From the Western Vascular Society

High rates of nonindex limb amputation in the Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia (BEST-CLI) trial

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ABSTRACT

Objective: To evaluate the incidence and risk factors associated with nonindex limb (NIL) above-ankle amputations among BEST-CLI (Best Endovascular vs Best Surgical Therapy in Patients with Critical Limb Ischemia) trial participants.

Background: BEST-CLI compared endovascular therapy and infrainguinal bypass for patients with chronic limb-threatening ischemia (CLTI), focusing on the ipsilateral index limb. However, it is recognized that peripheral artery disease (PAD) can also impact the contralateral limb. We sought to evaluate the incidence and risk factors associated with NIL above-ankle amputations among BEST-CLI trial participants.

Methods: We analyzed data from 1400 participants in BEST-CLI. The primary outcome was the occurrence of above-ankle amputation in the NIL. Secondary outcomes included revascularization in the NIL, above-ankle amputation in the index limb, and mortality at the 3-year follow-up for the cohort that underwent NIL above-ankle amputations. Multivariable Cox regression was used to identify factors associated with above-ankle amputation in the NIL.

Results: Ninety-six participants (6.9%) underwent a NIL above-ankle amputation over the course of follow-up. These patients were more likely to be younger at enrollment (63 vs 67 years; $P < .001$), have diabetes mellitus (81.3% vs 66.1%; $P = .002$), end-stage renal disease (ESRD) (28.1% vs 9.0%; $P < .001$), and lower NIL toe pressure at enrollment (52 ± 31.6 mm Hg vs 64 ± 32.2 mm Hg; $P = .015$). Participants who underwent NIL amputation had significantly higher rates of open or endovascular revascularization in NIL (90.6% vs 17.7%; hazard ratio [HR], 10.95; 95% CI, 8.56-14.01; $P < .001$) and above-ankle amputations in the index limb (45.8% vs 12.1%; HR, 4.62; 95% CI, 3.28-6.50; $P < .001$). On 3-year Kaplan-Meier analysis, there was no significant difference in all-cause mortality between participants with and without NIL amputations (26.2% vs 28.2%; HR, 1.28; 95% CI, 0.92-1.77; $P = .15$). In multivariable Cox regression, NIL above-ankle amputation was associated with younger age at baseline (HR, 0.94; 95% CI, 0.89-1.00; $P = .047$), ESRD (HR, 10.73; 95% CI, 3.09-37.30; $P < .001$), and lower NIL toe pressure at baseline (HR, 0.98; 95% CI, 0.97-1.00; $P = .049$).

Conclusions: In the BEST-CLI trial cohort, NIL above-ankle amputations were associated with ESRD, lower NIL toe pressure, and younger age. A significant proportion of patients who had a NIL above-ankle amputation also underwent revascularization of NIL and an index limb above-ankle amputation within 3 years. Our findings highlight the need for targeted preventive strategies that focus on both limbs in high-risk populations to enhance limb preservation after revascularization for peripheral artery disease. (J Vasc Surg 2025;■:1-9.)

Keywords: Chronic limb-threatening ischemia; Critical limb ischemia; Contralateral amputation; Non-index limb amputation

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Presented at the 40th Western Vascular Society Annual Meeting, September 14-17, 2025, Ojai, California.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

https://doi.org/10.1016/j.jvs.2025.11.009

Peripheral artery disease (PAD) affects >237 million individuals globally, imposing a substantial health burden owing to high morbidity, mortality, and health care costs.[1,2] Although it may remain asymptomatic or present as intermittent claudication,[3] PAD can progress to chronic limb-threatening ischemia (CLTI), its most severe form.[4] CLTI, characterized by ischemic rest pain or tissue loss, significantly decreases quality of life and functional independence.[5] Even with revascularization, CLTI is associated with a 20% risk of major amputation within 1 year.[6,7]

The primary treatment approach for CLTI focuses on limb preservation. Although CLTI typically presents with a dominant symptomatic limb requiring revascularization, the systemic nature of atherosclerosis and prevalence of polyvascular disease places patients at risk for bilateral occlusive arterial disease and ischemia, in turn increasing the risk of tissue loss and amputation of the contralateral limb. Existing studies on contralateral disease progression predominantly examine patients who have already undergone an initial above-ankle amputation.[8-12] Risks of contralateral amputation after an initial amputation are reported to range from 3.0% to 29.5%, varying with follow-up duration and patient population.[9-12] However, prospective data on contralateral limb outcomes in CLTI patients remains limited, highlighting critical gaps in understanding the broader risks and mechanisms of bilateral limb loss.

This study examined the incidence and risk factors for contralateral nonindex limb (NIL) above-ankle amputations among participants in BEST-CLI (Best Endovascular vs Best Surgical Therapy in Patients with CLI). As the largest randomized trial comparing revascularization strategies in CLTI, this analysis provides insights to inform targeted strategies for decreasing bilateral limb loss rates in patients with advanced PAD.

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter randomized controlled trial
- **Key Findings:** A total of 96 of 1400 patients (6.6%) with chronic limb-threatening ischemia in the Best Endovascular vs Best Surgical Therapy in Patients with Critical Limb Ischemia trial underwent nonindex limb above-ankle amputation. These patients were more likely to be younger, have a lower toe pressures on presentation, and have end-stage renal disease.
- **Take Home Message:** Patients who are younger, have end-stage renal disease, and have lower toe pressures are at increased risk of nonindex limb above-ankle amputation and require diligent surveillance programs to maximize limb salvage.

METHODS

BEST-CLI was an international, multicenter, multispecialty, pragmatic, randomized controlled trial that compared infrainguinal bypass and endovascular therapy in patients with CLTI who were candidates for both revascularization strategies (NCT02060630). Patients were enrolled at 150 study sites between August 2014 and October 2019. A total of 1830 participants were randomized 1:1 into two cohorts based on availability of single-segment great saphenous vein (SSGSV). Cohort 1 (n = 1434) included participants with an adequate SSGSV, and cohort 2 (n = 396) included those who lacked adequate SSGSV, thereby requiring bypass with an alternative conduit. Scheduled follow-up occurred at 30 days, 3 and 6 months, and therefore every 6 months for ≤84 months, with additional telephone follow-ups at 30 months and annually. Owing to funding limitations, follow-up for cohort 2 were discontinued on December 31, 2019, whereas cohort 1 follow-up was continued until October 20, 2021. The study was approved by the institutional review board or its equivalent at each site, and primary results have been published elsewhere.[6]

This secondary analysis focused on 1400 participants (1093 from cohort 1 and 307 from cohort 2). We excluded 430 participants, including 276 with missing data on NIL, 32 who had NIL above-knee amputations at baseline, 72 who had NIL below-knee amputations at baseline, and 50 who did not undergo revascularization of the index limb. The primary outcome was above-ankle amputation of the NIL throughout the follow-up period. Secondary outcomes included all-cause mortality, revascularization of the NIL (open or endovascular), and above-ankle amputation of the index limb. Death was treated as a censored event in time-to-event analyses.

Univariable analyses were conducted using the χ^2 test for categorical variables and Kaplan-Meier estimates for time-to-event outcomes, with comparisons between two groups (those with and without NIL above-ankle amputations) performed using log-rank tests. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using univariable and multivariable Cox regression models. Variables with clinical relevance or significant univariate associations were included in multivariable models. Cases with missing variables, such as toe pressure (including those with incompressible vessels), were excluded from the multivariable analysis. A subgroup analysis was performed on patients with diabetes as they have an elevated risk for NIL amputation. Statistical significance was defined as a P value of <.05. All analyses were performed using SAS Enterprise Guide software (SAS Institute).

RESULTS

Of the 1400 participants, 96 (6.9%) underwent amputation of the NIL during the study period. At 3 years, 219 (15.6%; Kaplan-Meier, 17.0%) underwent above-ankle amputations, including 171 (12.2%; Kaplan-Meier, 14.7%)

involving the index limb and 81 (5.8%; Kaplan-Meier, 6.6%) involving the NIL. A total of 41 (2.9%; Kaplan-Meier, 3.2%) participants underwent bilateral above-ankle amputations. All-cause mortality rate was 23.6% (n = 330; Kaplan-Meier, 28.0%), and 291 participants (20.8%; Kaplan-Meier, 23.3%) underwent open or endovascular revascularization in the NIL.

Compared with those who did not undergo NIL above-ankle amputations, patients who underwent NIL above-ankle amputations were younger at enrollment, more likely to be Hispanic, had higher rates of diabetes mellitus, chronic kidney disease or end-stage renal disease (ESRD), and either required assistance with ambulation or were nonambulatory (Table I). Although ankle pressures and ankle-brachial indices did not differ significantly between the groups, participants who underwent NIL above-ankle amputations had lower NIL toe pressures at baseline. No significant differences were observed in gender, smoking history, or use of statin or antiplatelet agents.

Midterm outcomes. Participants who underwent NIL amputation had significantly higher rates of open or endovascular revascularization in the NIL (90.6% vs 17.7%; HR, 10.95; 95% CI, 8.56-14.01; $P < .001$), and above-ankle amputations in the index limb (45.8% vs 12.1%; HR, 4.62; 95% CI, 3.28-6.50; $P < .001$) (Table II). On 3-year Kaplan-Meier analysis, there was no significant difference in all-cause mortality between participants with and without NIL amputations (26.2% vs 28.2%; HR, 1.28; 95% CI, 0.92-1.77; $P = .15$) (Fig).

On multivariable cox regression, younger age (HR, 0.94; 95% CI, 0.89-1.00; $P = .047$), ESRD (HR, 10.73; 95% CI, 3.09-37.30; $P < .0001$), and lower baseline NIL toe pressure (HR, 0.98; 95%, CI 0.97-1.00; $P = .049$) were associated with an increased risk of NIL above-ankle amputations (Table III). A lower toe pressure (HR, 0.98; 95% CI, 0.97-0.99; $P < .0001$) was also associated with a higher likelihood of NIL revascularization. Older age (HR, 1.06; 95% CI, 1.03-1.10; $P < .0001$), need for assistance with ambulation (HR, 1.61; 95% CI, 1.01-2.58; $P = .047$), and ESRD (HR, 2.34; 95% CI, 1.11-4.92; $P = .026$) were independently associated with an increased risk of all-cause mortality, whereas a higher albumin level was associated with a lower mortality risk (0.45; 95% CI, 0.30-0.68; $P < .0001$).

Participants with amputations in either limb or bilateral amputations. On multivariable Cox regression, younger age (HR, 0.95; 95% CI, 0.91-0.98; $P = .004$), ESRD (HR, 3.38; 95% CI, 1.50-7.62; $P = .003$), male sex (HR, 2.38; 95% CI, 1.09-5.26; $P = .03$), and African American race (vs. White; HR, 2.07; 95% CI, 1.09-3.93; $P = .023$) were associated with an increased risk of either index limb or NIL amputations. No variables were significant associated with bilateral amputations on multivariable analysis.

Participants with diabetes and NIL amputations. Among the 940 participants with diabetes mellitus, 171 (18.2%) underwent above-ankle amputations in either limb, including 134 (14.3%) in the index limb and 66 (7.0%) in the NIL, and 36 (3.8%) underwent bilateral above-ankle amputations. The all-cause mortality rate in this subgroup was 26.2% (n = 246), and 22.6% (n = 212) underwent endovascular or open revascularization of the NIL.

Participants with diabetes mellitus who underwent NIL above-ankle amputations had significantly higher rates of open or endovascular intervention in the NIL (89.7% vs 18.8%; HR, 10.61; 95% CI, 8.01-14.05; $P < .001$) and above-ankle amputations of the index limb (48.0% vs 14.0%; HR, 4.09; 95% CI, 2.81-5.95; $P < .001$). On 3-year Kaplan-Meier analysis, there was no significant difference in all-cause mortality between participants with and without NIL amputations (26.1% vs 31.3%; HR, 1.13; 95% CI, 0.79-1.61; $P = .51$).

DISCUSSION

This study identified two key findings regarding the natural history of the contralateral limb in patients with ipsilateral CLTI, which was presumably asymptomatic at the time of enrollment. Revascularization (21%) or above-ankle amputations (6%) of the contralateral NIL was substantial after revascularization of the symptomatic index limb. Participants who underwent contralateral above-ankle amputations were more likely to undergo revascularization of the NIL and experienced higher rates of above-ankle amputations of the index limb. These findings highlight the susceptibility of the asymptomatic limb in patients with CLTI and emphasize the need for vigilant monitoring, aggressive cardiovascular risk management, and timely intervention.

Interventions for the symptomatic limb are critical for patients with CLTI, but the high rates of revascularization and amputation in the contralateral limb have important clinical implications. Twenty percent of this patient population underwent revascularization during the study time frame. These data support the need for structured surveillance protocols for both the revascularized limb and the contralateral asymptomatic limb in CLTI patients, particularly those with younger age at CLTI onset, ESRD, and lower baseline NIL toe pressure, which may indicate more advanced PAD. Among these factors, ESRD was associated with the greatest risk.[8,11] Implementation of risk-stratified surveillance programs, aggressive patient education, and timely intervention may help to decrease the significant burden of bilateral limb loss in these high-risk populations. Toe pressure, significantly lower in BEST CLI participants at the time of enrollment who under NIL amputations, may serve as a valuable screening tool to identify those at risk for limb amputations.

Prior studies have found comparable results regarding the increased risk of contralateral limb amputation after an above-ankle amputation. In a single-center study, 5.7% and 11.5% of patients (77% diabetes) underwent

Table I. Baseline characteristics of patients who did or did not undergo nonindex limb (*NIL*) above-ankle amputations (*Amp*).

Characteristics	Overall (n = 1400)	No NIL amputations (n = 1304)	NIL amputations (n = 96)	*P* value
Demographics				
Age, years				
Mean ± SD	67.6 ± 9.5 (1400)	67.9 ± 9.4 (1304)	63.2 ± 9.9 (96)	<.001
Median (Q1, Q3)	67.3 (61.3, 74.0)	67.4 (61.6, 74.2)	63.9 (56.3, 70.6)	
(Min, max)	(28.7, 93.1)	(28.7, 93.1)	(38.6, 85.4)	
Gender				.132
Male	71.4% (1000/1400)	70.9% (925/1304)	78.1% (75/96)	
Female	28.6% (400/1400)	29.1% (379/1304)	21.9% (21/96)	
Race				.075
White	72.4% (1003/1385)	73.2% (943/1289)	62.5% (60/96)	
Black	19.7% (273/1385)	19.2% (248/1289)	26.0% (25/96)	
Other	7.9% (109/1385)	7.6% (98/1289)	11.5% (11/96)	
Ethnicity				
Hispanic	11.5% (161/1400)	11.0% (144/1304)	17.7% (17/96)	.048
Comorbidities				
BMI, kg/m^2				
Mean ± SD	27.9 ± 5.9 (1354)	27.8 ± 5.9 (1260)	28.7 ± 6.9 (94)	.175
Median (Q1, Q3)	27.2 (23.5, 31.3)	27.1 (23.5, 31.2)	28.1 (24.3, 32.9)	
(Min, max)	(14.3, 52.5)	14.3, (52.5)	(14.4, 49.5)	
Obese (BMI ≥ 30)	32.1% (435/1354)	31.8% (401/1260)	36.2% (34/94)	.384
Hypertension	87.4% (1224/1400)	87.4% (1140/1304)	87.5% (84/96)	.983
Previous MI	50.2% (311/620)	49.7% (286/576)	56.8% (25/44)	.360
Prior CABG	45.7% (284/622)	45.3% (262/578)	50.0% (22/44)	.549
Prior PCI	43.2% (269/622)	42.6% (246/578)	52.3% (23/44)	.210
Prior CABG/PCI	74.4% (463/622)	73.5% (425/578)	86.4% (38/44)	.060
Previous coronary artery disease	83.4% (519/622)	82.7% (478/578)	93.2% (41/44)	.071
Congestive heart failure	5.6% (79/1399)	5.8% (76/1303)	3.1% (3/96)	.267
COPD	15.4% (215/1400)	15.5% (202/1304)	13.5% (13/96)	.609
Stroke	13.8% (193/1400)	14.3% (186/1304)	7.3% (7/96)	.056
TIA	4.9% (69/1400)	5.0% (65/1304)	4.2% (4/96)	.721
History of TIA/stroke	16.7% (234/1400)	17.3% (225/1304)	9.4% (9/96)	.046
CKD grade				<.001
No CKD	74.7% (1025/1373)	75.6% (966/1277)	61.5% (59/96)	
Stage 3	12.4% (170/1373)	12.6% (161/1277)	9.4% (9/96)	
Stage 4	2.5% (34/1373)	2.6% (33/1277)	1.0% (1/96)	
Dialysis dependent	10.5% (144/1373)	9.2% (117/1277)	28.1% (27/96)	
ESRD	10.3% (144/1399)	9.0% (117/1303)	28.1% (27/96)	
Smoking history				.572
Never	21.1% (296/1400)	20.9% (272/1304)	25.0% (24/96)	
Prior (>1 year)	34.9% (489/1400)	34.9% (489/1400)	37.5% (36/96)	
Prior (2 weeks to 1 year)	7.6% (106/1400)	7.6% (99/1304)	7.3% (7/96)	
Smoking status				.389
Never	21.1% (296/1400)	20.9% (272/1304)	25.0% (24/96)	
Prior (>1 year)	34.9% (489/1400)	34.7% (453/1304)	37.5% (36/96)	
Diabetes	67.1% (940/1400)	66.1% (862/1304)	81.3% (78/96)	.002

Table I. Continued.

Characteristics	Overall (n = 1400)	No NIL amputations (n = 1304)	NIL amputations (n = 96)	*P* value
Ambulatory status				.019
Ambulatory without assistance	58.5% (818/1399)	59.5% (775/1303)	44.8% (43/96)	
Ambulatory with assistance	32.0% (448/1399)	31.2% (407/1303)	42.7% (41/96)	
Uses wheelchair or bedbound	9.5% (133/1399)	9.3% (121/1303)	12.5% (12/96)	
Living at home	95.1% (1332/1400)	95.3% (1243/1304)	92.7% (89/96)	.250
Albumin				
Mean ± SD	3.6 ± 0.6 (754)	3.6 ± 0.6 (695)	3.4 ± 0.7 (59)	.111
Median (Q1, Q3)	3.6 (3.2, 4.0)	3.6 (3.2, 4.0)	3.5 (2.9, 4.0)	
(Min, max)	(1.0, 5.1)	(1.2, 5.1)	(1.0, 5.0)	
Medications				
Statin	72.3% (1012/1400)	71.9% (937/1304)	78.1% (75/96)	.185
Use Antiplatelet				.939
None	27.8% (389/1400)	27.8% (362/1304)	28.1% (27/96)	
Any single	72.2% (1011/1400)	72.2% (942/1304)	71.9% (69/96)	
DAPT	0.0% (0/1400)	0.0% (0/1304)	0.0% (0/96)	
Use anticoagulant	11.3% (158/1400)	11.6% (151/1304)	7.3% (7/96)	.200
Index limb details				
Previous infrainguinal revascularization	5.9% (82/1398)	5.8% (75/1302)	7.3% (7/96)	.538
WIFI stage				.143
1	6.3% (77/1221)	6.5% (74/1138)	3.6% (3/83)	
2	29.4% (359/1221)	30.1% (342/1138)	20.5% (17/83)	
3	29.9% (365/1221)	29.6% (337/1138)	33.7% (28/83)	
4	34.4% (420/1221)	33.8% (385/1138)	42.2% (35/83)	
ASA classification				
1	5.9% (82/1393)	5.9% (77/1297)	5.2% (5/96)	.439
2	14.3% (199/1393)	14.6% (189/1297)	10.4% (10/96)	
3	65.7% (915/1393)	65.7% (852/1297)	65.6% (63/96)	
4	14.1% (197/1393)	13.8% (179/1297)	18.8% (18/96)	
ABI index limb				
Mean ± SD	0.6 ± 0.3 (978)	0.6 ± 0.3 (915)	0.6 ± 0.4 (63)	.223
Median (Q1, Q3)	0.5 (0.4, 0.7)	0.5 (0.4, 0.7)	0.5 (0.4, 0.7)	
(Min, max)	(0.0, 2.4)	(0.0, 2.4)	(0.0, 2.4)	
Toe pressure index limb				
Mean ± SD	34.2 ± 25.6 (599)	34.2 ± 25.9 (556)	30.1 ± 20.1 (43)	.285
Median (Q1, Q3)	31.0 (19.0, 44.0)	31.0 (19.5, 45.0)	30.0 (18.0, 43.0)	
(Min, max)	(0.0, 250.0)	(0.0, 250.0)	(0.0, 102.0)	
Ankle pressure index limb				
Mean ± SD	81.9 ± 46.9 (1014)	81.4 ± 46.1 (949)	89.9 ± 57.2 (65)	.159
Median (Q1, Q3)	70.0 (53.0, 98.0)	70.0 (53.0, 97.0)	74.0 (55.0, 108.0)	
(Min, max)	(0.0, 329.0)	(0.0, 329.0)	(0.0, 300.0)	
NIL details				
ABI NIL				
Mean ± SD	0.8 ± 0.3 (956)	0.8 ± 0.3 (904)	0.8 ± 0.4 (52)	.787
Median (Q1, Q3)	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)	
(Min, max)	(0.0, 2.4)	(0.0, 2.3)	(0.2, 2.4)	

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Table I. Continued.

Characteristics	Overall (n = 1400)	No NIL amputations (n = 1304)	NIL amputations (n = 96)	*P* value
Toe pressure NIL				
Mean ± SD	63.1 ± 32.3 (730)	63.9 ± 32.2 (680)	52.4 ± 31.6 (50)	.015
Median (Q1, Q3)	58.0 (40.0, 82.0)	59.0 (42.0, 82.0)	44.0 (29.0, 66.0)	
(Min, max)	(0.0, 250.0)	(0.0, 250.0)	(0.0, 146.0)	
Ankle pressure index limb				
Mean ± SD	120.3 ± 47.9 (988)	120.1 ± 47.1 (934)	123.6 ± 60.0 (54)	.599
Median (Q1, Q3)	114.0 (86.0, 148.5)	114.0 (87.0, 148.0)	109.0 (85.0, 150.0)	
(Min, max)	(1.0, 300.0)	(1.0, 298.0)	(34.0, 300.0)	

ABI, Ankle-brachial index; *ASA*, American Society of Anesthesiologists; *BMI*, body mass index; *CABG*, coronary artery bypass graft; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *DAPT*, dual antiplatelet therapy; *ESRD*, end-stage renal disease; *MI*, myocardial infarct; *PCI*, percutaneous coronary intervention; *SD*, standard deviation; *TIA*, transient ischemic attack; *WIfI*, Wound, Infection, Ischemia.

Table II. Mid-term outcomes of patients who did or did not undergo nonindex limb (*NIL*) above-ankle amputations

	All participants (n = 1400)		No NIL above-ankle amputations (n = 1304)		NIL above ankle amputations (n = 96)		
	Events	3-Year KM %	Events	3-Year KM %	Events	3-Year KM %	HR (96% CI), *P* value
NIL above-ankle amputation	81 (5.79)	6.63			81 (84.38)	84.38	
NIL open or endovascular revascularization	291 (20.79)	23.29	204 (15.64)	17.71	87 (90.63)	90.63	10.95 (8.56-14.01), $P < .001$
IL major or minor reintervention	551 (39.36)	45.41	505 (38.73)	44.94	46 (47.92)	51.49	1.33 (0.99-1.79), $P = .060$
IL above-ankle amputation	171 (12.21)	14.72	132 (10.12)	12.10	39 (40.63)	45.81	4.62 (3.28-6.50), $P < .001$
Amputation in both IL and NIL	41 (2.93)	3.18			41 (42.71)	45.85	
All-cause death	330 (23.57)	28.04	307 (23.54)	28.18	23 (23.96)	26.19	1.28 (0.92-1.77), $P = .148$

CI, Confidence interval; *HR*, hazard ratio; *KM*, Kaplan-Meier.
Values are number (%) unless otherwise noted.

contralateral major amputations at 1 and 5 years, respectively.[10] A meta-analysis of 22 studies in patients with diabetes reported a 20.5% incidence of contralateral amputations, including at the foot, ankle, and above-ankle levels, at 5 years (interquartile range, 13.3%-27.2%).[13] Most studies on contralateral limb status have focused on patients after above-ankle or minor amputations, with limited data addressing the natural history of contralateral limb outcomes after the development of CLTI. It is important to note that the incidence of NIL amputation in this clinical trial cohort maybe artificially low, given a significant number of participants underwent revascularization as part of the trial participation. This study represents the first prospectively collected dataset describing the outcomes of the contralateral limb in a patient population that is undergoing rigorous surveillance and standard follow-up as a part of the trial.

A study of 533 patients with diabetes and CLTI reported CLTI a prevalence of 50% in patients' contralateral limb over a 6-year period, with 6.7% requiring major amputations.[8,14] Similarly, a recent single-center retrospective study of 439 patients with CLTI found that 36% developed contralateral limb CLTI and 22% underwent above-ankle amputations of the contralateral limb.[15] Expanding on this literature, the BEST-CLI cohort demonstrated 3-year rates of NIL revascularization and above-ankle amputations of 21% and 6%, respectively, after initial revascularization of the index limb. In a case series comparing 381 patients with and without diabetes after above-ankle amputations, the mean time to above-ankle amputations of the contralateral limb or death was shorter in those without diabetes mellitus, whereas CLTI patients with diabetes mellitus had higher rates of contralateral limb amputation.[16] In the BEST-CLI cohort, participants with diabetes mellitus had higher rates of all-cause mortality (26.2% vs 23.6%), NIL revascularization (22.6% vs 20.8%), and NIL above-ankle amputation (7.0% vs 5.8%) compared with the overall study cohort.

Our results showed that Hispanic patients had higher rates of NIL amputations, and African American patients were more likely to undergo either index or NIL amputations on multivariable analysis. These findings are consistent with prior studies demonstrating disproportionately

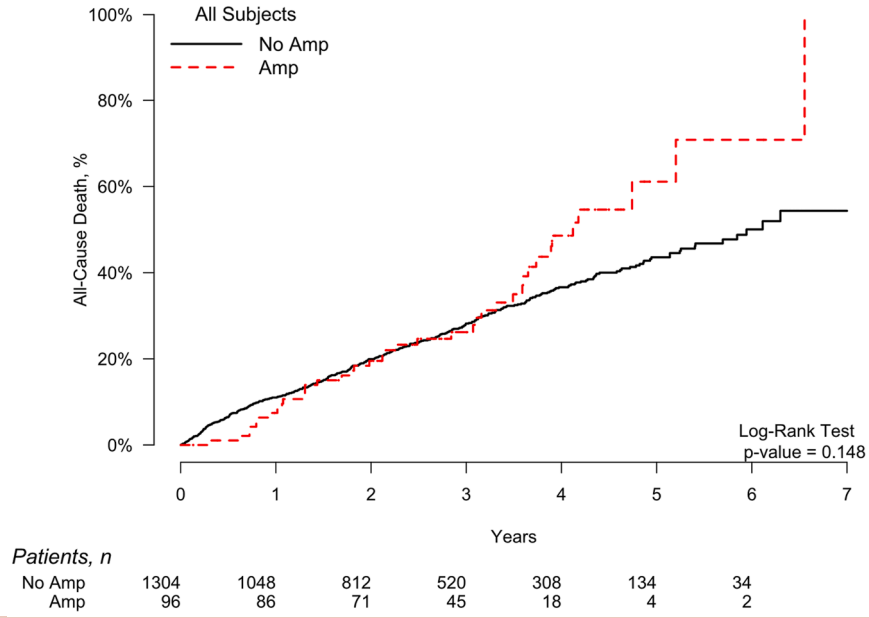

Fig. Kaplan-Meier analysis of 3-year all-cause mortality among participants with and without nonindex limb (NIL) amputations.

Table III. Multivariable Cox regression analysis of risk factors for nonindex limb (*NIL*) above-ankle amputation

Covariate	HR (95% CI), *P* value
Age at baseline	0.94 (0.89-1.00), $P = .047$
Sex	
Female vs male	0.55 (0.16-1.81), $P = .322$
Race	
Black vs White	2.02 (0.71-5.74), $P = .185$
Other vs White	6.42 (0.87-47.60), $P = .069$
Ethnicity	
Hispanic vs non-Hispanic	2.74 (0.66-11.43), $P = .167$
ESRD	10.73 (3.09-37.30), $P < .0001$
Diabetes	0.32 (0.08-1.34), $P = .119$
Albumin	0.64 (0.29-1.42), $P = .273$
Ambulatory status	
Assistance vs no assistance	1.60 (0.60-4.24), $P = .347$
Wheelchair or bed bound vs no assistance	1.57 (0.31-8.02), $P = .585$
NIL toe pressure at baseline	0.98 (0.97-1.00), $P = .049$
Index limb WIfI classification	
Class 0/1 vs 2/3	0.99 (0.27-3.63), $P = .987$

CI, Confidence interval; *ESRD,* end-stage renal disease; *HR,* hazard ratio; *WIfI,* Wound, Infection, Ischemia.

higher rates of limb loss among racial and ethnic minorities.[17-19] The persistence of these disparities, even within a controlled clinical trial setting where follow-up schedules and treatment intensity were standardized, likely reflects complex interactions between social determinants of health and CLTI outcomes. These results underscore the need for targeted interventions to address structural and access-related inequities in limb preservation care.

This study has several limitations. First, it is a secondary analysis of BEST-CLI, which included a selected population of patients with CLTI who were candidates for either open or endovascular revascularization, potentially limiting the generalizability of the findings to broader

populations of CLTI. Additionally, the study was not powered for this analysis and patient follow-up was conducted under the protocol for a randomized controlled trial, which may not reflect real-world clinical practice. Second, the absence of detailed data on the contralateral NIL, including the timing of symptom onset before revascularization or amputation, specific indications and types of revascularization procedures, and the outcomes of these procedures may have limited the ability to comprehensively evaluate risk factors. Although it is likely that most NILs were asymptomatic at baseline, symptom onset data were not collected, and we were therefore unable to verify this assumption across all patients. Third, information on patient adherence to medical therapy, the details of cardiovascular risk management, and access to specialized limb preservation care were not consistently available, which may have impacted the observed outcomes. Although all participants were enrolled in a clinical trial and were assumed to have comparable access to follow-up and treatment intensity for both limbs, limb-specific data on care processes and access were not systemically collected.

CONCLUSIONS

This analysis of the BEST-CLI cohort demonstrates that patients with CLTI face significant risk of contralateral adverse limb events, with 21% requiring revascularization and 6% undergoing above-ankle amputations within 3 years of their index limb revascularization. The risk is higher in younger patients, those with ESRD, and those with lower baseline toe pressure. Our findings highlight the need for targeted strategies to address both limbs in high-risk populations, with the goal of enhancing limb preservation following revascularization for PAD.

AUTHOR CONTRIBUTIONS

Conception and design: TT, KD, AF, GD, MM, KR, MC, NS
Analysis and interpretation: TT, KD, AF, GD, MM, KR, MC, MV, PK, MS, NS
Data collection: AF, GD, MM, KR
Writing the article: TT, KD
Critical revision of the article: TT, KD, AF, GD, MM, KR, MC, MV, PK, MS, NS
Final approval of the article: TT, KD, AF, GD, MM, KR, MC, MV, PK, MS, NS
Statistical analysis: GD
Obtained funding: AF, MM, KR
Overall responsibility: TT

FUNDING

BEST-CLI was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health 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): Vascular InterVentional Advances (VIVA), 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, and Society for Vascular Medicine; and industry sources: Janssen, Gore, Becton Dickinson and Company, Medtronic, Cook, Boston Scientific, Abbott, Cordis, and Cardiovascular Systems Inc. As of September 1, 2022, ongoing BEST-CLI research is funded primarily by Grant Number NNF22SA0078610 from the Novo Nordisk Foundation.

DISCLOSURES

N.S. is a member of the Medtronic regional scientific advisory board. M.C. reports Data Safety Monitoring Board membership for Abbott Vascular; a research grant from BioGenCell; and a research grant from Medistim. M.V. is on the advisory board for IsoMab, is the Finnish PI in Voyager (Bayer), and on the advisory board regarding hybrid facilities for Philips. M.M. is an advisor for Janssen. A.F. is a grant recipient (Novo Nordisk Foundation); a consultant for Sanifit, LeMaitre, and BioGenCell; and on the advisory board for Dialysis-X and iThera Medical.

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Submitted Jul 10, 2025; accepted Nov 8, 2025.