The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 22, 2022 VOL. 387 NO. 25

Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia

A. Farber, M.T. Menard, M.S. Conte, J.A. Kaufman, R.J. Powell, N.K. Choudhry, T.H. Hamza, S.F. Assmann,* M.A. Creager, M.J. Cziraky, M.D. Dake, M.R. Jaff, D. Reid, F.S. Siami, G. Sopko, C.J. White, M. van Over, M.B. Strong, M.F. Villarreal, M. McKean, E. Azene, A. Azarbal, A. Barleben, D.K. Chew, L.C. Clavijo, Y. Douville, L. Findeiss, N. Garg, W. Gasper, K.A. Giles, P.P. Goodney, B.M. Hawkins, C.R. Herman, J.A. Kalish, M.C. Koopmann, I.A. Laskowski, C. Mena-Hurtado, R. Motaganahalli, V.L. Rowe, A. Schanzer, P.A. Schneider, J.J. Siracuse, M. Venermo, and K. Rosenfield, for the BEST-CLI Investigators†

ABSTRACT

BACKGROUND

Patients with chronic limb-threatening ischemia (CLTI) require revascularization to improve limb perfusion and thereby limit the risk of amputation. It is uncertain whether an initial strategy of endovascular therapy or surgical revascularization for CLTI is superior for improving limb outcomes.

METHODS

In this international, randomized trial, we enrolled 1830 patients with CLTI and infrainguinal peripheral artery disease in two parallel-cohort trials. Patients who had a single segment of great saphenous vein that could be used for surgery were assigned to cohort 1. Patients who needed an alternative bypass conduit were assigned to cohort 2. The primary outcome was a composite of a major adverse limb event — which was defined as amputation above the ankle or a major limb reintervention (a new bypass graft or graft revision, thrombectomy, or thrombolysis) — or death from any cause.

RESULTS

In cohort 1, after a median follow-up of 2.7 years, a primary-outcome event occurred in 302 of 709 patients (42.6%) in the surgical group and in 408 of 711 patients (57.4%) in the endovascular group (hazard ratio, 0.68; 95% confidence interval [CI], 0.59 to 0.79; P<0.001). In cohort 2, a primary-outcome event occurred in 83 of 194 patients (42.8%) in the surgical group and in 95 of 199 patients (47.7%) in the endovascular group (hazard ratio, 0.79; 95% CI, 0.58 to 1.06; P=0.12) after a median follow-up of 1.6 years. The incidence of adverse events was similar in the two groups in the two cohorts.

CONCLUSIONS

Among patients with CLTI who had an adequate great saphenous vein for surgical revascularization (cohort 1), the incidence of a major adverse limb event or death was significantly lower in the surgical group than in the endovascular group. Among the patients who lacked an adequate saphenous vein conduit (cohort 2), the outcomes in the two groups were similar. (Funded by the National Heart, Lung, and Blood Institute; BEST-CLI ClinicalTrials.gov number, NCT02060630.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Farber can be contacted at alik.farber@bmc.org or at the Division of Vascular and Endovascular Surgery, Boston Medical Center, Boston University School of Medicine, Department of Surgery, 85 E. Concord St., 3rd Fl., Rm. 3000, Boston, MA 02118.

*Deceased.

†The BEST-CLI Investigators are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Farber and Menard contributed equally to this article.

This article was published on November 7, 2022, at NEJM.org.

N Engl J Med 2022;387:2305-16.
DOI: 10.1056/NEJMoa2207899

A Quick Take is available at NEJM.org

Chronic limb-threatening ischemia (CLTI), the most severe manifestation of peripheral artery disease, is defined by ischemic foot pain at rest, ischemic ulcerations, or gangrene.[1] More than 200 million people have peripheral artery disease worldwide; CLTI affects up to 11% of this population.[1,2] Aside from the severe health outcomes associated with CLTI, the economic effect of the condition is substantial, with an estimated annual cost of approximately $12 billion in the United States alone.[3]

Treatment for CLTI includes guideline-directed medical therapy to reduce cardiovascular risk, revascularization to improve limb perfusion, and local care to control infection and improve wound healing.[4] Without timely revascularization, the incidence of limb amputation is approximately 25% at 1 year after diagnosis.[5,6] Surgical bypass and endovascular therapy are the principal revascularization strategies used to treat CLTI.[4] The choice of surgery or endovascular therapy as the initial treatment varies greatly among providers and is based on the patient's arterial disease pattern, surgical risk, availability of an autogenous conduit for vein bypass, and patient preference, along with such physician factors as training, skill set, and treatment bias.[7-9] The extent to which this variability affects clinical outcomes in patients with CLTI is unknown.[7,9,10] We performed the Best Endovascular versus Best Surgical Therapy in Patients with CLTI (BEST-CLI) trial to determine whether endovascular revascularization was superior to surgical revascularization in patients with CLTI caused by infrainguinal peripheral artery disease who were judged to be suitable candidates for both approaches.

Methods

Trial Design

BEST-CLI was an international, prospective, randomized, open-label, multicenter, superiority trial, as described previously[11] and in the trial protocol, available with the full text of this article at NEJM.org. Patients were enrolled at 150 sites in the United States, Canada, Finland, Italy, and New Zealand (as detailed in the Supplementary Appendix, also available at NEJM.org). The trial consisted of two parallel studies that were based on a preprocedural assessment of the availability of autogenous conduit for vein bypass: either a single segment of great saphenous vein (cohort 1) or the need for an alternative bypass conduit (cohort 2). The trial protocol was approved by the ethics committee or the national equivalent at each participating site. All the patients provided written informed consent.

Enrollment began in August 2014 and continued through October 2019. The patients in cohort 1 were followed through October 2021, and those in cohort 2 were followed through December 2019.

Patient Population

Eligible patients were at least 18 years old and had received a diagnosis of CLTI, which was defined as arterial insufficiency of the lower limb with ischemic foot pain at rest, a nonhealing ischemic ulcer, or gangrene, as corroborated by hemodynamic criteria. Patients were excluded from the trial if they had excessive risk associated with open vascular surgery according to the criteria of the American Heart Association and the American College of Cardiology or according to the medical judgment of the investigator. Details regarding the representativeness of the patient sample are provided in Table S1 in the Supplementary Appendix.[12]

Randomization

Patients were enrolled into one of two parallel-trial cohorts according to prerandomization duplex ultrasonography of the right and left great saphenous veins. Within each cohort, eligible patients were stratified according to clinical criteria (ischemic rest pain or tissue loss) and anatomical criteria (presence or absence of considerable infrapopliteal arterial occlusive disease) with the use of permuted randomized blocks. The patients were then randomly assigned in a 1:1 ratio to receive surgical or endovascular treatment. All the patients were expected to receive their assigned treatment within 30 days after randomization. An investigator with expertise in surgical bypass procedures had to agree with another investigator with expertise in endovascular revascularization procedures that clinical equipoise existed in the randomization of each patient.[11,13]

In the surgical group, surgeons were allowed to choose any bypass technique that was currently being used in clinical practice. In the endovascular group, interventionalists were allowed to choose any available endovascular technique. Follow-up data were collected at 30 days after

the procedure or 30 days after randomization if the index procedure had not been performed; follow-up was performed at 3 months, 6 months, and every 6 months thereafter up to 84 months after randomization. Telephone visits in lieu of clinic visits were planned at 30 months and every 12 months thereafter and at the end of the trial.

OUTCOMES

The primary outcome was a composite of major adverse limb events or death from any cause. A major adverse limb event was defined as above-ankle amputation of the index limb or a major index-limb reintervention (new bypass, interposition graft revision, thrombectomy, or thrombolysis).[14] The need for and timing of the reintervention was determined by the trial site investigator on the basis of clinical assessment. All first major reinterventions were adjudicated by an independent, multidisciplinary clinical-events committee. A modification of the criteria of the Peripheral Academic Research Consortium was used to define technical success (see the Methods section in the Supplementary Appendix).[13] Key secondary efficacy and safety outcomes were the occurrence of a major adverse limb event at any time or postoperative death within 30 days; minor reinterventions; a major adverse cardiovascular event, which was defined as a composite of myocardial infarction, stroke, or death from any cause; and serious adverse events (Table S2). Stroke and myocardial infarction were adjudicated by the clinical-events committee.

STATISTICAL ANALYSIS

We originally determined that the enrollment of 2100 patients (1620 in cohort 1 and 480 in cohort 2) would provide 85% power to detect a relative difference of 25% in the primary outcome favoring the surgical group (i.e., an event rate of 53.0% in the surgical group and 61.1% in the endovascular group) in cohort 1 and 80% power to detect a relative difference of 30% in the primary outcome favoring the endovascular group (i.e., an event rate of 53.0% in the surgical group and 45.3% in the endovascular group) in cohort 2. In the two cohorts, the null hypothesis was that there would be no difference in the time from randomization to a primary-outcome event between the surgical group and the endovascular group. In the two cohorts, the calculations were to be based on 2.95 years of follow-up and a type I error rate of 0.05; the sample sizes were determined to allow for crossover between groups, loss to follow-up, and the performance of two interim analyses at prespecified intervals. Trial enrollment was stopped early after 1830 patients had been enrolled owing to a lack of continued funding. Supplemental funding was raised to allow for 24 months of follow-up for all the patients in cohort 1. Details regarding revisions to the statistical analysis plan are provided in the trial protocol.

The primary and secondary outcome analyses were performed according to the intention-to-treat principle. Analyses were carried out separately in each cohort. Time-to-event outcomes were described with the use of Kaplan–Meier plots, and the two treatment groups were compared with the use of log-rank test statistics. We used a prespecified covariate-adjusted Cox model that was stratified according to randomization categories to calculate hazard ratios and their 95% confidence intervals. Missing baseline covariates were imputed with the use of multiple imputation. We used Cox models that had been adjusted for the imputed covariates to calculate the results of secondary efficacy and safety analyses. In the primary analysis, a P value of less than 0.045 after correction for two interim analyses was considered to indicate statistical significance. The widths of the confidence intervals have not been adjusted for multiplicity, so confidence intervals should not be used for hypothesis testing. All the analyses were performed with the use of SAS Enterprise Guide software, version 8.3 (SAS Institute), and R software, version 4.02. Additional details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

COHORT 1

Patients

From August 2014 through October 2019, a total of 1434 patients with a single segment of great saphenous vein underwent randomization in cohort 1 (718 to receive surgical treatment and 716 to receive endovascular therapy) and were followed for up to 7 years, with a median follow-up of 2.7 years (interquartile range, 1.6 to 4.0) in the surgical group and 2.7 years (interquartile range, 1.6 to 4.1) in the endovascular group (Fig. 1). Excluded from the primary analysis were 14 patients (1.0%) — 9 in the surgical group and

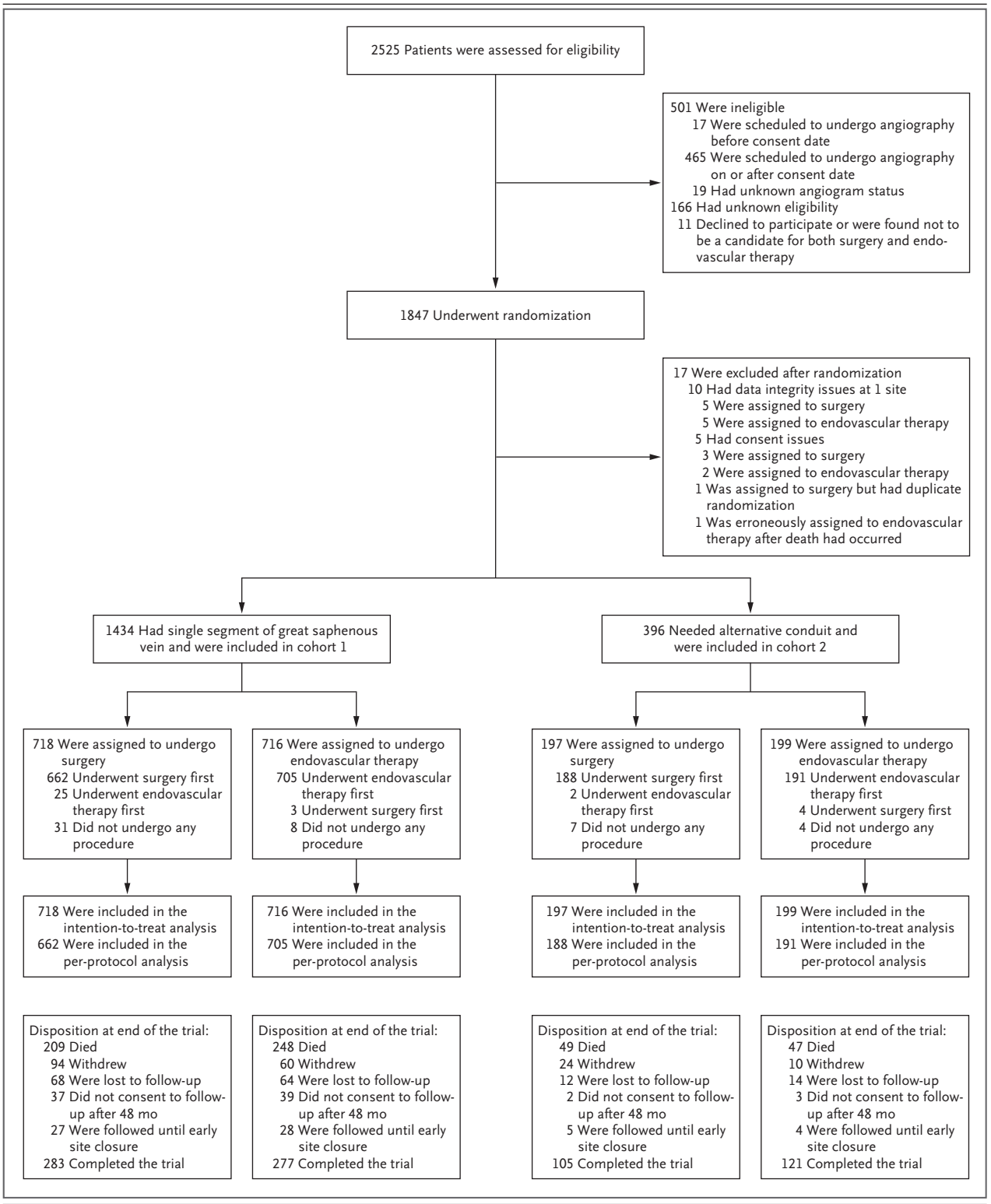

Figure 1 (facing page). Randomization and Outcomes.

Shown are data for patients with a single segment of great saphenous vein (who were included in cohort 1) and those who needed an alternative bypass conduit (who were included in cohort 2). The patients in each cohort subsequently underwent separate randomization to undergo either surgery or endovascular therapy. In the description of the patients' disposition at the end of the trial, the patients who provided limited consent until follow-up at 48 months completed the 48-month visit but did not consent to receive additional follow-up, as outlined in version 5.0 of the protocol.

5 in the endovascular group — because of missing baseline data regarding diabetes, smoking status, end-stage renal disease, or previous infrainguinal revascularization; the secondary efficacy and safety analyses were adjusted for imputed covariates and did not exclude patients (Table S3). The characteristics of the patients were well balanced between the groups, with the exception of more Black patients in the surgical group than in the endovascular group (Table 1 and Tables S4 and S5).

Index Procedure

The median time until the index procedure was 4 days (interquartile range, 1 to 11) in the surgical group and 1 day (interquartile range, 0 to 7) in the endovascular group. Procedures that were performed in the surgical group included 307 femoral–popliteal, 276 femoral–tibial or pedal, and 115 popliteal–tibial or pedal bypass operations; 85% of the procedures were performed with a single segment of great saphenous vein (Table S6). Procedures in the endovascular group included 487 that were performed on the superficial femoral artery, 382 on the popliteal artery, and 381 on the tibial or pedal arteries. The type of endovascular procedure varied depending on the arterial segment that was treated (Table S6). Endovascular interventions were performed by vascular surgeons in 73% of cases, by interventional cardiologists in 15% of cases, and by interventional radiologists in 13% of cases. The technical success of the index procedure was 98% in the surgical group and 85% in the endovascular group. Of the 108 cases of early technical failure in the endovascular group, 66 were treated with a bypass operation within 30 days.

Outcomes

The primary outcome of major adverse limb events or death from any cause occurred in 302 of 709 patients (42.6%) in the surgical group and in 408 of 711 patients (57.4%) in the endovascular group (hazard ratio, 0.68; 95% confidence interval [CI], 0.59 to 0.79; P<0.001) (Table 2 and Table S7). This result was similar in the per-protocol and the as-treated analyses (Table S8). The time until a primary-outcome event is shown in Figure 2A. Major reinterventions occurred in 65 of 709 patients (9.2%) in the surgical group and in 167 of 711 patients (23.5%) in the endovascular group (hazard ratio, 0.35; 95% CI, 0.27 to 0.47) (Fig. 2B). Above-ankle amputation of the index limb occurred in 74 of 709 patients (10.4%) in the surgical group and in 106 of 711 patients (14.9%) in the endovascular group (hazard ratio, 0.73; 95% CI, 0.54 to 0.98) (Fig. 2C). The incidences of death from any cause and perioperative death were similar in the two groups (Fig. 2D and Fig. S1A).

Subgroup analysis of the primary outcome suggested a treatment effect across most prespecified groups that appeared to favor the surgical group as compared with the endovascular group, with the exceptions of patients who were older than 80 years of age, Black patients, and those with previous limb revascularization on the same side, grade 3 wounds, or renal dysfunction (Fig. S2). Patients in the surgical group had a lower incidence rate of new or recurrent CLTI events than those in the endovascular group (incidence rate ratio, 0.82; 95% CI, 0.70 to 0.95).

Adverse Events

Major adverse cardiovascular events occurred in 56 of 1434 patients (3.9%) from randomization through 30 days after the index procedure and in 578 of 1434 patients (40.3%) through the end of follow-up. There were no material between-group differences in the incidence of major adverse cardiovascular events overall or at 30 days or of myocardial infarction or stroke (Table 2, Table S7, and Fig. S1). From randomization through 30 days after the procedure, 427 serious adverse events occurred in the surgical group and 379 in the endovascular group, including in 12 of 687 patients (1.7%) with perioperative death in the surgical group and in 9 of 708 pa-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Cohort 1			Cohort 2		
	Overall (N=1434)	Surgery (N=718)	Endovascular Therapy (N=716)	Overall (N=396)	Surgery (N=197)	Endovascular Therapy (N=199)
Demographic						
Age — yr	66.9±9.9	66.9±9.8	67.0±10.0	68.6±9.2	68.4±8.8	68.8±9.6
Female sex — no./total no. (%)	408/1434 (28.5)	201/718 (28.0)	207/716 (28.9)	111/396 (28.0)	56/197 (28.4)	55/199 (27.6)
Race or ethnic group — no./total no. (%)†						
White	1028/1423 (72.2)	500/711 (70.3)	528/712 (74.2)	275/390 (70.5)	143/194 (73.7)	132/196 (67.3)
Black	275/1423 (19.3)	156/711 (21.9)	119/712 (16.7)	96/390 (24.6)	40/194 (20.6)	56/196 (28.6)
Asian	20/1423 (1.4)	13/711 (1.8)	7/712 (1.0)	2/390 (0.5)	2/194 (1.0)	0/196
Other	100/1423 (7.0)	42/711 (5.9)	58/712 (8.1)	17/390 (4.4)	9/194 (4.6)	8/196 (4.1)
Hispanic	187/1433 (13.0)	82/717 (11.4)	105/716 (14.7)	53/396 (13.4)	28/197 (14.2)	25/199 (12.6)
Medical history						
Body-mass index‡	28.2±6.0	28.2±6.3	28.3±5.8	26.9±5.7	26.8±5.1	27.0±6.2
Coexisting condition — no./total no. (%)						
Hypertension	1238/1424 (86.9)	620/712 (87.1)	618/712 (86.8)	350/395 (88.6)	171/196 (87.2)	179/199 (89.9)
Hyperlipidemia	1041/1423 (73.2)	521/712 (73.2)	520/711 (73.1)	299/395 (75.7)	147/196 (75.0)	152/199 (76.4)
Diabetes	1023/1424 (71.8)	513/712 (72.1)	510/712 (71.6)	238/395 (60.3)	122/196 (62.2)	116/199 (58.3)
Current smoking	509/1424 (35.7)	264/712 (37.1)	245/712 (34.4)	140/395 (35.4)	69/196 (35.2)	71/199 (35.7)
Coronary artery disease	617/1424 (43.3)	301/712 (42.3)	316/712 (44.4)	204/395 (51.6)	97/196 (49.5)	107/199 (53.8)
Congestive heart failure	79/1422 (5.6)	38/711 (5.3)	41/711 (5.8)	27/395 (6.8)	12/196 (6.1)	15/199 (7.5)
Stroke	190/1424 (13.3)	91/712 (12.8)	99/712 (13.9)	62/395 (15.7)	38/196 (19.4)	24/199 (12.1)
Chronic obstructive pulmonary disease	208/1424 (14.6)	100/712 (14.0)	108/712 (15.2)	69/395 (17.5)	34/196 (17.3)	35/199 (17.6)
End-stage kidney disease	151/1423 (10.6)	67/712 (9.4)	84/711 (11.8)	45/395 (11.4)	25/196 (12.8)	20/199 (10.1)

Medication						
Statin — no./total no. (%)	1001/1424 (70.3)	503/713 (70.5)	498/711 (70.0)	307/394 (77.9)	153/195 (78.5)	154/199 (77.4)
Aspirin — no./total no. (%)	953/1424 (66.9)	476/713 (66.8)	477/711 (67.1)	280/394 (71.1)	139/195 (71.3)	141/199 (70.9)
Clopidogrel — no./total no. (%)	312/1424 (21.9)	137/713 (19.2)	175/711 (24.6)	97/394 (24.6)	55/195 (28.2)	42/199 (21.1)
Prasugrel — no./total no. (%)	5/1424 (0.4)	2/713 (0.3)	3/711 (0.4)	1/394 (0.3)	0/195	1/199 (0.5)
Ticagrelor — no./total no. (%)	10/1424 (0.7)	4/713 (0.6)	6/711 (0.8)	4/394 (1.0)	0/195	4/199 (2.0)
Direct-acting oral anticoagulant — no./total no. (%)	55/1424 (3.9)	27/713 (3.8)	28/711 (3.9)	22/394 (5.6)	9/195 (4.6)	13/199 (6.5)
Warfarin — no./total no. (%)	93/1424 (6.5)	46/713 (6.5)	47/711 (6.6)	31/394 (7.9)	12/195 (6.2)	19/199 (9.5)
Previous intervention						
Tobacco cessation — no./total no. (%)	97/1424 (6.8)	49/712 (6.9)	48/712 (6.7)	26/395 (6.6)	11/196 (5.6)	15/199 (7.5)
Infrainguinal revascularization of index limb — no./total no. (%)	77/1423 (5.4)	40/711 (5.6)	37/712 (5.2)	40/393 (10.2)	20/194 (10.3)	20/199 (10.1)
Limb status						
Ankle–brachial index in index limb§	0.58±0.32	0.58±0.31	0.59±0.34	0.54±0.30	0.53±0.27	0.54±0.32
Ankle pressure — mm Hg¶	84.9±47.7	85.2±46.2	84.5±49.2	81.3±49.6	80.4±47.3	82.2±51.8
Toe pressure — mm Hg‖	36.3±25.7	36.5±27.7	36.1±23.5	31.0±21.7	37.0±23.5	25.5±18.4

* Plus–minus values are means ±SD. Cohort 1 included patients who had a single segment of great saphenous vein, and cohort 2 included patients who needed an alternative bypass conduit.

† Race and ethnic group were reported by the patients.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data regarding body-mass index were missing for 67 patients (36 in the surgical group and 31 in the endovascular group) in cohort 1 and for 19 patients (9 in the surgical group and 10 in the endovascular group) in cohort 2.

§ The ankle–brachial index is the systolic blood pressure in the ankle divided by the systolic blood pressure in the arm; an index between 0.9 and 1.2 is considered to be normal. The index value was missing for 463 patients (224 in the surgical group and 239 in the endovascular group) in cohort 1 and for 116 patients (62 in the surgical group and 54 in the endovascular group) in cohort 2.

¶ Data regarding ankle pressure were missing for 426 patients (205 in the surgical group and 221 in the endovascular group) in cohort 1 and for 108 patients (57 in the surgical group and 51 in the endovascular group) in cohort 2.

‖ Data regarding toe pressure were missing for 826 patients (418 in the surgical group and 408 in the endovascular group) in cohort 1 and for 227 patients (117 in the surgical group and 110 in the endovascular group) in cohort 2.

Table 2. Efficacy and Safety Outcomes in Cohort 1.*

Outcome	Surgery	Endovascular Therapy	Hazard Ratio (95% CI)†	P Value
Efficacy				
Primary outcome: major adverse limb event or death from any cause — no./total no. (%)‡	302/709 (42.6)	408/711 (57.4)	0.68 (0.59–0.79)	<0.001
Secondary outcomes — no./total no. (%)				
Death from any cause	234/709 (33.0)	267/711 (37.6)	0.98 (0.82–1.17)	
Above-ankle amputation of the index limb	74/709 (10.4)	106/711 (14.9)	0.73 (0.54–0.98)	
Intervention in index limb				
Major	65/709 (9.2)	167/711 (23.5)	0.35 (0.27–0.47)	
Minor	205/718 (28.6)	237/716 (33.1)	0.85 (0.70–1.02)	
Perioperative death§	12/687 (1.7)	9/708 (1.3)	1.54 (0.64–3.68)	
Major adverse limb event or perioperative death	139/687 (20.2)	246/708 (34.7)	0.53 (0.43–0.65)	
Myocardial infarction	75/718 (10.4)	85/716 (11.9)	0.97 (0.71–1.33)	
Stroke	39/718 (5.4)	44/716 (6.1)	0.93 (0.60–1.43)	
Safety				
Major adverse cardiovascular event — no. of patients with ≥1 event/total no. of patients (%)				
Event ≤30 days after procedure¶	33/718 (4.6)	23/716 (3.2)	1.46 (0.86–2.50)	0.16
Event during follow-up	269/718 (37.5)	309/716 (43.2)	0.94 (0.80–1.11)	0.48
Serious adverse event				
Event occurred ≤30 days after index procedure — no. of patients with ≥1 event/total no. of patients (%)‖	244/718 (34.0)	226/716 (31.6)		0.34
No. of events ≤30 days after index procedure	427	379		0.10
No. of patients with ≥1 event/total no. of patients (%)	590/718 (82.2)	614/716 (85.8)		0.07
No. of events during follow-up	3141	3468		<0.001
Technical success of index procedure — no./total no. (%)**	651/662 (98.3)	596/704 (84.7)		
Length of hospital stay after index procedure††				
No. of days	7.5±6.2	5.9±7.3		
Median no. of days (IQR)	6 (4–9)	3 (1–8)		

* Plus–minus values are means ±SD. In various categories, denominators differ because of missing baseline covariates in the regression model or the restriction of the analysis to patients who underwent the assigned index procedure. IQR denotes interquartile range.

† The widths of the confidence intervals have not been adjusted for multiplicity, so the confidence intervals should not be used for hypothesis testing.

‡ Data for the outcomes of death from any cause and above-ankle amputation of the index limb were collected until the end of the trial. Data for a major or minor reintervention in the index limb and major adverse cardiovascular events were collected until the end of the follow-up period.

§ Perioperative death was defined as death from any cause within 30 days after the index procedure.

¶ Included in this category were major adverse cardiovascular events that occurred after randomization through 30 days after the index procedure or within 30 days after randomization if the index procedure was not performed.

‖ Serious adverse events were evaluated from the date of randomization through 30 days after the index procedure or within 30 days after randomization if the index procedure was not performed.

** Technical success of the index procedure was defined according to prespecified criteria.

†† The length of the hospital stay was the number of days from the date of the index procedure through discharge or 30 days after the procedure, whichever came first. Data regarding the length of hospital stay were missing for 33 patients in the surgical group and for 125 patients in the endovascular group.

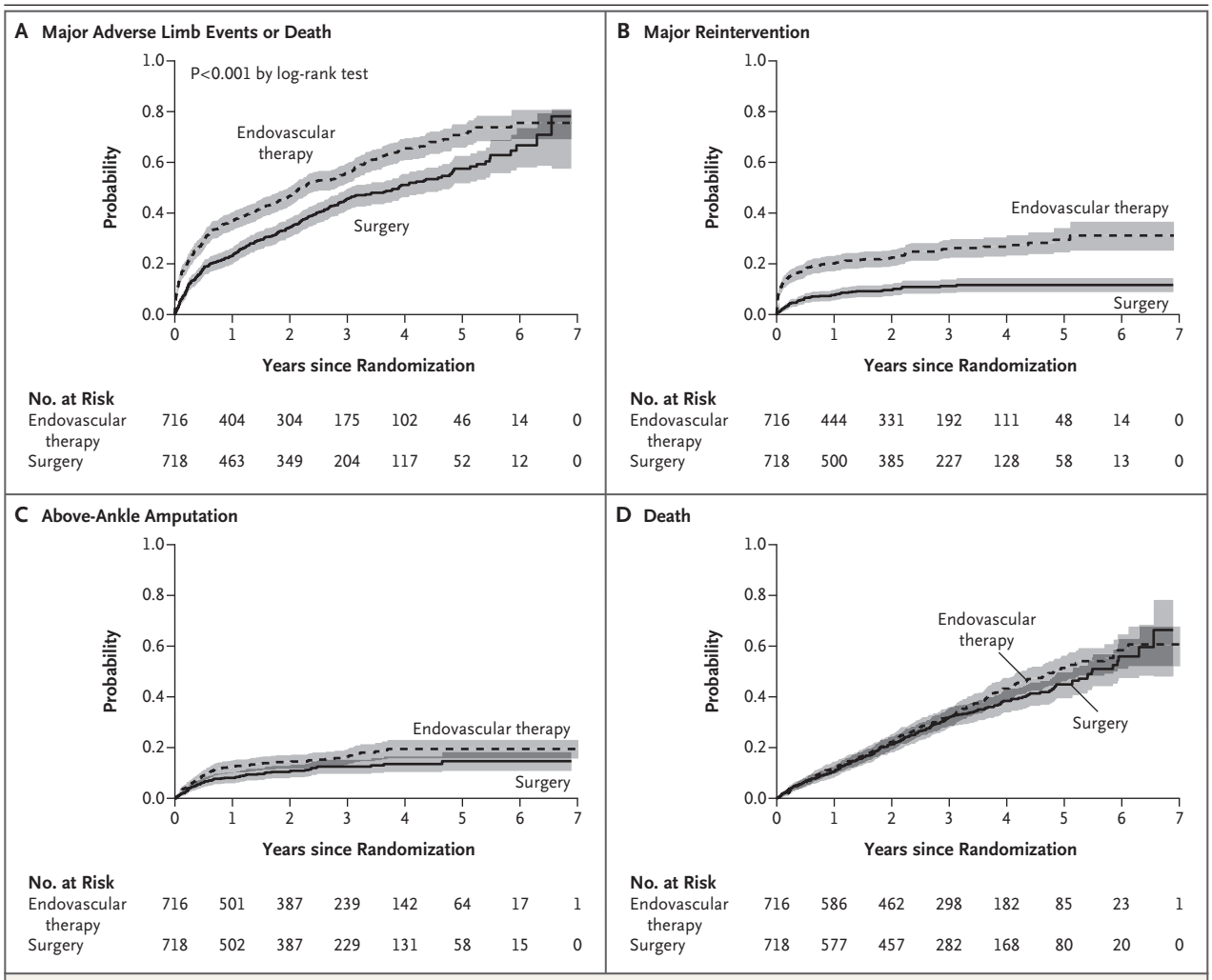

Figure 2. Kaplan–Meier Curves of the Primary Outcome and Its Components in Cohort 1.

Shown is the primary outcome — a composite of major adverse limb events or death from any cause — among patients in the surgical group and the endovascular group in cohort 1 (which included patients who had a single segment of great saphenous vein) (Panel A). The components of the primary outcome were a major index-limb reintervention, including a new bypass graft or graft revision, thrombectomy, or thrombolysis (Panel B); above-ankle amputation of the index limb (Panel C); and death from any cause (Panel D). Shading indicates the 95% confidence interval.

tients (1.3%) in the endovascular group. The median length of hospital stay was longer in the surgical group than in the endovascular group (6 days vs. 3 days).

COHORT 2

Patients

In cohort 2, a total of 396 patients without a single segment of great saphenous vein underwent randomization (197 to receive surgical treatment and 199 to receive endovascular therapy) and were followed for a median of 1.6 years (interquartile range, 0.7 to 2.8) in the surgical group and 1.6 years (interquartile range, 0.7 to 3.1) in the endovascular group. Excluded from the primary analysis were 3 patients (0.8%) — all in the surgical group — because of missing baseline data regarding diabetes, smoking status, end-stage renal disease, or previous infrainguinal revascularization. The secondary efficacy and safety outcome analyses were adjusted for imputed covariates and did not exclude patients. The characteristics of the patients were well balanced between the two groups except that the baseline toe pressures were higher in the surgical group (Table 1).

Index Procedure

The median time until the index procedure was 4 days (interquartile range, 1 to 13) in the surgical group and 1 day (interquartile range, 0 to 7) in the endovascular group. The technical success was 100% in the surgical group and 80.6% in the endovascular group. Of the 37 early cases of technical failure in the endovascular group, 26 patients underwent surgical bypass within 30 days.

In the surgical group, 105 femoral–popliteal, 86 femoral–tibial or pedal, and 18 popliteal–tibial or pedal bypasses were performed. There were 48 bypasses involving alternative autogenous veins and 119 bypasses involving a prosthetic conduit. In 19% of cases, the surgeon unexpectedly identified a single segment of great saphenous vein that was suitable for bypass surgery. Among the endovascular interventions, 133 were performed on the superficial femoral artery, 114 on the popliteal artery, and 86 on the tibial or pedal arteries (Table S6).

Outcomes

The primary outcome of major adverse limb events or death from any cause occurred in 83 of 194 patients (42.8%) in the surgical group and in 95 of 199 patients (47.7%) in the endovascular group (hazard ratio, 0.79; 95% CI, 0.58 to 1.06; P=0.12) (Fig. S3A and Tables S9 and S10). The time until a major reintervention favored the surgical group (hazard ratio, 0.47; 95% CI, 0.29 to 0.76) (Fig. S3B). There were no material between-group differences in the time until above-ankle amputation or death from any cause (Fig. S3C and S3D and Tables S9 and S10). Similar results were obtained across subgroups (Fig. S4) and in the per-protocol and as-treated analyses of the primary outcome (Table S11). There was no material difference between the surgical group and the endovascular group regarding the incidence of new or recurrent CLTI events (incidence rate ratio, 0.87; 95% CI, 0.64 to 1.17).

Adverse Events

Major adverse limb events occurred in 13 of 396 patients (3.3%) from the date of randomization through 30 days after the index procedure and in 124 of 396 patients (31.3%) through the end of the trial. There were no material between-group differences in the time until a major adverse limb event overall or at 30 days or until myocardial infarction or stroke (Tables S9 and S10 and Fig. S5A through S5G). The median length of hospital stay was longer in the surgical group.

DISCUSSION

In recent years, the frequency of endovascular therapy as the initial revascularization strategy has increased. This trend notwithstanding, in our trial, we saw a compelling primary role for initial surgical revascularization in the treatment of CLTI. In patients with a good-quality great saphenous vein for conduit (cohort 1), a surgery-first strategy was associated with a 32% lower risk of a composite of major adverse limb events or death than was the endovascular strategy, a result that appeared to be driven by fewer major reinterventions and above-ankle amputations in the surgical group. However, in patients without a great saphenous vein for conduit (cohort 2), overall efficacy and safety outcomes appeared to be similar in the two treatment groups, findings that emphasize the importance of individualized patient-level decision making in patients without an appropriate bypass conduit.

Patients in the two groups had similar incidences of adverse cardiovascular events and death. In cohort 1, the 30-day mortality, incidence of major adverse cardiovascular events, and long-term survival over a median 2.7 years of follow-up were in line with the data in two large registry studies.[15,16] These findings indicate that in contemporary practice, revascularization in appropriately selected patients with CLTI can be performed with low morbidity and high limb salvage. In agreement with the findings from one of these registry studies,[15] our trial showed that the majority of patients who were predicted to have preferential benefit from surgical revascularization safely underwent surgery.

In cohort 1, the between-group difference in reintervention was most pronounced during the first 6 months, and 99 of 233 first reintervention events (42.5%) occurred within 30 days. This early increase in major reintervention may have been related to a higher incidence of initial technical failure in the endovascular group (15%) than in the surgical group (<2%). Although it is likely that the majority of these major reinterventions were clinically driven, the choice and timing of reintervention were based on the judgment of the treating physician. Causes of the technical failures, which may have influenced

the higher rate of major reinterventions in the endovascular group, are not known.

Overall, the findings from this large, international trial suggest that preprocedural planning of treatment in patients with CLTI should include a surgical risk assessment and a determination of saphenous-vein availability. Our findings suggest that among the trial patients with an adequate saphenous vein who were suitable candidates for both surgical and endovascular revascularization, bypass with a vein was a superior initial strategy. However, many patients with CLTI who are appropriate candidates for limb-preserving interventions do not have adequate conduit, and others may still prefer an endovascular approach after fully informed, shared decision making. Additional analyses regarding anatomical patterns of vascular disease, predictors of technical failure, effect on quality of life, cost, and role of patient preference will further elucidate subgroups of patients who are most likely to benefit from each approach.

In the randomized, controlled Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial,[17] which compared surgery with endovascular therapy in 452 patients, investigators found no material between-group difference in the primary outcome of amputation-free survival. Analyses of secondary outcomes in our trial results add evidence to support complementary roles for surgical and endovascular procedures, as endorsed in clinical practice guidelines.[1,18,19] Factors such as conduit availability for bypass, advanced age, and renal failure are key considerations in planning revascularization procedures. Our data also highlight the importance of a team approach that leverages experience with both strategies to most effectively treat patients with CLTI.

Our study has several limitations. Trial results may have been influenced by selection and operator bias as a consequence of its pragmatic design and implementation. Eligibility was determined locally and varied according to the site and the individual investigator; patients who underwent randomization were those in whom the enrolling team believed there was equipoise between endovascular intervention and bypass surgery. Although the majority of patients (66%) had substantial infrapopliteal-artery involvement, an anticipated future review of angiographic data will elucidate the degree of anatomical complexity among these patients. Because investigators used their preferred techniques, there was procedural heterogeneity within each trial group. The reliance on the judgment of individual operators in defining successful revascularization also could have influenced treatment outcomes. The percentage of women in the trial (28%) was lower than the targeted number. Because of difficulties with enrollment, the planned number of patients who were enrolled in the trial was not met. Additional funds that were raised enabled the planned minimum of 24 months of follow-up in cohort 1 but not in cohort 2. Finally, a meta-analysis[19] that had been published toward the end of the trial enrollment period aroused concern regarding a risk of death associated with the use of paclitaxel-coated balloons and stents. These devices have been shown to reduce the need for reintervention in the superficial femoral and proximal popliteal arteries.[20] This concern may have reduced the use of paclitaxel-coated balloons and stents in the trial.

In patients with CLTI who had an adequate single segment of great saphenous vein for conduit and were considered to be suitable candidates for both endovascular intervention and surgical bypass, initial bypass surgery was associated with a lower incidence of major adverse limb events or death than initial endovascular intervention. In patients without a suitable great saphenous vein, results associated with initial endovascular intervention were not significantly different from those associated with initial bypass surgery.

Supported by the National Heart, Lung, and Blood Institute.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Alik Farber, M.D., Matthew T. Menard, M.D., Michael S. Conte, M.D., John A. Kaufman, M.D., Richard J. Powell, M.D., Niteesh K. Choudhry, M.D., Ph.D., Taye H. Hamza, Ph.D., Susan F. Assmann, Ph.D., Mark A. Creager, M.D., Mark J. Cziraky, Pharm.D., Michael D. Dake, M.D., Michael R. Jaff, D.O., Diane Reid, M.D., Flora S. Siami, M.P.H., George Sopko, M.D., Christopher J. White, M.D., Max van Over, M.P.H., Michael B. Strong, M.A., Maria F. Villarreal, M.D., Michelle McKean, M.P.H., Ezana Azene, M.D., Ph.D., Amir Azarbal, M.D., Andrew Barleben, M.D., David K. Chew, M.D., Leonardo C. Clavijo, M.D., Ph.D., Yvan Douville, M.D., Laura Findeiss, M.D., Nitin Garg, M.B., B.S., M.P.H., Warren Gasper, M.D., Kristina A. Giles, M.D., Philip P. Goodney, M.D., Beau M. Hawkins, M.D., Christine R. Herman, M.D., Jeffrey A. Kalish, M.D., Matthew C. Koopmann, M.D., Igor A. Laskowski, M.D., Ph.D., Carlos Mena-Hurtado, M.D., Raghu Motaganahalli, M.D., Vincent L. Rowe, M.D., Andres Schanzer, M.D., Peter A. Schneider, M.D., Jeffrey J. Siracuse, M.D., Maarit Venermo, M.D., Ph.D., and Kenneth Rosenfield, M.D.

The authors' affiliations are as follows: the Division of Vascular and Endovascular Surgery, Boston Medical Center, Boston University School of Medicine (A.F., M.F.V., J.A. Kalish, J.J.S.), the Division of Vascular and Endovascular Surgery (M.T.M., M.B.S.) and the Department of Medicine (N.K.C.), Brigham and Women's Hospital, Harvard Medical School (M.R.J.), and the Section of Vascular Medicine and Intervention, Massachusetts General Hospital (K.R.), Boston, HealthCore, Watertown (T.H.H., S.F.A., M.J.C., M.O., M.M.), and the Division of Vascular Surgery, UMass Memorial Health, Worcester (A.S.) — all in Massachusetts; the Division of Vascular and Endovascular Surgery, University of California, San Francisco, San Francisco (M.S.C., W.G., P.A.S.), the Division of Vascular Surgery, UC San Diego Health, La Jolla (A.B.), Coastal Cardiology, French Hospital Medical Center, San Luis Obispo (L.C.C.), and the Division of Vascular Surgery and Endovascular Therapy, University of Southern California, Los Angeles (V.L.R.) — all in California; the Department of Interventional Radiology (J.A. Kaufman) and the Division of Vascular Surgery, School of Medicine (A.A.), Oregon Health and Science University, and the Operative Care Division, Portland VA Medical Center (M.C.K.) — all in Portland; the Heart and Vascular Center, Dartmouth Hitchcock Medical Center, Geisel School of Medicine at Dartmouth, Lebanon, NH (R.J.P., M.A.C., P.P.G.); the Department of Medical Imaging, University of Arizona Health Sciences, Tucson (M.D.D.), and the Division of Vascular Surgery, Peak Heart and Vascular, Glendale (N.G.) — both in Arizona; the National Heart, Lung, and Blood Institute, Bethesda, MD (D.R., G.S.); the Medical Device Innovation Consortium, National Evaluation System for Health Technology Coordinating Center, Arlington, VA (F.S.S.); the Department of Cardiovascular Diseases, Ochsner Clinical School, University of Queensland, Brisbane, Australia (C.J.W.); the Department of Interventional Radiology, Gundersen Health System, La Crosse, WI (E.A.); the Iowa Heart Center, Des Moines (D.K.C.); the Division of Vascular Surgery, Centre Hospitalier Universitaire de Quebec–Université Laval, Quebec City (Y.D.), and Dalhousie University, Division of Cardiac and Vascular Surgery, Department of Surgery, Nova Scotia Health Association, Halifax (C.R.H.) — both in Canada; the Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta (L.F.); the Division of Vascular and Endovascular Surgery, Maine Medical Center, Portland (K.A.G.); the Cardiovascular Section, University of Oklahoma Health Sciences Center, Oklahoma City (B.M.H.); Westchester Medical Center and the Department of Surgery, Section of Vascular Surgery, New York Medical College — both in Valhalla, NY (I.A.L.); the Vascular Medicine Outcomes Program, Yale University, New Haven, CT (C.M.-H.); the Division of Vascular Surgery, Indiana University School of Medicine, Indianapolis (R.M.); and the Department of Vascular Surgery, University of Helsinki, and Helsinki University Hospital — both in Helsinki (M.V.).

REFERENCES

1. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg 2019;69(6S):3S-125S.e40.
2. Fowkes FGR, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet 2013;382:1329-40.
3. Mustapha JA, Katzen BT, Neville RF, et al. Determinants of long-term outcomes and costs in the management of critical limb ischemia: a population-based cohort study. J Am Heart Assoc 2018;7(16):e009724.
4. Farber A. Chronic limb-threatening ischemia. N Engl J Med 2018;379:171-80.
5. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease) — summary of recommendations. J Vasc Interv Radiol 2006;17:1383-97.
6. Creager MA, Matsushita K, Arya S, et al. Reducing nontraumatic lower-extremity amputations by 20% by 2030: time to get to our feet: a policy statement from the American Heart Association. Circulation 2021;143(17):e875-e891.
7. Almasri J, Adusumalli J, Asi N, et al. A systematic review and meta-analysis of revascularization outcomes of infrainguinal chronic limb-threatening ischemia. J Vasc Surg 2019;69:6S:126S-136S.
8. Bradbury A, Wilmink T, Lee AJ, et al. Bypass versus angioplasty to treat severe limb ischemia: factors that affect treatment preferences of UK surgeons and interventional radiologists. J Vasc Surg 2004;39:1026-32.
9. Farber A, Eberhardt RT. The current state of critical limb ischemia: a systematic review. JAMA Surg 2016;151:1070-7.
10. Goodney PP, Travis LL, Nallamothu BK, et al. Variation in the use of lower extremity vascular procedures for critical limb ischemia. Circ Cardiovasc Qual Outcomes 2012;5:94-102.
11. Menard MT, Farber A, Assmann SF, 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(7):e003219.
12. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:2215-45.
13. Powell R, Menard M, Farber A, et al. Comparison of specialties participating in the BEST-CLI trial to specialists treating peripheral arterial disease nationally. J Vasc Surg 2019;69:1505-9.
14. Conte MS, Geraghty PJ, Bradbury AW, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. J Vasc Surg 2009;50(6):1462-73.e1-3.
15. Simons JP, Schanzer A, Flahive JM, et al. Survival prediction in patients with chronic limb-threatening ischemia who undergo infrainguinal revascularization. J Vasc Surg 2019;69(6S):137S-151S.e3.
16. Iida O, Takahara M, Soga Y, Kodama A, Terashi H, Azuma N. Three-year outcomes of surgical versus endovascular revascularization for critical limb ischemia: the SPINACH study (Surgical Reconstruction Versus Peripheral Intervention in Patients With Critical Limb Ischemia). Circ Cardiovasc Interv 2017;10(12):e005531.
17. Adam DJ, Beard JD, Cleveland T, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet 2005;366:1925-34.
18. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135(12):e726-e779.
19. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2018;7(24):e011245.
20. Aboyans V, Ricco J-B, Bartelink M-LEL, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Eur Heart J 2018;39:763-816.