
Never	21.9% (390/1778)	21.3% (132/619)	20.3% (48/236)	22.8% (210/923)	
Prior (>1 y)	34.1% (606/1778)	32.8% (203/619)	35.6% (84/236)	34.6% (319/923)	
Current or <1 y prior	44.0% (782/1778)	45.9% (284/619)	44.1% (104/236)	42.7% (394/923)	
Diabetes	69.2% (1230/1778)	71.4% (442/619)	64.8% (153/236)	68.8% (635/923)	0.166
Ambulatory status					0.320
Without assistance	54.6% (970/1777)	55.5% (343/618)	55.5% (131/236)	53.7% (496/923)	
With assistance	32.6% (580/1777)	33.3% (206/618)	33.9% (80/236)	31.9% (294/923)	
Wheelchair/bed-bound	12.8% (227/1777)	11.2% (69/618)	10.6% (25/236)	14.4% (133/923)	
Living home	94.4% (1677/1777)	95.6% (592/619)	95.8% (226/236)	93.2% (859/922)	0.072
Baseline medications					
Statin	72.0% (1281/1780)	69.7% (433/621)	79.2% (187/236)	71.6% (661/923)	0.020
Use antiplatelet					0.001
No antiplatelet	26.9% (478/1780)	29.5% (183/621)	20.8% (49/236)	26.7% (246/923)	
Single antiplatelet	55.1% (981/1780)	57.2% (355/621)	58.9% (139/236)	52.8% (487/923)	
DAPT	18.0% (321/1780)	13.4% (83/621)	20.3% (48/236)	20.6% (190/923)	
Anticoagulant	10.9% (194/1780)	8.9% (55/621)	14.4% (34/236)	11.4% (105/923)	0.053
Randomization strata					0.290
Stratum-I	9.6% (170/1780)	8.4% (52/621)	12.7% (30/236)	9.5% (88/923)	
Stratum-II	24.0% (428/1780)	22.7% (141/621)	26.3% (62/236)	24.4% (225/923)	

(*Continued*)

Table 1. Continued

Characteristics	Overall (N=1780)	SSGSV (n=621)	AC (n=236)	ENDO (n=923)	*P* value
Stratum-III	12.8% (228/1780)	12.7% (79/621)	14.0% (33/236)	12.6% (116/923)	
Stratum-IV	53.6% (954/1780)	56.2% (349/621)	47.0% (111/236)	53.5% (494/923)	

Randomization strata: (I) rest pain, no IP disease; (II) tissue loss, no IP disease; (III) rest pain with IP disease; and (IV) tissue loss with IP disease). AC indicates alternative conduits; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; ENDO, endovascular intervention; ESRD, end-stage renal disease; IP, infrapopliteal; MI, myocardial infarction; PCI, percutaneous coronary intervention; SSGSV, single-segment great saphenous vein conduit; and TIA, transient ischemic attack.

100 person-years. Among the 923 patients treated with ENDO, 720 reinterventions were performed for a rate of 35.2 per 100 person-years.

Cox proportional hazards models for selected end points identified other important predictors (Table S4). End-stage renal disease was significantly associated

Table 2. Summary of Key Limb and Procedural Details by Treatment Received (All Subjects)

Characteristics	Overall (N=1780)	SSGSV (n=621)	AC (n=236)	ENDO (n=923)	*P* value
Limb related					
Prior infrainguinal revascularization of index limb	6.5% (115/1777)	5.8% (36/619)	8.9% (21/235)	6.3% (58/923)	0.240
WIFI wound grade					0.134
0	21.2% (365/1724)	19.6% (117/597)	25.1% (57/227)	21.2% (191/900)	
1	42.6% (734/1724)	39.9% (238/597)	44.5% (101/227)	43.9% (395/900)	
2	30.1% (519/1724)	33.3% (199/597)	25.6% (58/227)	29.1% (262/900)	
3	6.1% (106/1724)	7.2% (43/597)	4.8% (11/227)	5.8% (52/900)	
Ankle-brachial index in index limb					
Mean±SD	0.6±0.3 (1227)	0.6±0.3 (437)	0.5±0.3 (161)	0.6±0.3 (629)	0.368
Median (Q1, Q3)	0.5 (0.4, 0.7)	0.5 (0.4, 0.7)	0.5 (0.4, 0.6)	0.5 (0.4, 0.7)	
Toe pressure					
Mean±SD	35.2±24.9 (766)	35.4±23.9 (259)	35.9±26.6 (102)	34.9±25.2 (405)	0.933
Median (Q1, Q3)	32.0 (20.0, 47.0)	32.0 (20.0, 47.0)	32.0 (21.0, 45.0)	32.0 (20.0, 46.0)	
Procedure factors					
Aortoiliac intervention	9.3% (166/1780)	11.1% (69/621)	9.3% (22/236)	8.1% (75/923)	0.141
CFA endarterectomy	15.2% (271/1780)	22.1% (137/621)	26.3% (62/236)	7.8% (72/923)	<0.001
CFA endo treatment	2.6% (47/1780)	0.6% (4/621)	0.4% (1/236)	4.6% (42/923)	<0.001
Femoral/popliteal target	22.1% (394/1780)	43.8% (272/621)	51.7% (122/236)	0.0% (0/923)	<0.001
Tibial/pedal target	25.4% (452/1780)	56.0% (348/621)	44.1% (104/236)	0.0% (0/923)	<0.001
Endovascular therapy details					
SFA	34.7% (617/1780)	0.2% (1/621)	0.8% (2/236)	66.5% (614/923)	<0.001
Popliteal	27.9% (496/1780)	0.0% (0/621)	0.4% (1/236)	53.6% (495/923)	<0.001
SFA/POP	40.7% (724/1780)	0.2% (1/621)	1.3% (3/236)	78.0% (720/923)	<0.001
Tibias and pedals	26.0% (463/1780)	0.0% (0/621)	0.0% (0/236)	50.2% (463/923)	<0.001
Multilevel	19.4% (345/1780)	0.0% (0/621)	0.0% (0/236)	37.4% (345/923)	<0.001
Atherectomy	7.4% (132/1780)	0.0% (0/621)	0.0% (0/236)	14.3% (132/923)	<0.001
Drug elution (DCB or DES)	23.9% (426/1780)	0.0% (0/621)	0.4% (1/236)	46.0% (425/923)	<0.001
Level treated (combination of OPEN and ENDO)					0.003
FP only	45.3% (755/1668)	42.5% (257/605)	54.1% (120/222)	44.9% (378/841)	
IP only	15.0% (251/1668)	18.5% (112/605)	9.5% (21/222)	14.0% (118/841)	
FP+IP	39.7% (662/1668)	39.0% (236/605)	36.5% (81/222)	41.0% (345/841)	
Technical success					<0.001
No	9.0% (157/1746)	0.3% (2/618)	3.9% (9/232)	16.3% (146/896)	
Yes	91.0% (1589/1746)	99.7% (616/618)	96.1% (223/232)	83.7% (750/896)	

AC indicates alternative conduits; CFA, common femoral artery; DCB, drug-coated balloon; DES, drug-eluting stent; ENDO, endovascular intervention; FP, femoropopliteal; IP, infrapopliteal; OPEN, open surgical bypass; POP, popliteal artery; SFA, superficial femoral artery; SSGSV, single-segment great saphenous vein conduit; and WIFI, wound, ischemia and foot infection staging system.

Table 3. Key Periprocedural (30-Day) Outcomes by Treatment Received (All Subjects)

Outcome % (n/N)	SSGSV (n=621)	AC (n=236)	ENDO (n=923)	*P* value
MACE	4.5% (28/621)	4.7% (11/236)	2.6% (24/923)	0.084
Mortality	1.3% (8/621)	2.5% (6/236)	0.9% (8/923)	0.114
MI	2.9% (18/621)	2.5% (6/236)	1.7% (16/923)	0.301
Stroke	0.8% (5/621)	0.4% (1/236)	0.4% (4/923)	0.603
MALE	2.7% (17/621)	3.0% (7/236)	13.1% (121/923)	<0.001
Major reintervention	1.8% (11/621)	2.5% (6/236)	11.5% (106/923)	<0.001
Above ankle amputation	1.0% (6/621)	1.3% (3/236)	2.0% (18/923)	0.284
SAE	30.4% (189/621)	30.1% (71/236)	31.9% (294/923)	0.785

AC indicates alternative conduits; ENDO, endovascular intervention; MACE, major adverse cardiovascular event; MALE, major adverse limb event; MI, myocardial infarction; SAE, serious adverse event; and SSGSV, single-segment great saphenous vein conduit.

with all-cause mortality, MALE-death, major amputation, and RAD ($P<0.001$ for all). Diabetes was associated with major amputation ($P=0.01$) and all-cause mortality ($P=0.04$). Prior index limb revascularization was associated with RAD or any target limb reintervention ($P=0.05$). Randomization strata (tissue loss versus rest pain, presence of significant infrapopliteal disease versus none) were associated with all-cause mortality, MALE-death, major amputation, and RAD ($P<0.01$ for all).

Outcomes After Exclusion of Subjects Experiencing TF

When excluding patients who experienced early TF, there were 616 SSGSV, 223 AC, and 750 ENDO treatments. Superior outcomes for SSGSV in comparison to ENDO remained evident for the end points of MALE-death (HR, 0.81 [95% CI, 0.69–0.95]; $P=0.01$), major amputation (HR, 0.73 [95% CI, 0.54–0.99]; $P=0.041$), MALE-POD (HR, 0.74 [95% CI, 0.59–0.92]; $P=0.008$), and RAD (HR, 0.83 [95% CI, 0.72–0.95]; $P=0.007$). There were no significant differences between AC bypass and ENDO subgroups once TFs were excluded. Estimated KM event rates at 3 years for patients who experienced technical success are summarized in Table 5 and survival curves are illustrated in Figure S3.

DISCUSSION

Analysis of the as-treated outcomes from the BEST-CLI trial demonstrates that, among patients with infrainguinal CLTI who were deemed acceptable candidates for either OPEN or ENDO treatment strategies, those undergoing initial bypass with SSGSV experienced significantly fewer major amputations, major or any reinterventions, and no difference in all-cause mortality in comparison to those receiving initial ENDO procedures. These differences remained significant, albeit with attenuated effect size when patients with early TF were excluded. These results should be viewed as supplementary to those reported from the primary trial ITT analysis and provide further confirmation of those findings. They also justify the parallel trial design of BEST-CLI based on preoperative assessment of GSV quality, a determination readily made in clinical practice using noninvasive ultrasound vein mapping.

Recent reports from propensity-matched cohort studies provide similar findings to BEST-CLI. Ricco et al[12] reported on a multicenter retrospective study of 793 patients who underwent first-time infrainguinal bypass or ENDO for CLTI. Propensity-matched analysis (N=472) demonstrated superior amputation-free survival and wound healing, and reduced MALE and major amputation, in those treated with open bypass (81% autogenous conduits). There were no differences in all-cause mortality or major adverse cardiovascular events between groups. Liu et al[13] reported a single institution series of patients with CLTI (N=413) who underwent revascularization and had complete wound, ischemia, and foot infection staging system staging available. Using inverse propensity weighting, they identified improved limb salvage for those treated with autogenous vein bypass (29% of cohort) versus endovascular or nonautogenous bypass; notably, the benefit was greatest among patients presenting with advanced limb threat (wound, ischemia, and foot infection staging system stage 4). Zarrintan et al[14] conducted a Medicare-linked Vascular Quality Initiative (VQI-VISION [Vascular Quality Initiative-Vascular Implant Surveillance and Interventional Outcomes Network]) analysis of patients who had undergone either open bypass or ENDO for CLTI over a 10-year period (2010–2019) employing a robust propensity score matching approach. They subdivided open bypass by those employing GSV conduit versus AC. They found that open bypass with GSV was associated with reduced hazard for death, amputation, and combined amputation/death at both 2 and 4 years. In their study, the improved outcomes for GSV bypass versus ENDO were evident across all 3 anatomic levels of disease (femoropopliteal, infrapopliteal, femoropopliteal+infrapopliteal). In contrast, a contemporary Medicare claims analysis found that patients with CLTI in the Medicare population were older, had more comorbidities, and experienced higher

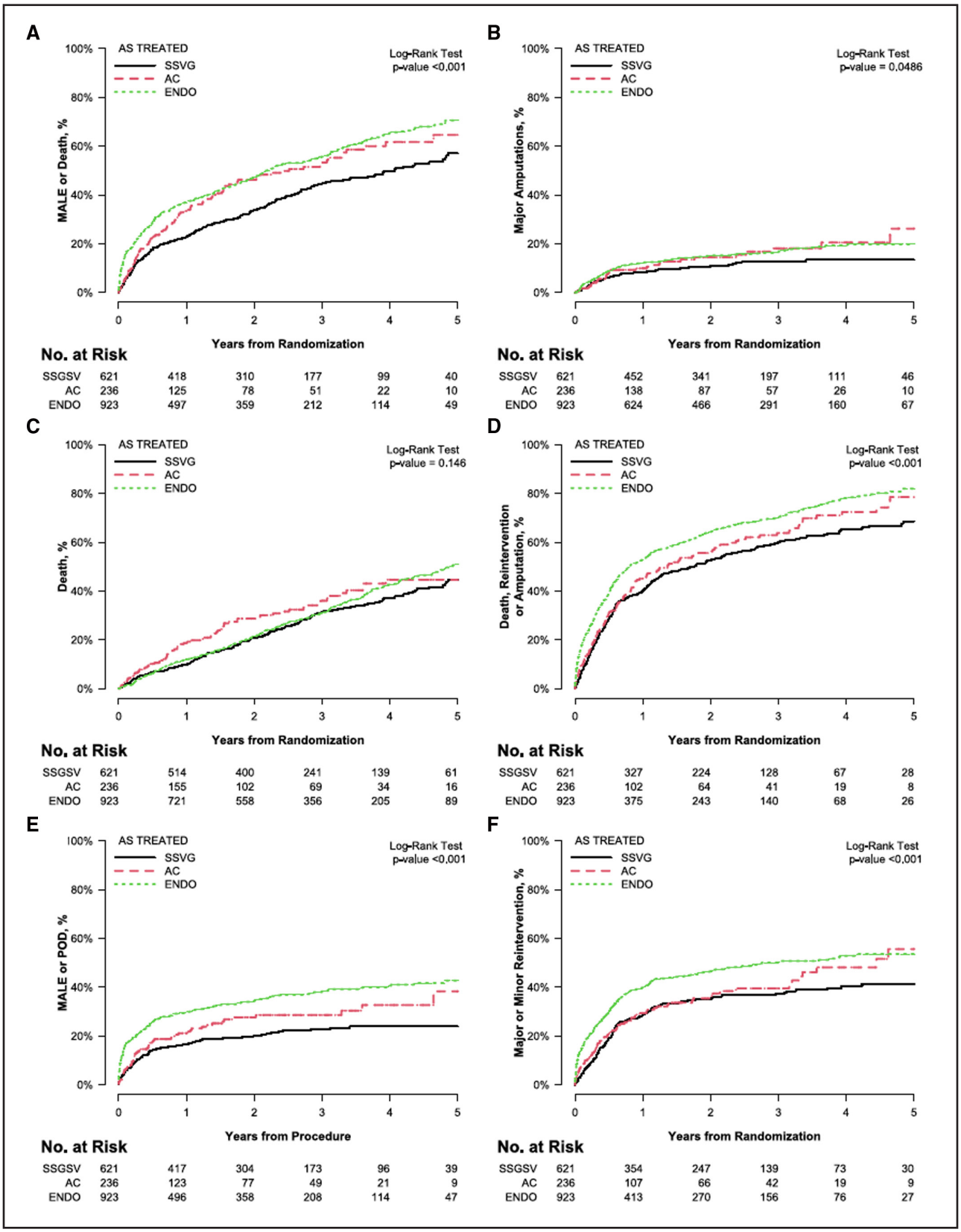

Figure. Unadjusted Kaplan-Meier curves for key outcomes by as-treated subgroups.
Unadjusted Kaplan-Meier curves for (**A**) major adverse limb event (MALE) or all-cause death, (**B**) major amputation, (**C**) all-cause death, (**D**) reintervention-amputation-death, (**E**) MALE at any time or perioperative (30 day) death (MALE-POD), and (**F**) or any target limb reintervention, by initial treatment received (all subjects). AC indicates alternative conduits; ENDO, endovascular intervention; SSGSV, single-segment great saphenous vein conduit; and SSVG, single-segment great saphenous vein graft.

Table 4. KM Estimated Event Rates (3 Years) for the Individual Study End Points for All As-Treated Patients

All subjects	SSGSV (n=621)		AC (n=236)		ENDO (n=923)	
Outcomes	KM rate	HR (95% CI)	KM rate	HR (95% CI)	KM rate	HR (95% CI)
MALE-death	44.6%	0.65 (0.56–0.76)	53.3%	0.87 (0.71–1.07)	55.7%	REF
Major amp	12.9%	0.70 (0.52–0.94)	18.1%	0.98 (0.67–1.46)	16.5%	REF
Death	31.4%	0.91 (0.77–1.09)	36.0%	1.18 (0.92–1.52)	31.1%	REF
MALE-POD	22.9%	0.51 (0.41–0.62)	28.6%	0.69 (0.52–0.92)	38.2%	REF
RAD	60.1%	0.69 (0.61–0.79)	63.8%	0.79 (0.66–0.95)	70.2%	REF
Any reint.	37.4%	0.64 (0.55–0.76)	39.5%	0.73 (0.57–0.93)	50.1%	REF
Amp or death	38.9%	0.86 (0.73–1.01)	46.1%	1.15 (0.91–1.44)	40.3%	REF

HR was computed by Cox proportional hazards models with ENDO as the referent group for all. AC indicates alternative conduits; Amp or death, major amputation or death at any time; ENDO, endovascular intervention; HR, hazard ratio; KM, Kaplan-Meier; MALE, major adverse limb event; MALE-POD, MALE at any time or postoperative (30-day) death; RAD, reintervention-amputation-death; REF, reference; reint, reintervention; and SSGSV, single-segment great saphenous vein conduit.

mortality and MALE after bypass surgery than what was observed in the surgical arm of BEST-CLI.[15]

Numerous published studies demonstrate the safety and superiority of SSGSV bypass over alternative bypass conduits in patients with CLTI. The results obtained in BEST-CLI align well with these prior reports. For example, Arvela et al[3] reported an institutional series of 1109 open bypass procedures among which 818 (74%) were constructed using SSGSV. They observed primary patency rates of 74.4% and 67.1% at 1 and 3 years, and limb salvage rates of 88.9% and 86.9%, respectively. The present results from BEST-CLI compare favorably, with a 1-year rate of any reintervention of 28.6% and major amputation in 8.1% among those treated with SSGSV. Further comparative outcomes by conduit types used in BEST-CLI are beyond the scope of the present report and are a subject of ongoing analysis. It is also notable that among the patients enrolled in BEST-CLI who were assessed preoperatively as likely to be able to undergo an SSGSV bypass (cohort 1), 88% of those assigned to OPEN had their bypass completed using SSGSV. Conversely, 20% of those assigned to OPEN in cohort 2 were still able to receive an SSGSV bypass at time of surgery. This implies that the specificity of the preoperative assessment for GSV quality was high, but the sensitivity was somewhat less so. Since the approach to preoperative vein mapping was not standardized in the trial, we are unable to shed further light on this. However, experienced surgeons may explore GSV conduits deemed marginal on preoperative ultrasound or modify the inflow and outflow targets to achieve an SSGSV graft.

The incidence, causes, and downstream consequences of early TF in BEST-CLI are the subject of a separate analysis. Much has been made of the TF rate reported in the trial, yet it appears largely concordant with data reported from other contemporary trials and registries, particularly in the setting of complex anatomy.[12,16,17] TF after ENDO was an important driver of the observed differences in MALE in both the reported ITT results and the as-treated analysis. However, the present analysis demonstrates that SSGSV bypass remained superior to ENDO across multiple efficacy end points even when those who experienced early TF were excluded. Superior outcomes with respect to the need for repeat interventions and limb salvage speak to

Table 5. KM Estimated Event Rates (3 Years) for the Individual Study End Points After Excluding Those With Early Technical Failure

ITF excluded	SSGSV (n=616)		AC (n=223)		ENDO (n=750)	
Outcomes	KM rate	HR (95% CI)	KM rate	HR (95% CI)	KM rate	HR (95% CI)
MALE-death	44.7%	0.81 (0.69–0.95)	52.6%	1.08 (0.87–1.34)	49.3%	REF
Major amp	13%	0.73 (0.54–0.99)	17.2%	0.96 (0.63–1.45)	16%	REF
Death	31.5%	0.94 (0.78–1.13)	34.7%	1.15 (0.88–1.5)	29.8%	REF
MALE-POD	22.8%	0.74 (0.59–0.92)	27.5%	0.99 (0.73–1.34)	30.1%	REF
RAD	60.2%	0.83 (0.72–0.95)	63.8%	0.94 (0.78–1.14)	65.8%	REF
Any reint.	37.5%	0.86 (0.72–1.03)	39.6%	0.98 (0.76–1.26)	43.3%	REF
Amp or death	39.1%	0.90 (0.76–1.07)	45.0%	1.14 (0.89–1.45)	38.5%	REF

HR was computed by Cox proportional hazards models with ENDO as the referent group for all. AC indicates alternative conduits; Amp or death, major amputation or death at any time; ENDO, endovascular intervention; HR, hazard ratio; ITF, immediate technical failure (see text); KM, Kaplan-Meier; MALE, major adverse limb event; MALE-POD, MALE at any time or postoperative (30-day) death; RAD, reintervention-amputation-death; REF, reference; reint, reintervention; and SSGSV, single-segment great saphenous vein conduit.

the greater durability and likely greater hemodynamic gain associated with SSGSV bypass. As the clinical indications underlying repeat interventions were not fully captured in the BEST-CLI database, it remains unclear to what extent ongoing or repeat CLTI symptoms were the primary drivers of these secondary procedures. We recently reported an ITT analysis from the trial focused on index limb reinterventions, which highlighted the superior durability associated with OPEN treatment assignment in the trial.[18] Another preplanned ITT analysis reported on several novel secondary outcomes such as time to resolution of CLTI symptoms, recurrence of CLTI, and hemodynamic failure; all of these end points favored the OPEN treatment assignment within cohort 1 of the trial.[19]

In contrast to BEST-CLI, the recently reported BASIL-2 (Bypass Versus Angioplasty in Severe Ischemia of the Leg Trial-2) conducted primarily in the United Kingdom compared initial OPEN versus ENDO strategies in patients with CLTI with infrapopliteal disease and found that amputation-free survival was better for those initially treated with ENDO.[17] The apparently conflicting results between BEST-CLI and the BASIL-2 trial have been the topic of much debate and discussion in the field. Important differences in the study populations, trial design, and healthcare systems have been enumerated and ongoing work between the study groups is looking to better clarify areas of concordance.[20] BEST-CLI demonstrated significant differences in limb-related outcomes, but not overall patient mortality, by treatment strategy; BASIL-2 essentially had the opposite findings. BASIL-2 has not reported an as-treated analysis to date. Differences in the surgical outcomes from the 2 trials are most relevant. In both the ITT and the as-treated analyses of the BEST-CLI trial, there were no significant differences in perioperative or long-term mortality between ENDO and OPEN strategies. Notably the perioperative mortality reported here for SSGSV bypass (1.3%) and even AC bypass (2.5%), is lower than for those assigned to open bypass with vein (6%) in BASIL-2. The BASIL-2 study reported a 53% mortality for the open bypass group at a median follow-up time of 40 months, which also appears substantially higher than the 31.4% 3-year mortality reported here for patients who received SSGSV bypass in the BEST-CLI trial. Importantly, BASIL-2 enrolled subjects who required treatment of infrapopliteal disease, and the extent of femoropopliteal disease among subjects in that trial is unclear. It is thus of interest that we found the greatest differences between SSGSV bypass and ENDO outcomes in BEST-CLI in patients treated for femoropopliteal-only disease (who would have been excluded from BASIL-2). A post hoc analysis of angiographic patterns of disease in BEST-CLI is currently ongoing and will provide greater insight into anatomic determinants of treatment outcomes. Further work is needed to better unravel the confounders in these topline comparisons between the 2 trials.

This study has limitations. First, the as-treated analysis, by its nature, is subject to confounding and selection bias associated with any nonrandomized comparison. We adjusted for multiple baseline variables to reduce such confounding. Intrinsic differences between subjects enrolled in the 2 randomization cohorts are reflected in the contrasts between the surgical conduit subgroups. A second major limitation is the lack of anatomic details on the disease patterns of patients in BEST-CLI, an area of ongoing post hoc study. Third, BEST-CLI was a pragmatic trial and thus there was a lack of standardization of procedures within the randomized arms. Fourth, the protocol did not mandate surveillance imaging after index revascularizations, and as data from surveillance studies was not reliably collected, we are unable to ascertain primary or secondary patency rates in the trial. Finally, enrollment in the BEST-CLI trial was limited to patients judged by the investigators or CLI team to be eligible for both OPEN and ENDO treatment approaches, and in whom there was equipoise.

CONCLUSIONS

Among patients with CLTI deemed suitable for either open bypass or ENDO for infrainguinal disease, open bypass with SSGSV was associated with superior long-term clinical effectiveness and similar safety in comparison to ENDO. AC bypass also demonstrated lower rates of reintervention but was otherwise equivalent to ENDO. The improved results obtained with SSGSV bypass in comparison to ENDO were evident even when patients who experienced early TF were excluded. Patients with CLTI who are acceptable surgical candidates are recommended to undergo evaluation of GSV conduit availability to allow for optimal shared decision-making regarding their treatment options.

ARTICLE INFORMATION

Received September 10, 2024; accepted January 15, 2025.

Affiliations

Division of Vascular and Endovascular Surgery, University of California, San Francisco (M.S.C.). Division of Vascular and Endovascular Surgery, Boston Medical Center, Boston University Chobanian & Avedisian School of Medicine, MA (A.F., J.J.S.). Division of Vascular Surgery, University of California San Diego Health, La Jolla (A.B.). Department of Surgery, Vascular Surgery Division, San Giovanni di Dio Hospital, Florence, Italy (E.C.). Boston University School of Public Health, MA (G.D.). Frederik Meijer Heart and Vascular Institute, Corewell Health, Grand Rapids, MI (V.S.K.). Division of Vascular Surgery, University of Toronto, Ontario, Canada (A.K.). Department of Biomedical and Preclinical Sciences, University of Liège, Belgium (P.K.). The Warren Alpert Medical School of Brown University, Providence, RI (C.C.M.). Division of Vascular Surgery, Henry Ford Health, Detroit, MI (T.N.). Section of Vascular Medicine and Intervention Massachusetts General Hospital (K.R.) and Division of Vascular and Endovascular Surgery, Brigham and Women's Hospital (M.B.S., M.T.M.), Harvard Medical School, Boston. Division of Vascular Surgery and Endovascular Surgery, David Geffen School of Medicine, University of Southern California, Los Angeles (V.L.R.). Division of Vascular Surgery, UMass Chan Medical School, Worcester, MA (A.S.). Division of Vascular Surgery, University of Washington/Harborview Medical Center, Seattle (N.S.).

Sources of Funding

The BEST-CLI trial (Best Endovascular Versus Best Surgical Therapy in Patients With Critical Limb Ischemia) was supported by the National Heart, Lung, and Blood Institute of the NIH under Award Numbers U01HL107407, U01HL107352, and U01HL115662. The following entities also provided funding to the BEST-CLI trial during the follow-up period (2019-2021). These include Physician Societies: Vascular InterVentional Advances, Society for Vascular Surgery, New England Society for Vascular Surgery, Western Vascular Society, Eastern Vascular Society, Midwest Vascular Surgery Society, Southern Association of Vascular Surgeons, Canadian Society for Vascular Surgery, Society for Clinical Vascular Surgery, Society of Interventional Radiology, Vascular and Endovascular Surgery Society, Society for Vascular Medicine; and Industry sources: Janssen, Gore, Becton Dickinson and Company, Medtronic, Cook, Boston Scientific, Abbott, Cordis, Cardiovascular Systems Inc. As of September 1, 2022, ongoing BEST-CLI research is funded primarily by the Novo Nordisk Foundation.

Disclosures

Dr Conte serves on the Data Safety Monitoring Board for Abbott Vascular and acts as a consultant for BioGenCell. Dr Farber is a grant recipient from the Novo Nordisk Foundation and provides consulting services to Sanifit, LeMaitre, and BioGenCell. He also serves on the advisory board for Dialysis-X and iThera Medical. Dr Rosenfield holds consulting or scientific advisory board positions with Abbott Vascular, Althea Medical, Angiodynamics, Auxetics, Becton Dickinson, Boston Scientific, Contego, Crossliner, Innova Vascular, Inspire MD, Janssen/Johnson and Johnson, Magneto, Mayo Clinic, MedAlliance, Medtronic, Neptune Medical, Penumbra, Philips, Surmodics, Terumo, Thrombolex, Truvic, Vasorum, and Vumedi; has equity or stock options in Access Vascular, Aerami, Althea Medical, Auxetics, Contego, Crossliner, Cruzar Systems, Endospan, Imperative Care/Truvic, Innova Vascular, InspireMD, JanaCare, Magneto, MedAlliance, Neptune Medical, Orchestra, Prosomnus, Shockwave, Skydance, Summa Therapeutics, Thrombolex, Vasorum, and Vumedi; has received research grants from the NIH, Abiomed, Boston Scientific, Novo Nordisk Foundation, Penumbra, and Gettinge-Atrium; and is a member of the Board of Directors for The National PERT (Pulmonary Embolism Response Team) Consortium. Dr Singh is a member of the Medtronic Regional Scientific Advisory Board. Dr Siracuse has received an education grant from WL Gore to Boston University and an education grant from Becton Dickinson to Boston University. Dr Menard serves as an advisor to Janssen. The other authors report no conflicts.

Supplemental Material

Tables S1–S4
Figures S1–S3

REFERENCES

1. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, Mills JL, Ricco JB, Suresh KR, Murad MH; GVG Writing Group. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J Vasc Surg*. 2019;69:3S.e40–125S.e40. doi: 10.1016/j.jvs.2019.02.016
2. Schanzer A, Hevelone N, Owens CD, Belkin M, Bandyk DF, Clowes AW, Moneta GL, Conte MS. Technical factors affecting autogenous vein graft failure: observations from a large multicenter trial. *J Vasc Surg*. 2007;46:1180–90; discussion 1190. doi: 10.1016/j.jvs.2007.08.033
3. Arvela E, Venermo M, Soderstrom M, Alback A, Lepantalo M. Outcome of infrainguinal single-segment great saphenous vein bypass for critical limb ischemia is superior to alternative autologous vein bypass, especially in patients with high operative risk. *Ann Vasc Surg*. 2012;26:396–403. doi: 10.1016/j.avsg.2011.08.013
4. Almasri J, Adusumalli J, Asi N, Lakis S, Alsawas M, Prokop LJ, Bradbury A, Kolh P, Conte MS, Murad MH. A systematic review and meta-analysis of revascularization outcomes of infrainguinal chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. 2019;58:S110–S119. doi: 10.1016/j.ejvs.2019.04.013
5. Stavroulakis K, Katsogridakis E, Torsello G, Zayed H, van Herzeele I, Coscas R, Nasr B, Gonzalez TM, Troisi N, Saratzis A; RANDOM-STOP group. Editor's choice—randomisation screening for drug coated or drug eluting device randomised trials among patients undergoing endovascular femoropopliteal procedures (RANDOM-STOP study). *Eur J Vasc Endovasc Surg*. 2023;66:362–368. doi: 10.1016/j.ejvs.2023.06.038
6. Rueda CA, Nehler MR, Perry DJ, McLafferty RB, Casserly IP, Hiatt WR, Peyton BD. Patterns of artery disease in 450 patients undergoing revascularization for critical limb ischemia: implications for clinical trial design. *J Vasc Surg*. 2008;47:995–999, discussion 999. doi: 10.1016/j.jvs.2007.11.055
7. Menard MT, Farber A, Assmann SF, Choudhry NK, Conte MS, Creager MA, Dake MD, Jaff MR, Kaufman JA, Powell RJ, et al. Design and rationale of the best endovascular versus best surgical therapy for patients with critical limb ischemia (BEST-CLI) trial. *J Am Heart Assoc*. 2016;5:e003219. doi: 10.1161/JAHA.116.003219
8. Farber A, Menard MT, Conte MS, Kaufman JA, Powell RJ, Choudhry NK, Hamza TH, Assmann SF, Creager MA, Cziraky MJ, et al; BEST-CLI Investigators. Surgery or endovascular therapy for chronic limb-threatening ischemia. *N Engl J Med*. 2022;387:2305–2316. doi: 10.1056/NEJMoa2207899
9. Conte MS, Geraghty PJ, Bradbury AW, Hevelone ND, Lipsitz SR, Moneta GL, Nehler MR, Powell RJ, Sidawy AN. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. *J Vasc Surg*. 2009;50:1462–1473. doi: 10.1016/j.jvs.2009.09.044
10. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509. doi: 10.1080/01621459.1999.10474144
11. Gebski V, Gares V, Gibbs E, Byth K. Data maturity and follow-up in time-to-event analyses. *Int J Epidemiol*. 2018;47:850–859. doi: 10.1093/ije/dyy013
12. Ricco JB, Roiger RJ, Schneider F, Guetarni F, Thaveau F, Illuminati G, Pasqua R, Chaufour X, Porterie J, Hostalrich A. Editor's choice—infra-inguinal endovascular revascularisation and bypass surgery for chronic limb threatening ischaemia: a retrospective European multicentre cohort study with propensity score matching. *Eur J Vasc Endovasc Surg*. 2023;66:531–540. doi: 10.1016/j.ejvs.2023.06.031
13. Liu IH, El Khoury R, Wu B, Gasper WJ, Schneider PA, Hiramoto JS, Vartanian SM, Conte MS. Presenting limb severity is associated with long-term outcomes after infrainguinal revascularization for chronic limb-threatening ischemia. *J Vasc Surg*. 2023;77:1137.e3–1146.e3. doi: 10.1016/j.jvs.2022.12.036
14. Zarrintan S, Rahgozar S, Ross EG, Farber A, Menard MT, Conte MS, Malas MB. Endovascular therapy versus bypass for chronic limb-threatening ischemia in a real-world practice. *J Vasc Surg*. 2024;80:1169–1181. doi: 10.1016/j.jvs.2024.04.067
15. Butala NM, Chandra V, Beckman JA, Parikh SA, Lookstein R, Misra S, Secemsky EA. Contextualizing the BEST-CLI trial results in clinical practice. *J Soc Cardiovasc Angiogr Interv*. 2023;2:101036. doi: 10.1016/j.jscai.2023.101036
16. Shirasu T, Takagi H, Gregg A, Kuno T, Yasuhara J, Kent KC, Clouse WD. Predictability of the Global Limb Anatomic Staging System (GLASS) for technical and limb related outcomes: a systematic review and meta-analysis. *Eur J Vasc Endovasc Surg*. 2022;64:32–40. doi: 10.1016/j.ejvs.2022.03.044
17. Bradbury AW, Moakes CA, Popplewell M, Meecham L, Bate GR, Kelly L, Chetter I, Diamantopoulos A, Ganeshan A, Hall J, et al; BASIL-2 Investigators. A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial. *Lancet*. 2023;401:1798–1809. doi: 10.1016/S0140-6736(23)00462-2
18. Conte MS, Azene E, Doros G, Gasper WJ, Hamza T, Kashyap VS, Guzman R, Mena-Hurtado C, Menard MT, Rosenfield K, et al. Secondary interventions following open vs endovascular revascularization for chronic limb threatening ischemia in the BEST-CLI trial. *J Vasc Surg*. 2024;79:1428.e4–1437.e4. doi: 10.1016/j.jvs.2024.02.005
19. Menard MT, Farber A, Doros G, McGinigle KL, Chisci E, Clavijo LC, Kayssi A, Schneider PA, Hawkins BM, Dake MD, et al. The impact of revascularization strategy on clinical failure, hemodynamic failure, and chronic limb-threatening ischemia symptoms in the BEST-CLI Trial. *J Vasc Surg*. 2024;80:1755.e4–1765.e4. doi: 10.1016/j.jvs.2024.07.085
20. Conte MS, O'Banion LA. Apples and oranges? A comparison of BEST-CLI to BASIL-2. *J Vasc Surg*. 2023;78:265–268. doi: 10.1016/j.jvs.2023.05.042