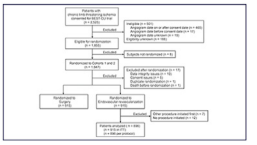
CLINICAL STUDY



The Incidence and Consequences of Endovascular Technical Failure in Patients with Chronic Limb-Threatening Ischemia: Results from the Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb-Threatening Ischemia (BEST-CLI) Trial

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ABSTRACT

Purpose: To analyze the causes and clinical impacts of endovascular technical failure (ETF) in the Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb-Threatening Ischemia (BEST-CLI) trial, which compared endovascular therapy with bypass surgery in patients with chronic limb-threatening ischemia (CLTI).

Materials and Methods: Patients with CLTI were randomized to infrainguinal bypass or endovascular therapy. ETF was defined as the inability to complete the endovascular procedure. Patients with ETF were compared with those without ETF. Causes of ETF and impact on major adverse limb event (MALE), above-ankle amputation, and death were analyzed. ETF occurred in 16% (146 of 896) of endovascular procedures.

Results: Patients who experienced ETF were older (69 years [SD ± 10] vs 67 years [SD ± 10], $P = .007$), were less frequently Hispanic, and had more complex infrainguinal arterial occlusive disease than those without ETF. ETF had more multilevel arterial occlusions involving a combination of both the superficial femoral artery (SFA)/popliteal segments and tibial segments (52% vs 41%, $P = .029$); Wound, Ischemia, and foot Infection ischemia Grade 3 (70.3% vs 53.1%, $P = .002$); and occlusion of the proximal SFA (37% vs 19%, $P < .001$). Causes of ETF included inability to cross the lesion in 82%. Following ETF, 67% underwent bypass surgery within 2 weeks of ETF. ETF was associated with a higher rate of MALE (81% vs 29%, $P < .0001$) but similar rates of above-ankle amputation (18.7% vs 16.0%, $P = .528$) and all-cause death (38.6% vs 29.8%, $P = .260$) at 3 years compared with no ETF.

Conclusions: ETF occurred in 16% of patients with CLTI and was associated with multilevel occlusions and proximal SFA occlusion. ETF was due to inability to cross the lesion in 82%. It did not impact long-term above-ankle amputation or death but was associated with increased major revascularization.

ABBREVIATIONS

BASIL = Bypass versus Angioplasty in Severe Ischaemia of the Leg, BEST-CLI = Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb-Threatening Ischemia, CLTI = chronic limb-threatening ischemia, ETF = endovascular technical failure, FDA = U.S. Food and Drug Administration, MACE = major adverse cardiovascular event, MALE = major adverse limb event, SFA = superficial femoral artery, SIMC = Surgical and Interventional Management Committee, SSGSV = single-segment great saphenous vein, VQI = Vascular Quality Initiative

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RESEARCH HIGHLIGHTS

- Endovascular technical failure (ETF) occurred in 16% of patients enrolled into the Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb-Threatening Ischemia trial.
- ETF was associated with the presence of hyperlipidemia and more complex vascular disease. Alternatively, Hispanic ethnicity was associated with the absence of ETF.
- In the vast majority of cases, ETF was due to inability to cross the lesion or lesions with a guide wire.
- Two thirds of patients underwent open bypass surgery within 2 weeks of ETF.
- There was no impact of ETF on major amputation or death.
- ETF was associated with increased risk of late major revascularization and major adverse cardiovascular events.

STUDY DETAILS

Study type: Prospective randomized clinical trial

Level of evidence: 2 (SIR-B)

The Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb-Threatening Ischemia (BEST-CLI) trial compared infrainguinal bypass with endovascular therapy as first-line revascularization strategy in patients with chronic limb-threatening ischemia (CLTI) who were candidates for both treatments. This trial demonstrated superior outcomes for infrainguinal bypass using single-segment great saphenous vein (SSGSV) compared with endovascular therapy (1). Notwithstanding, endovascular technical failure (ETF) occurred in 16% of patients randomized to the endovascular first treatment group. There has been a range in the incidence of technical failure reported in patients with CLTI undergoing endovascular treatment in an attempt at limb salvage. Although ETF rate of 6% has been reported by some registry data and device evaluation trials, others have reported rates as high as 28% among those with more complex anatomical disease patterns (2–6). However, in most industry-sponsored endovascular CLTI trials of specific devices, there are strict entry criteria regarding the lesion length and degree of calcification. In addition, patients in these trials are typically not considered enrolled until the target lesion has been successfully crossed with a wire. Registries, such as the Vascular Quality Initiative (VQI), do not record unsuccessful endovascular procedures in patients with CLTI; only successful or partially successful procedures are reported. As a result, there are limited data regarding the true incidence and impact of ETF in patients with CLTI who are known to have a broad range of disease patterns. This is all the more so in those with disease for which there is equipoise such that the patient is thought suitable to undergo surgical bypass.

The factors associated with ETF in patients with CLTI are not well known. Knowing which patients are at high risk of ETF will allow better informed patient decision making and more precise determination of an effective treatment plan, particularly when both open surgical bypass and endovascular therapy are believed to be appropriate options.

The purpose of this report is to determine the incidence of, factors associated with, and impact of ETF in patients with CLTI treated with endovascular therapy for a broad range of anatomical patterns of occlusive disease. Patients who experienced technical failure were compared with those who did not experience technical failure. A comparison of the patient-specific demographic and anatomical variables was performed. The impact of ETF on major reintervention, major limb amputation, and all-cause death was evaluated.

MATERIALS AND METHODS

The BEST-CLI trial was a prospective, randomized, open-label, multicenter, superiority, pragmatic trial designed to compare the effectiveness of endovascular and surgical revascularization in patients with CLTI (1,7). Patients were enrolled at 150 sites in the United States, Canada, Finland, Italy, and New Zealand. The trial enrolled patients with CLTI and infrainguinal peripheral artery disease who were eligible for both endovascular therapy and open surgical bypass. Based on availability of adequate SSGSV, patients were placed into 2 parallel studies; Cohort 1 included those with adequate SSGSV, whereas those without adequate SSGSV who would require an alternative bypass conduit were placed in Cohort 2. Patients were stratified by clinical presentation (ischemic rest pain alone vs tissue loss with or without ischemic rest pain) and anatomy (presence or absence of significant tibial disease defined as hemodynamically significant occlusive disease in all tibial runoff vessels).

A pragmatic design allowed for investigator discretion related to the techniques used within the standard of care spectrum. The U.S. Food and Drug Administration (FDA) granted an investigational device exemption for off-label use of endovascular devices. All subjects provided written informed consent, and the protocol was approved by the ethics committee at each participating institution.

An independent data and safety monitoring board was appointed by the National Heart, Lung, and Blood Institute. Enrollment began in August 2014 and continued through October 2019. Participants in Cohort 1 were followed through October 2021, and those in Cohort 2 were followed through December 2019.

Criteria for enrollment included that 2 study investigators at every site, 1 credentialed in surgical and 1 in endovascular revascularization, agreed that any given patient

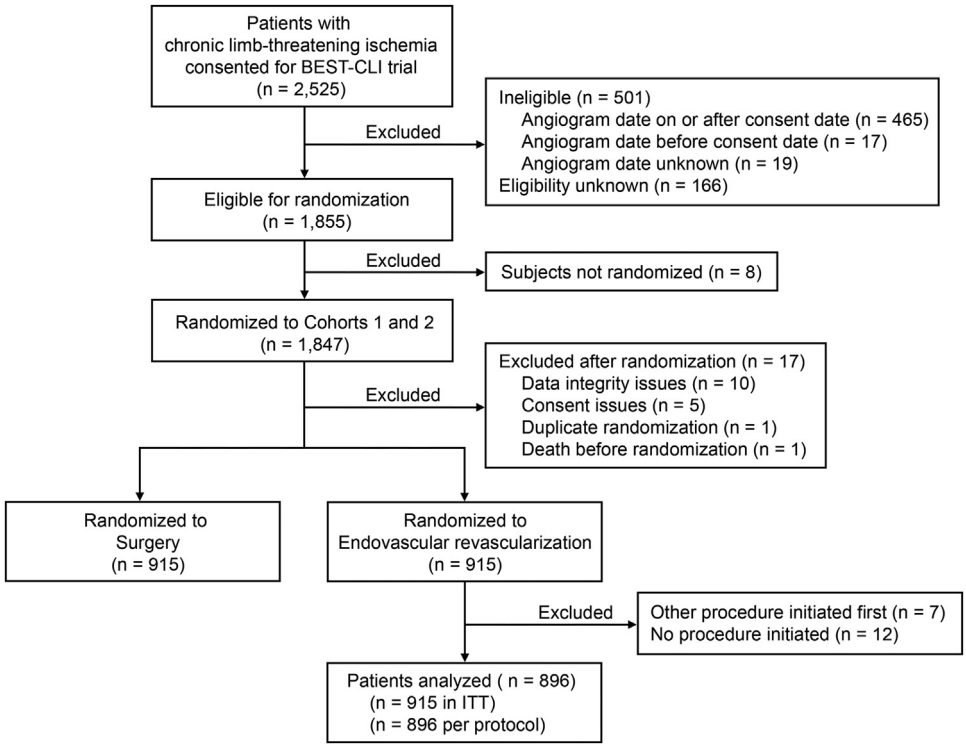

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. BEST-CLI = Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb-Threatening Ischemia; ITT = intention-to-treat.

could be treated with either open or endovascular techniques with accepted equipoise between strategies (8). Eligible patients were randomized (1:1) to 1 of 2 treatment arms (surgical or endovascular) within each of 4 strata defined by clinical (ischemic rest pain vs tissue loss) and anatomical (presence or absence of significant infrapopliteal occlusive disease). All patients were expected to receive their assigned treatment within 30 days of randomization. Endovascular methods were left to the discretion of the interventionalist, and any currently accepted techniques were allowed. Follow-up was performed at 30 days, 3 months, 6 months, and every 6 months thereafter up to 84 months after randomization.

All open surgical and endovascular investigators were approved by the Surgical and Interventional Management Committee (SIMC). Investigators needed to have appropriate training in open surgical and/or endovascular therapy (8). This typically required board certification in interventional cardiology, interventional radiology, vascular medicine, or vascular surgery. To qualify as a surgeon, the investigator needed to have performed 10 leg bypasses in patients with CLTI over the 2 years prior to the initiation of trial enrollment, 5 with vein and 5 to below-the-knee targets. Interventionalists needed to have performed 12 below-the-knee interventions over the previous 2 years in patients with CLTI. All investigators signed an attestation that they met these criteria. A random audit of 10% of study sites was performed in which operative notes and procedure notes were obtained from each site and reviewed by the SIMC prior to site initiation of enrollment. As the trial progressed, new investigators at trial sites were similarly reviewed and approved by the SIMC prior to initiation of enrollment.

Trial Population

In the current analysis, all patients on an intention-to-treat basis who were randomized to endovascular therapy were combined from Cohorts 1 and 2. Patients who experienced ETF were compared with those who did not experience ETF. ETF was defined as inability to complete the initial endovascular procedure due to the following: (*a*) inability to cross all of the vascular lesions requiring treatment with a wire, (*b*) a residual stenosis of >50%, and (*c*) lesion complication such as embolization, dissection, or vessel rupture that could not be treated endovascularly. Investigators were permitted to stage the initial endovascular procedure over a period up to 4 days in order to allow for treatment of complex vascular disease. Detailed descriptions of the access sites, ancillary devices, and endovascular techniques (eg, subintimal and crossing devices) used in each procedure were not recorded. The specific type of intervention such as atherectomy, drug-coated device, and stent was recorded, as was the specific complication that occurred and the techniques used to treat the complication.

Table 1. Baseline Patient Demographics

Characteristics	Overall (N = 896)	Technical failure (n = 146)	No failure (n = 750)	*P* value
Age (y)				
Mean ± SD	67.4 ± 9.9 (896)	69.4 ± 10.3 (146)	67.0 ± 9.8 (750)	**.007**
Median (Q1, Q3)	67.3 (61.0, 73.6)	69.3 (63.9, 76.3)	66.9 (60.9, 73.4)	
Minimum, maximum	(27.9, 93.1)	(27.9, 91.8)	(29.5, 93.1)	
Sex				.151
Male	71.1% (637/896)	76.0% (111/146)	70.1% (526/750)	
Female	28.9% (259/896)	24.0% (35/146)	29.9% (224/750)	
Race				.238
White	72.6% (645/889)	73.8% (107/145)	72.3% (538/744)	
Black	19.2% (171/889)	21.4% (31/145)	18.8% (140/744)	
Other	8.2% (73/889)	4.8% (7/145)	8.9% (66/744)	
Hispanic	14.2% (127/896)	8.9% (13/146)	15.2% (114/750)	**.046**
BMI (kg/m^2)	28.0 ± 5.9 (860)	28.0 ± 5.3 (140)	28.0 ± 6.0 (720)	.999
Hypertension	87.5% (784/896)	91.8% (134/146)	86.7% (650/750)	.087
Hyperlipidemia	74.0% (663/896)	84.2% (123/146)	72.0% (540/750)	**.002**
Diabetes	68.9% (617/896)	66.4% (97/146)	69.3% (520/750)	.489
Current smoking	34.9% (313/896)	30.8% (45/146)	35.7% (268/750)	.255
Coronary artery disease	46.4% (416/896)	52.1% (76/146)	45.3% (340/750)	.136
Congestive heart failure	6.0% (54/895)	5.5% (8/146)	6.1% (46/749)	.759
Stroke	13.6% (122/896)	15.1% (22/146)	13.3% (100/750)	.576
Chronic obstructive pulmonary disease	15.8% (142/896)	17.8% (26/146)	15.5% (116/750)	.478
End-stage kidney disease	11.6% (104/895)	12.3% (18/146)	11.5% (86/749)	.770
Statin	71.8% (643/896)	75.3% (110/146)	71.1% (533/750)	.294
Aspirin	68.3% (612/896)	67.8% (99/146)	68.4% (513/750)	.888
Clopidogrel	24.2% (217/896)	18.5% (27/146)	25.3% (190/750)	.078
Prasugrel	0.4% (4/896)	0.0% (0/146)	0.5% (4/750)	.376
Ticagrelor	1.1% (10/896)	0.0% (0/146)	1.3% (10/750)	.161
Direct-acting oral anticoagulant	4.5% (40/896)	6.2% (9/146)	4.1% (31/750)	.277
Warfarin	7.1% (64/896)	7.5% (11/146)	7.1% (53/750)	.841
Tobacco cessation	7.0% (63/896)	8.9% (13/146)	6.7% (50/750)	.333
Previous infrainguinal revascularization of index limb	6.4% (57/896)	8.2% (12/146)	6.0% (45/750)	.315
Ankle-brachial index (mean ± SD)	0.51 ± 0.20 (575)	0.49 ± 0.20 (88)	0.51 ± 0.20 (487)	.244
Ankle pressure (mean ± SD)	71.6 ± 27.6 (577)	66.4 ± 24.2 (86)	72.5 ± 28.0 (491)	.060
Toe pressure (mean ± SD)	33.3 ± 20.3 (388)	29.5 ± 22.5 (56)	34.0 ± 19.9 (332)	.129
Cohort				.194
1	78.7% (705/896)	15.4%% (109/705)	79.5% (596/750)	
2	21.3% (191/896)	19.3% (37/191)	20.5% (154/750)	
Clinical classification				.982
Ischemic rest pain	22.0% (197/896)	21.9% (32/146)	22.0% (165/750)	
Tissue loss	78.0% (699/896)	78.1% (114/146)	78.0% (585/750)	
WIfI ischemia grade				**.002**
0	0.0% (0/781)	0.0% (0/128)	0.0% (o/653)	
1	13.2% (103/781)	7.8% (10/128)	14.2% (93/653)	
2	30.9% (241/781)	21.9% (28/128)	32.6% (213/653)	
3	56.0% (437/781)	70.3% (90/128)	53.1% (127/738)	

Note–Statistically significant values are presented in bold.
BMI = body mass index; WIfI = Wound, Ischemia, foot Infection.

Outcome/Endpoints

The primary effectiveness outcome was a composite of major adverse limb event (MALE), defined as the time to above-ankle amputation or major index limb reintervention (new bypass graft, jump/interposition graft revision, surgical thrombectomy, or thrombolysis) or all-cause death. Repeat endovascular therapy was not considered a major revascularization unless it involved thrombolysis. The need and timing for reintervention were determined by trial site investigators on the basis of clinical assessment. First major reintervention was adjudicated by an independent, multidisciplinary Clinical Events Committee. Safety included major adverse cardiovascular events (MACEs), defined as the composite of myocardial infarction, stroke, or death

Table 2. Anatomical Characteristics

Anatomical characteristics	Overall	Technical failure	No failure	*P* value
Location based on baseline angiography (>70% stenosis)				.945
SFA/Pop	22.5% (200/889)	22.1% (32/145)	22.6% (168/744)	
TIB/PED	17.0% (151/889)	17.9% (26/145)	16.8% (125/744)	
SFA/Pop + TIB/PED	60.5% (538/889)	60.0% (87/145)	60.6% (451/744)	
Location based on baseline angiography (occluded)				**.029**
SFA/Pop	26.6% (214/806)	24.5% (35/143)	27.0% (179/663)	
TIB/PED	30.5% (246/806)	23.1% (33/143)	32.1% (213/663)	
SFA/Pop + TIB/PED	42.9% (346/806)	52.4% (75/143)	40.9% (271/663)	
Proximal third SFA segment occluded				**<.001**
No	77.7% (696/896)	63.0% (92/146)	80.5% (604/750)	
Yes	22.3% (200/896)	37.0% (54/146)	19.5% (146/750)	

Note–Statistically significant values are presented in bold.
PED = pedal; Pop = popliteal; SFA = superficial femoral artery; TIB = tibial.

from any cause, and serious adverse events (1). In order to determine the impact of ETF on subsequent MALE independent of open surgical revascularization at the time of ETF, MALE was also evaluated independently of ETF beginning at 30 days after initial procedure (MALE landmarked at 30 days). MALE landmarked at 30 days was chosen to account for early emergent or urgent open revascularization following ETF but to minimize missing revascularizations performed in the patients who did not experience ETF.

Demographics

The disposition of patients randomized to endovascular therapy is shown in the **Figure**. ETF occurred in 16% of all patients who underwent attempted endovascular therapy. As shown in **Table 1**, patients who experienced ETF were significantly older than those who did not experience failure. In addition, patients who experienced ETF were less frequently of Hispanic descent but more frequently had hyperlipidemia. The mean ankle pressure in patients who experienced ETF was 66 mm Hg (SD ± 24), compared with 73 mm Hg (SD ± 28) ($P = .06$) in those who did not experience ETF. ETF occurred in 15% (109 of 705) in Cohort 1 and 19.3% (37 of 191) in Cohort 2 ($P = .19$). Likewise, there was no difference in ETF in patients who presented with ischemic rest pain versus tissue loss ($P = .98$). The impact of the anatomical pattern of disease is shown in **Table 2**. Patients who experienced ETF had significantly more severe arterial disease manifested as a higher number of chronic total occlusions involving both the superficial femoral artery (SFA)/popliteal artery and tibial arteries than those who did not exhibit ETF ($P = .029$). Patients with ETF also presented more frequently with Wound, Ischemia, and foot Infection ischemia Grade 3 than those without ETF (70.3% vs 50.1%, $P = .002$). Importantly, patients with ETF more frequently had occlusion of the first third of the SFA than those who did not have failure (37% vs 19.5%, $P < .001$).

Statistical Analysis

Time-to-event outcomes are described using Kaplan-Meier plots, and treatment arms were compared using log-rank test statistics. A Cox model was used to calculate the hazard ratio and 95% CIs. A *P* value of less than .05 was considered significant. All analyses were performed using SAS Enterprise Guide v8.3 (SAS Institute, Cary, North Carolina) and R version 4.02 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Causes of ETF

Overall technical failure occurred in 16% of cases, and 82% of these were due to inability to cross the lesion with a guide wire. Additional causes and frequencies for technical failure are shown in **Table 3**. The incidence of flow-limiting dissection was not significantly different ($P = .46$) in patients who ultimately had ETF (7.7%) versus those who did not (9.7%). Stents were used to treat the dissection more frequently in patients without ETF (73%) than in those who experienced ETF (9%, $P < .001$). Similarly, only 3% of patients with ETF with perforation were treated with covered stents, whereas 35% of those without ETF had covered stents ($P = .016$). Open surgery was performed within 2 weeks in 67% (97 of 145) of patients who had ETF.

Impact of ETF on Outcomes

The primary composite endpoint of this study (MALE or all-cause death) was significantly higher in patients with ETF than in those without ETF (**Table 4**). An analysis of the subcomponents of the composite primary endpoint

Table 3. Procedure Characteristics by Technical Failure

Characteristics	Overall (N = 896)	Technical failure (n = 146)	No failure (n = 750)	*P* value
Reason for unsuccess				–
Unable to cross total occlusion or stenotic lesion	13.2% (119/896)	82.1% (119/145)	0.0% (0/0)	
Residual stenosis >50% in treatment site (due to recoil, inability to dilate, or otherwise)	0.8% (8/896)	5.5% (8/145)	0.0% (0/0)	
Target artery compromised due to distal embolization, thrombosis, or other complication	0.6% (6/896)	4.1% (6/145)	0.0% (0/0)	
Other	1.3% (12/896)	8.3% (12/145)	0.0% (0/0)	
Was an open surgical procedure performed?				–
No	5.3% (48/896)	33.1% (48/145)	0.0% (0/0)	
Yes	10.8% (97/896)	66.9% (97/145)	0.0% (0/0)	
Arterial thrombosis				.081
No	96.7% (863/892)	94.4% (134/142)	97.2% (729/750)	
Yes	3.3% (29/892)	5.6% (8/142)	2.8% (21/750)	
Treatment				.530
Endovascular intervention	96.6% (28/29)	100.0% (8/8)	95.2% (20/21)	
Surgery	3.4% (1/29)	0.0% (0/8)	4.8% (1/21)	
Arterial embolization				.656
No	96.4% (860/892)	95.8% (136/142)	96.5% (724/750)	
Yes	3.6% (32/892)	4.2% (6/142)	3.5% (26/750)	
Treatment				.464
Endovascular intervention	93.3% (28/30)	100.0% (6/6)	91.7% (22/24)	
Surgery	6.7% (2/30)	0.0% (0/6)	8.3% (2/24)	
Flow-limiting dissection				.457
No	90.6% (808/892)	92.3% (131/142)	90.3% (677/750)	
Yes	9.4% (84/892)	7.7% (11/142)	9.7% (73/750)	
Treatment				**<.001**
Prolonged balloon inflation	23.8% (20/84)	36.4% (4/11)	21.9% (16/73)	
Stent	64.3% (54/84)	9.1% (1/11)	72.6% (53/73)	
Stent-graft	3.6% (3/84)	0.0% (0/11)	4.1% (3/73)	
Surgery	2.4% (2/84)	18.2% (2/11)	0.0% (0/73)	
No specific treatment	6.0% (5/84)	36.4% (4/11)	1.4% (1/73)	
Perforation or rupture				**<.001**
No	96.0% (856/892)	90.8% (129/142)	96.9% (727/750)	
Yes	4.0% (36/892)	9.2% (13/142)	3.1% (23/750)	
Treatment				**.016**
Prolonged balloon inflation	25.0% (9/36)	23.1% (3/13)	26.1% (6/23)	
Stent	5.6% (2/36)	0.0% (0/13)	8.7% (2/23)	
Stent-graft	22.2% (8/36)	0.0% (0/13)	34.8% (8/23)	
Surgery	8.3% (3/36)	23.1% (3/13)	0.0% (0/23)	
No specific treatment	38.9% (14/36)	53.8% (7/13)	30.4% (7/23)	

Note–Statistically significant values are presented in bold.

showed that there was no significant difference in major amputation or all-cause death in patients who experienced ETF versus those who did not experience ETF. There was also no difference in amputation-free survival between the 2 groups. The occurrence of a major revascularization is the factor that drove the difference in the composite primary endpoint. When the need for major revascularization was landmarked at 30 days after the initial endovascular therapy, there was a higher need for late recurrent major revascularization at 3 years in patients with ETF than in those who did not have ETF (38.7% vs 26.9%, $P = .003$) (Table 4). There was also a higher incidence of MACEs in patients who experienced technical failure (49.2% vs 38.4%, $P = .027$).

Multivariable Cox Regression

In multivariable Cox regression analyses, there was no association between ETF and major amputation, all-cause death, or amputation-free survival (Tables 5–8). There was an association between ETF and the need for major revascularization.

Table 4. Intention-to-Treat Analysis of Endpoints at 3 Years in Subjects

Endpoints	All patients (N = 896)		Technical failure (n = 146)		No failure (n = 750)		Hazard ratio (95% CI) (open vs endovascular)	*P* value
	Patients with events (%)	KM% at 3 y	Patients with events (%)	KM% at 3 y	Patients with events (%)	KM% at 3 y		
Above-ankle amputation of the index leg while on study	123 (13.7%)	16.4%	22 (15.1%)	18.7%	101 (13.5%)	16.0%	1.16 (0.74–1.81)	.528
CEC-confirmed major intervention of the index leg while on the study	211 (23.6%)	27.2%	107 (73.3%)	77.4%	104 (13.9%)	17.6%	12.86 (9.75–16.97)	<.001
MALE or all-cause death	441 (49.2%)	55.6%	121 (82.9%)	88.9%	320 (42.7%)	49.3%	5.61 (4.55–6.91)	<.001
All-cause death	232 (25.9%)	31.2%	46 (31.5%)	38.6%	186 (24.8%)	29.8%	1.18 (0.88–1.58)	.260
MALE	292 (32.6%)	37.4%	112 (76.7%)	81.4%	180 (24.0%)	29.0%	8.36 (6.57–10.63)	<.001
MALE (landmarked at 30 d)	203 (22.7%)	28.8%	44 (30.1%)	38.7%	159 (21.2%)	26.9%	1.66 (1.19–2.31)	.003
Amputation or all-cause death	304 (33.9%)	40.1%	57 (39.0%)	49.1%	247 (32.9%)	38.5%	1.27 (0.98–1.66)	.075
Reintervention and amputation or all-cause death	572 (63.8%)	70.5%	131 (89.7%)	94.8%	441 (58.8%)	65.8%	5.24 (4.30–6.38)	<.001
MACE	290 (32.4%)	40.1%	56 (38.4%)	49.2%	234 (31.2%)	38.4%	1.35 (1.03–1.76)	.027

CEC = Clinical Events Committee; KM = Kaplan-Meier; MACE = major adverse cardiovascular event; MALE = major adverse limb event.

Table 5. Multivariable Cox Regression Models: Above-the-Ankle Amputation

Covariate (effect)	HR (95% CI), *P* value
Index leg, ABI	2.08 (0.53–8.17), *P* = .295
Age at baseline	0.97 (0.94–0.99), *P* = **.008**
Diabetes	0.04
Yes vs no	1.88 (1.03–3.44), *P* = **.040**
Sex	0.20
Female vs male	0.69 (0.40–1.21), *P* = .199
Technical failure	0.73
ETF vs no ETF	0.88 (0.43–1.81), *P* = .726
Hispanic	0.40
Yes vs no	1.36 (0.66–2.80), *P* = .402
Hypertension	0.02
Yes vs no	3.95 (1.19–13.10), *P* = **.025**
Hyperlipidemia	0.35
Yes vs no	0.76 (0.42–1.36), *P* = .352
WIfI ischemia grade	0.19
Level ENDO occluded (angiography)	0.02
SAF/pop vs SFA/pop/tibial/pedal	0.47 (0.25–0.87), *P* = **.017**
Tibial/pedal vs SFA/pop/tibial/pedal	0.48 (0.23–1.01), *P* = .052
SFA first segment occluded	0.78
Yes vs no	1.08 (0.62–1.90), *P* = .778

Note–Statistically significant values are presented in bold.
ABI = ankle-brachial index; ENDO = endovascular; ETF = endovascular technical failure; HR = hazard ratio; pop = popliteal; SFA = superficial femoral artery; WIfI = Wound, Ischemia, foot Infection.

Table 6. Multivariable Cox Regression Models: All-Cause Death

Covariate (effect)	HR (95% CI), *P* value
Index leg, ABI	0.66 (0.26–1.69), *P* = .387
Age at baseline	1.03 (1.02–1.05), *P* = **.000**
Diabetes	0.04
Yes vs no	1.46 (1.01–2.10), *P* = **.044**
Sex	0.34
Female vs male	0.84 (0.59–1.20), *P* = .337
Technical failure	0.25
ETF vs no ETF	1.28 (0.84–1.94), *P* = .248
Hispanic	0.35
Yes vs no	1.27 (0.77–2.11), *P* = .351
Hypertension	0.50
Yes vs no	1.19 (0.72–1.96), *P* = .503
Hyperlipidemia	0.00
Yes vs no	0.54 (0.37–0.79), *P* = **.001**
WIfI ischemia grade	0.16
Level ENDO occluded (angiography)	0.60
SAF/pop vs SFA/pop/tibial/pedal	0.82 (0.55–1.21), *P* = .320
Tibial/pedal vs SFA/pop/tibial/pedal	0.90 (0.55–1.46), *P* = .666
SFA first segment occluded	0.81
Yes vs no	1.05 (0.72–1.53), *P* = .813

Note–Statistically significant values are presented in bold.
ABI = ankle-brachial index; ENDO = endovascular; ETF = endovascular technical failure; HR = hazard ratio; pop = popliteal; SFA = superficial femoral artery; WIfI = Wound, Ischemia, foot Infection.

DISCUSSION

It is unclear how frequently technical failure occurs during attempted endovascular therapy in CLTI and more importantly what if any are the detrimental effects of ETF. In the current analysis, ETF occurred in the 16% of patients enrolled into the endovascular arm of the BEST-CLI trial. The most common cause of endovascular failure that occurred in more than 80% of patients was the inability to cross the lesion with a guide wire. This is in distinction to alternative endovascular failure modes related to the actual intervention such as embolization, acute thrombosis, or dissection, which were uncommon occurrences. Following failed endovascular therapy, 67% of the patients subsequently underwent a lower extremity bypass within 2 weeks

Table 7. Multivariable Cox Regression Models: Above-the-Ankle Amputation–Free Survival

Covariate (effect)	HR (95% CI), *P* value
Index leg, ABI	1.23 (0.55–2.76), *P* = .608
Age at baseline	1.01 (1.00–1.03), *P* = .125
Diabetes	0.01
Yes vs no	1.50 (1.08–2.08), *P* = **.015**
Sex	0.07
Female vs male	0.74 (0.54–1.03), *P* = .073
Technical failure	0.15
ETF vs no ETF	1.31 (0.90–1.91), *P* = .152
Hispanic	0.15
Yes vs no	1.37 (0.89–2.10), *P* = .153
Hypertension	0.09
Yes vs no	1.51 (0.94–2.42), *P* = .088
Hyperlipidemia	0.00
Yes vs no	0.61 (0.43–0.85), *P* = **.004**
WIfI ischemia grade	0.13
Level ENDO occluded (angiography)	0.08
SAF/pop vs SFA/pop/tibial/pedal	0.68 (0.48–0.97), *P* = **.034**
Tibial/pedal vs SFA/pop/tibial/pedal	0.77 (0.50–1.18), *P* = .227
SFA first segment occluded (angiography)	0.27
Yes vs no	1.20 (0.86–1.68), *P* = .272

Note–Statistically significant values are presented in bold.
ABI = ankle-brachial index; ENDO = endovascular; ETF = endovascular technical failure; HR = hazard ratio; pop = popliteal; SFA = superficial femoral artery; WIfI = Wound, Ischemia, foot Infection.

Table 8. Multivariable Cox Regression Models: Clinical Events Committee–Adjudicated Major Reintervention

Covariate (effect)	HR (95% CI), *P* value
Index leg, ABI	1.00 (0.36–2.74), *P* = .998
Age at baseline	0.97 (0.95–0.98), *P* = **.000**
Diabetes	0.18
Yes vs no	0.79 (0.55–1.12), *P* = .180
Sex	0.71
Female vs male	0.93 (0.63–1.37), *P* = .707
Technical failure	0.00
ETF vs no ETF	12.02 (8.28–17.46), *P* = **.000**
Hispanic	0.47
Yes vs no	1.25 (0.68–2.30), *P* = .470
Hypertension	0.89
Yes vs no	0.96 (0.57–1.63), *P* = .885
Hyperlipidemia	0.45
Yes vs no	1.18 (0.77–1.82), *P* = .447
WIfI ischemia grade	0.41
Level ENDO occluded (angiography)	0.00
SAF/pop vs SFA/pop/tibial/pedal	0.47 (0.32–0.71), *P* = **.000**
Tibial/pedal vs SFA/pop/tibial/pedal	0.32 (0.17–0.58), *P* = **.000**
SFA first segment occluded	0.28
Yes vs no	1.23 (0.85–1.77), *P* = .276

Note–Statistically significant values are presented in bold.
ABI = ankle-brachial index; ENDO = endovascular; ETF = endovascular technical failure; HR = hazard ratio; pop = popliteal; SFA = superficial femoral artery; WIfI = Wound, Ischemia, foot Infection.

of the ETF. Overall, ETF did not have a significant impact on major amputation or death at 3 years, although it was associated with a higher incidence of MALE as well as MACE. ETF was associated with more advanced age, the presence of hyperlipidemia, and more complex vascular disease. Alternatively, Hispanic ethnicity was associated with absence of ETF. The association of these individual variables does not necessarily imply causation. Complex vascular disease manifested as more advanced Wound, Ischemia, foot Infection ischemia Grade 3, occlusions involving simultaneously the femoral-popliteal segment and tibial arteries, or occlusions present in the proximal one third of the SFA were all more common in patients who experienced ETF.

Previous trials examining the effectiveness of endovascular therapy in patients with CLTI have demonstrated lower rates of technical failure than that observed in the current report. For instance, the Drug-Eluting Resorbable Scaffold versus Angioplasty for Infrapopliteal Artery Disease Trial (LIFE-BTK) trial recently reported that ETF occurred in 6% of patients treated with drug-eluting resorbable scaffolds in the tibial arteries (5). It is important to note that in this trial, infrapopliteal lesion length was limited to 170 mm and femoropopliteal disease had to already have been treated successfully; moreover, patients were not considered enrolled unless the lesion had been crossed by a guide wire. This is in comparison to the BEST-CLI trial in which 82% of the technical failures were related to inability to cross the lesion with a wire. Important exclusion criteria in the LIFE-BTK trial included inability to successfully treat the above-knee disease, presence of heavy calcification, lesion length greater than 170 mm, presence of patients with extensive Rutherford Category 6 tissue loss, and potential need for atherectomy. This resulted in a highly selected patient population with CLTI. In fact, in this particular trial, the baseline ankle-brachial index varied between 0.84 and 0.91 in a patient population with CLTI compared with 0.51 in BEST-CLI. The actual tibial artery lesion length reported in LIFE-BTK was only 4.4 cm.

Registry data frequently do not include endovascularly treated patients who experience technical failure. One such example is a recent study (2) that compared Medicare-linked VQI data in patients undergoing either lower extremity bypass or endovascular therapy for CLTI. In this report, the ETF rate for the endovascular arm is not mentioned. This is likely due to patients experiencing technical failure not being enrolled into the registry. Thus, although the VQI data are considered by many to be "real world," the lack of ability to account for the incidence and impact of technical failure in endovascularly treated patients can lead to significant bias.

There are limited data available that focus on the incidence and impact of technical failure during endovascular intervention in CLTI. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial comparing endovascular therapy with open surgery in patients with CLTI, which was reported in 2005, demonstrated an ETF rate of 27% (9). This is in contrast to recently released data from the BASIL-2 trial that demonstrated a 13% technical failure rate, which is similar to that in the BEST-CLI trial

(10). Differences in patient population between the BASIL-2 and BEST-CLI trials are significant. Notably, BASIL-2 consisted of patients with infrapopliteal disease who may or may not have had more proximal SFA disease. The causes and consequences of ETF in BASIL-2 have yet to be reported. A single-center retrospective review of endovascular therapy and the consequences of ETF in 181 limbs in 160 patients reported that the incidence of ETF was 15%, which was also similar to that in BEST-CLI (11). The cause of ETF, similar to that in BEST-CLI, was inability to cross the lesion in almost 90% of cases. The occurrence of ETF was associated with longer lesions and the presence of chronic total occlusions. There was no difference in survival; however, unlike in BEST-CLI, patients who experienced ETF had a shorter mean time to major amputation (58 vs 45 months, $P = .047$). The association of more complex vascular disease and increased ETF has been reported in a meta-analysis of 2,204 patients with CLTI (4). Using the Global Limb Anatomic Staging System, these investigators found a 27.9% immediate technical failure rate following endovascular therapy in patients with Stage 3 disease compared with 3.9% in patients with Stage 1 disease and 5.3% in patients with Stage 2 disease. This was associated with worse amputation-free survival and MALE in patients with Stage 3 disease experiencing ETF than in patients with Stage 3 disease undergoing successful endovascular therapy. This was not the case for patients who underwent open bypass surgery. The clinical application of the findings in the current analysis is that although ETF occurred in 16% of all patients enrolled in BEST-CLI, it did not have a significant impact on major amputation or death. However, it is important to note that a high percentage (67%) of the patients who experienced ETF were treated with an open bypass in BEST-CLI, which likely mitigated these effects. When early need (<30 days) for revascularization was disregarded, there remained an increased incidence of late major revascularization and MACE in patients who experienced ETF. Also important was that in 82% of instances, ETF was related to inability to cross the lesion and that other complications such as embolization, perforation, and dissection were less infrequent, occurring in 18% of cases.

There are several limitations to the current report, the most notable of which is that radiographic images are not available to better compare the extent and complexity of vascular disease between patients with and without ETF. The authors are currently in the process of collecting baseline angiographic images, in order to more precisely evaluate these differences. In addition, because BEST-CLI had a pragmatic trial design, there is variability around investigator judgment of which lesions would be considered amenable to endovascular therapy and how best to handle technical complications such as dissection and perforation. Similarly, it is reasonable to assume that there is variability in both interventionist skill and persistence in crossing challenging lesions. In the current study, differences did exist in the use of bailout stent placement and stent-graft placement in patients who experienced dissection and perforation versus those who did not. However, the overwhelming cause of ETF in the current study was failure to cross the arterial lesion, and complete information around the persistence, techniques, and ancillary devices endovascular specialists used to cross these lesions is lacking. These results must be interpreted within the context of the BEST-CLI randomized trial design. By definition, both providers and patients were cognizant that enrolled patients were deemed by the investigator and CLI team to be suitable candidates for either open bypass or endovascular intervention, and the availability of great saphenous vein conduit was also known. In the context of limb-threatening symptoms, these factors may have influenced the decision to perform an open bypass in the setting of immediate technical failure. As such, comparison of these downstream events to other observational cohorts or registries is intrinsically confounded.

In conclusion, ETF was more common in patients with CLTI with more complex vascular disease and proximal SFA occlusion. The most common reason for ETF was inability to cross the lesion with a guide wire. ETF was not significantly associated with major amputation or death at 3 years but was associated with increased MALE and MACE.

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