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<https://escholarship.org/uc/item/21w297bw>

Journal

Journal of Vascular Surgery, 83(1)

ISSN

0741-5214

Authors

Alameddine, Dana

Hamouda, Mohammed

Doros, Gheorghe

et al.

Publication Date

2025-08-01

DOI

10.1016/j.jvs.2025.08.033

Peer reviewed

From the Eastern Vascular Society

Insulin therapy and outcomes of revascularization procedures for chronic-limb threatening ischemia in the BEST-CLI trial

Dana Alameddine, MD,^a Mohammed Hamouda, MD,^b Gheorghe Doros, MBA, PhD,^c Michael S. Conte, MD,^d Kenneth Rosenfield, MD, MHCDS,^e Michael B. Strong, MA,^f Matthew T. Menard, MD,^f Alik Farber, MD, MBA,^g Allen Hamdan, MD,^h Mahmoud Malas, MD,^b and
Cassius Ilyad Ochoa Chaar, MD, MPH, MS,^a *New Haven, CT; La Jolla and San Francisco, CA; and Boston, MA*

ABSTRACT

Objective: Diabetes mellitus (DM) is a major risk factor for amputation in patients with chronic limb-threatening ischemia (CLTI) undergoing lower extremity revascularization. Observational studies comparing patients with DM based on insulin therapy have reported inconsistent findings. This study compares the outcomes of patients with insulin-requiring DM (IRDM) and non-IRDM (NIRDM) based on high-quality prospective data.

Methods: Characteristics and outcomes of patients with IRDM and NIRDM enrolled in the BEST-CLI (Best Endovascular vs Best Surgical Therapy in Patients with CLTI) trial were compared. A Cox regression model was used to determine the association between insulin requirement and outcomes.

Results: The analysis included 1229 patients with DM, among whom 67.7% (N = 832) had IRDM. The mean age was 66.7 ± 9.9 years, with the IRDM group being younger (65.8 vs 68.6 years, $P < .001$) and more likely to be Hispanic (19% vs 13.1%, $P = .01$). Patients with IRDM were more likely to have renal disease and prior minor amputation (20.9% vs 13.9%, $P = .003$) but were less likely to be smokers (24.5% vs 38.3%, $P < .001$) compared with patients with NIRDM. Overall, only 26.8% of the cohort had adequate glucose control at study entry, with patients with NIRDM more likely to have a hemoglobin A1c (HbA1c) level <7 (19.2% vs 44%, $P < .001$). Patients with IRDM had significantly higher wound grade and more advanced overall WIfI (Wound, Ischemia, and foot Infection) stage compared with patients with NIRDM. At 3 years, patients with NIRDM were more likely to achieve resolution of CLTI, but there were no differences in other outcomes. Two years after revascularization, glucose control continued to be suboptimal, with only 37.3% of the cohort achieving HbA1c <7 . Regression analysis showed that insulin requirement was associated with decreased CLTI resolution (hazard ratio [HR] = 0.86 [0.75-0.99]) but not with other outcomes. Compared with endovascular therapy, open revascularization was associated with a lower risk of major amputation (HR = 0.65 [0.48-0.88]), major reintervention (HR = 0.41 [0.30-0.56]), and major adverse limb events or death (HR = 0.78 [0.66-0.91]), irrespective of insulin therapy. A spline model demonstrated that open revascularization was associated with a lower HR of major adverse limb events or death compared with endovascular regardless of the baseline HbA1c level.

Conclusions: Patients with IRDM undergoing lower extremity revascularization for CLTI present with worse glucose control and a more advanced CLTI stage compared with patients with NIRDM. Insulin requirement showed a modest association with the outcomes of revascularization in this cohort. Open revascularization was superior to endovascular in patients with DM, regardless of insulin therapy or the HbA1c level. (J Vasc Surg 2025;■:1-10.)

Keywords: Insulin; Diabetes mellitus; Chronic limb-threatening ischemia; Revascularization

From the Division of Vascular Surgery and Endovascular Therapy, Department of Surgery, Yale University School of Medicine, New Haven^a; the Division of Vascular & Endovascular Surgery, University of California San Diego, La Jolla^b; the Department of Biostatistics, Boston University School of Public Health, Boston^c; the Division of Vascular and Endovascular Surgery, University of California, San Francisco, San Francisco^d; the Section of Vascular Medicine and Intervention Massachusetts General Hospital,^e and Division of Vascular and Endovascular Surgery, Brigham and Women's Hospital,^f Harvard Medical School, Boston; the Division of Vascular and Endovascular Surgery, Boston Medical Center, Boston University Chobanian & Avedisian School of Medicine, Boston^g; and the Division of Vascular and Endovascular Surgery, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston.^h

Presented at the Thirty-ninth Annual Meeting of the Eastern Vascular Society, Nashville, Tenn, September 4-7, 2025.

Additional material for this article may be found online at www.jvascsurg.org.

Correspondence: Cassius Ilyad Ochoa Chaar, MD, MPH, MS, Yale University School of Medicine, 330 Cedar St, Boardman 204, New Haven, CT 06510 (e-mail: cassius.chaar@yale.edu).

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

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<https://doi.org/10.1016/j.jvs.2025.08.033>

Diabetes mellitus (DM) is a well-established risk factor for peripheral artery disease (PAD), contributing to an increased risk of developing chronic limb-threatening ischemia (CLTI), the most severe form of PAD.¹ Although DM is broadly associated with poor outcomes after lower extremity revascularization (LER), growing evidence suggests that the requirement of insulin therapy may further amplify that risk.^{2,3}

Prior studies have shown that insulin-requiring DM (IRDM) is a potential marker of worse outcomes after revascularization, including increased risk of major adverse limb events (MALE), amputation, and death compared with non-IRDM (NIRDM).⁴⁻⁶ However, the granularity of outcomes between these two subgroups has not been consistent. Retrospective studies showed controversial results, and there is a lack of large, multicenter, prospective study cohorts dedicated to answer this question.^{7,8} Thus, a detailed understanding of how insulin requirement may impact the outcomes of patients with CLTI who undergo LER remains critically needed to better stratify and benchmark patient outcomes.

The BEST-CLI (Best Endovascular vs Best Surgical Therapy in Patients with CLTI) trial was a multicenter prospective randomized controlled trial that enrolled patients with CLTI who underwent LER.⁹ The impact of DM on the outcomes of LER was examined, but the impact of IRDM compared with NIRDM has not been established.¹⁰ This study aims to leverage the BEST-CLI trial dataset to compare the characteristics and outcomes of patients with IRDM and NIRDM undergoing LER for CLTI to enhance risk stratification in patients with DM. Our hypothesis was that patients with IRDM undergoing LER for CLTI would demonstrate worse outcomes compared with those with NIRDM.

METHODS

Study design. The BEST-CLI trial was a multinational, prospective, open-label, multicenter, multispecialty randomized controlled trial. It compared outcomes of infrainguinal bypass and endovascular therapy in patients with CLTI caused by infrainguinal PAD who were eligible for both revascularization treatment approaches (NCT02060630).¹¹ The study included patients with CLTI who had adequate aortoiliac inflow and revascularization targets in the popliteal, tibial, or pedal arteries, with entry data detailed previously.⁹ Patients were stratified into two cohorts based on preprocedural assessment of the availability of single segment great saphenous vein (SSGSV). Subsequently, patients were randomized to the surgical arm with SSGSV (cohort 1) and with alternative conduit (cohort 2), or to the endovascular arm in each cohort.

This subgroup analysis involved a retrospective review of the prospectively collected data from BEST-CLI. All patients with DM were included and were categorized

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective analysis of a prospective randomized controlled trial data
- **Key Findings:** In a cohort of 1229 patients with diabetes mellitus and chronic limb-threatening ischemia (CLTI), insulin-requiring diabetes mellitus (IRDM) was associated with inferior CLTI resolution compared with non-IRDM. Open revascularization was associated with lower risks of major amputation and major adverse limb events or death as compared with endovascular treatment, regardless of insulin requirement.
- **Take Home Message:** Patients with IRDM undergoing revascularization for CLTI present with more advanced disease severity and are less likely to experience CLTI resolution after revascularization. Open revascularization provides better outcomes than endovascular therapy for patients with diabetes mellitus and CLTI, regardless of insulin requirement or glycemic control.

according to whether they had IRDM or NIRDM at the time of randomization, based on clinical history at the time of enrollment. Patients were classified as IRDM or NIRDM based on whether they were receiving insulin therapy at baseline, irrespective of whether they carried a diagnosis of type 1 or type 2 diabetes. The type of diabetes was not available in the database and could not be ascertained. Patients who enrolled but had missing DM status or did not undergo revascularization (whether due to withdrawal from the study, loss to follow-up, or death between enrollment and revascularization) were excluded. The institutional review board approved the protocol and consent process of each participating institution, and all participants provided informed consent before enrollment.

Patient characteristics. The demographic characteristics of patients with IRDM and NIRDM were compared, including age, sex, race, ethnicity, and mean body mass index. Cardiovascular comorbidities including hypertension, hyperlipidemia, coronary artery disease (CAD), congestive heart failure, and stroke were noted. In addition, chronic kidney disease (CKD), chronic obstructive pulmonary disease, and history of smoking were recorded. CKD stages were divided into 3 groups: CKD stages 1-2, CKD stages 3-5, and patients on dialysis. Patients with a functional renal transplant were included in the group of CKD stages 3-5. Previous minor amputation or infrainguinal revascularization of the index limb was compared at baseline. The medications reported were P2Y12 inhibitors, aspirin, clopidogrel, prasugrel, ticagrelor, dual antiplatelet therapy, statins, metformin, glucagon-like peptide-1 (GLP-1) agonists,

and sodium-glucose cotransporter (SGLT-2) inhibitors. Laboratory values included creatinine, albumin, mean hemoglobin A1c (HbA1c), estimated glomerular filtration rate, and lipid panel testing across all patients at baseline. In addition, HbA1c was analyzed at 12 and 24 months in patients with available data in both groups. Both the mean of HbA1c and the proportion of patients with HbA1c < 7 were compared to provide insights into glucose control in patients with IRDM and NIRDM.

Presentation and procedural characteristics. The mean ankle pressures, ankle-brachial index (ABI), and toe pressures were used to assess limb perfusion and were compared at baseline. Toe pressure data were used to complement ABI in characterizing ischemia severity, particularly in cases where ABI may be less reliable. The Wound, Ischemia, and foot Infection (WIFI) grades as well as overall WIFI stages were recorded. WIFI stages were grouped into early (stages 1-2) and late (stages 3-4). Patients were grouped by the first type of revascularization that they underwent (as-treated) regardless of the randomization in the trial. Thus, patients were divided into bypass with SSGSV, bypass with alternative conduit, and endovascular therapy. In the regression models, the two bypass subgroups were combined under open revascularization. Surgical revascularization procedures were further categorized by conduit type and anatomical bypass location. Endovascular therapy details included the anatomical location of intervention and the type of intervention used, including atherectomy, angioplasty, drug-coated balloon angioplasty, bare metal stents, drug-eluting stents, and stent grafts. The interventional data were analyzed per arterial segment and treatment level. The specialty of the operator was also recorded.

Perioperative outcomes. Short-term outcomes included above-ankle amputation, myocardial infarction, stroke, and mortality within 30 days of the index procedure. Kaplan-Meier (KM) analysis was performed to compare time-to-event outcomes and to estimate 30-day event rates.

Long-term outcomes. The primary outcome was the composite of MALE or all-cause death, which was the primary end point of the BEST-CLI trial. MALE was defined as above-ankle amputation or major reintervention of the index limb. Other long-term outcomes included CLTI resolution defined as resolution of rest pain, gangrene, and ulcers, as well as above-ankle amputation, reintervention, and death. KM analysis was performed to compare time to events and obtain estimates of long-term outcomes at 3 years.

Statistical analyses. Categorical variables were compared using the χ^2 test, whereas continuous

variables were assessed using the Student *t*-test. Multivariable Cox proportional hazards regression analysis was conducted for long-term outcomes to identify the risk factors independently associated with the outcomes. Factors adjusted for included age at revascularization, sex, race, ethnicity, hypertension, CAD, statin use, and antiplatelet use. Moreover, stratified by insulin use status, a Cox proportional hazards regression was performed to evaluate the association between the type of revascularization (open vs endovascular) and the risk of outcomes including CLTI resolution, above-ankle amputation, minor reintervention, major reintervention, and all reintervention, death, and MALE or death. Furthermore, spline modeling was performed across the range of HbA1c observed in study participants to identify a threshold HbA1c that impacted the effect of index revascularization surgery on the primary trial outcomes: MALE or all-cause mortality. For spline modeling, we used restricted cubic spline functions with five knots placed at equally spaced percentiles of time and a truncated-power-function basis and adjusted for the effect of HbA1c, its interaction with surgery type while adjusting for age at revascularization, sex, race, ethnicity, Hispanic, hypertension, CAD, statin use, and antiplatelet use.¹² Associations were reported as hazard ratios (HR) with 95% confidence intervals. A *P* value of <.05 was considered statistically significant for all testing.

RESULTS

Patient characteristics. A total of 1229 patients (69.2%) with DM were included from the BEST-CLI trial, of whom 67.7% (*N* = 832) had IRDM. The mean age of the population was 66.7 ± 9.9 years. Patients with IRDM more likely to be younger than those with NIRDM (65.8 vs 68.6 years; *P* < .001). They were also more likely to be of Hispanic ethnicity (19% vs 13.1%; *P* = .01). Gender and race distributions were not significantly different between the two groups. The mean body mass index was significantly higher in patients with IRDM (29.3 vs 28.3; *P* = .004). Patients with IRDM were more likely to have advanced CKD (34.6% vs 27.5% with stages 3-5 or dialysis, *P* = .038). Rates of hypertension and hyperlipidemia did not significantly differ, but patients with IRDM were less likely to be current smokers (24.5% vs 38.3%, *P* < .001). Patients with IRDM had higher rates of previous amputations (20.9% vs 13.9%, *P* = .003) and infrainguinal revascularization (7.1% vs 3.8%, *P* = .023).

Statin, aspirin, and P2Y12 inhibitor use was common and similar between the two groups. Patients with IRDM were more likely to be on clopidogrel (25.2% vs 19.6%, *P* = .03) and dual antiplatelet therapy (21.0% vs 15.6%, *P* = .024) compared with those with NIRDM. Among patients with NIRDM, the majority were on oral medications 24.1% (*N* = 296), whereas only 8.2% (*N* = 101) of the sample had DM treated with diet only. On the other hand, 38.9% (*N* = 478) were treated with

insulin only, whereas 28.8% (N = 354) received insulin and oral medications. Metformin use was higher in the NIRDM group (47.4% vs 22.1%, $P < .001$). The use of GLP-1 agonists (1.1%) and SGLT-2 inhibitors (2.3%) was very low in both groups (Table I).

Patients with IRDM had lower mean estimated glomerular filtration rate (65.96 vs 72.53, $P = .008$) and serum albumin (3.40 vs 3.54 g/dL, $P = .008$). HbA1c was

available for 61.6% of patients at baseline but for only 24.3% and 22.5% at 12 months and 24 months, respectively. Overall, 26.8% of the cohort had adequate glucose control with patients with NIRDM more likely to have an HbA1c level <7 . Also, patients with IRDM had significantly higher mean HbA1c levels (9.25 vs 8.11, $P = .007$) than those with NIRDM. At 12 months, patients with IRDM also had higher mean HbA1c levels than those

Table I. Baseline characteristics in patients with diabetes mellitus (DM) stratified by insulin requirement in the BEST-CLI trial

Characteristics	Overall (N = 1229)	NIRDM (N = 397)	IRDM (N = 832)	P value
Demographic				
Age, years, mean $\pm$ SD	66.7 $\pm$ 9.9 (1229)	68.6 $\pm$ 9.7 (397)	65.8 $\pm$ 9.8 (832)	<.001
Male, % (No.)	72.7 (893/1229)	73.3 (291/397)	72.4 (602/832)	.728
Race, % (No.)				.860
White	70.4 (857/1217)	69.4 (272/392)	70.9 (585/825)	
Black	20.1 (245/1217)	20.9 (82/392)	19.8 (163/825)	
Other	9.4 (115/1217)	9.7 (38/392)	9.3 (77/825)	
Hispanic	17.1 (210/1228)	13.1 (52/397)	19.0 (158/831)	.01
BMI, kg/m ² , mean $\pm$ SD	29.0 $\pm$ 5.9 (1181)	28.3 $\pm$ 5.5 (382)	29.3 $\pm$ 6.0 (799)	.004
Comorbidities, % (No.)				
Hypertension	90.3 (1110/1229)	88.4 (351/397)	91.2 (759/832)	.119
Hyperlipidemia	77.7 (955/1229)	76.3 (303/397)	78.4 (652/832)	.421
CKD stage				.038
Stages 1-2	67.8 (832/1228)	72.5 (288/397)	65.5 (544/831)	
Stages 3-5	18.9 (232/1228)	15.4 (61/397)	20.6 (171/831)	
Dialysis dependent	13.4 (164/1228)	12.1 (48/397)	14.0 (116/831)	
Stroke	14.4 (177/1229)	11.8 (47/397)	15.6 (130/832)	.077
Coronary artery disease	50.9 (626/1229)	49.1 (195/397)	51.8 (431/832)	.379
Congestive heart failure	6.8 (83/1227)	4.8 (19/396)	7.7 (64/831)	.058
Current smoking	29.0 (356/1229)	38.3 (152/397)	24.5 (204/832)	<.001
Chronic obstructive pulmonary disease	13.7 (168/1229)	13.6 (54/397)	13.7 (114/832)	.962
Prior ipsilateral revascularization	13.3 (163/1228)	12.8 (51/397)	13.5 (112/831)	.760
Prior ipsilateral infrainguinal revascularization	6.0 (74/1226)	3.8 (15/395)	7.1 (59/831)	.023
Prior ipsilateral minor amputation	18.6 (229/1228)	13.9 (55/397)	20.9 (174/831)	.003
Baseline medications, % (No.)				
P2Y12 inhibitors	24.7 (303/1229)	21.2 (84/397)	26.3 (219/832)	.050
Aspirin	69.2 (850/1229)	67.3 (267/397)	70.1 (583/832)	.317
Clopidogrel	23.4 (288/1229)	19.6 (78/397)	25.2 (210/832)	.03
Prasugrel	0.3 (4/1229)	0.3 (1/397)	0.4 (3/832)	.754
Ticagrelor	1.0 (12/1229)	1.3 (5/397)	0.8 (7/832)	.486
DAPT	19.3 (237/1229)	15.6 (62/397)	21.0 (175/832)	.024
Statin	74.5 (915/1229)	71.8 (285/397)	75.7 (630/832)	.139
Metformin	30.3 (372/1229)	47.4 (188/397)	22.1 (184/832)	<.001
GLP-1 agonists	1.1 (13/1229)	0.8 (3/397)	1.2 (10/832)	.475
SGLT-2 inhibitors	2.3 (28/1229)	2.8 (11/397)	2.0 (17/832)	.424

BMI, Body mass index; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; GLP, glucagon-like peptide-1; IRDM, insulin-requiring diabetes; NIRDM, non-insulin-requiring diabetes; SD, standard deviation; SGLT, sodium-glucose cotransporter-2. Boldface P values represent statistical significance.

with NIRDm (8.44 vs 7.33, $P < .001$), and the difference remained significant at 24 months (8.24 vs 7.36, $P < .001$). Furthermore, the proportion of patients with HbA1c $\geq 7\%$ was higher among those with IRDM at 12 months (74.9% vs 48.9%, $P < .001$) and 24 months (68% vs 49.4%, $P = .004$) (Table II).

Presentation and procedural characteristics. Patients with IRDM had a higher mean ABI than those with NIRDm (0.63 vs 0.58, $P = .044$), with no significant differences in ankle and toe pressures between the two groups. Patients with IRDM were more likely to present with higher Wifl wound grades ($P = .005$), with fewer having no wounds (11.0% vs 15.5%) and more having grade 3 wounds (8.5% vs 6.2%) compared with those with NIRDm. Ischemia and infection grades did not significantly differ between the groups. Patients with IRDM were more likely to have advanced Wifl stages (stages 3-4: 76.7% vs 67.6%, $P = .002$). Use of SSGSV, alternative conduits, and endovascular therapy was comparable between groups. Patients with IRDM were more likely to have infrapopliteal disease treated (61.2% vs 49.1%, $P < .001$) (Table III).

Patients with IRDM undergoing endovascular procedures were more likely to undergo tibial/pedal artery

intervention (31.5% vs 23.7%, $P = .005$) and were more frequently treated with angioplasty alone (31.5% vs 25.7%, $P = .037$) compared with NIRDm. In the popliteal artery, patients with IRDM were more likely to undergo angioplasty alone (35.1% vs 23.6%, $P = .045$), whereas in the tibial/pedal arteries, they were more likely to undergo both angioplasty (80.2% vs 79.8%, $P = .014$) and revascularization with drug-eluting stents (19.8% vs 13.8%, $P = .029$). There was no difference in operator specialty between the two groups (Supplementary Table I, online only).

Perioperative outcomes. At 30 days, there was no significant difference between the NIRDm and IRDM groups across all measured end points. The rates of above-ankle amputation (2.05% vs 1.59%; $P = .585$), myocardial infarction (2.28% vs 2.91%; $P = .522$), stroke (0.51% vs 0.73%; $P = .655$), and mortality (1.51% vs 1.92%; $P = .714$) were comparable between the two groups (Supplementary Table II, online only).

Long-term outcomes. KM analysis at 3 years showed that the rate of CLTI resolution was significantly higher in the NIRDm group than in the IRDM group (96.1% vs 93.7%; $P = .012$) (Fig. A). There were no significant

Table II. Laboratory values in patients with diabetes mellitus (DM) stratified by insulin requirement in the BEST-CLI trial

Laboratory values	Overall (N = 1229)	NIRDm (N = 397)	IRDM (N = 832)	P value
Baseline				
Creatinine, mean $\pm$ SD	1.97 $\pm$ 2.29 (1215)	1.93 $\pm$ 2.41 (390)	1.99 $\pm$ 2.23 (825)	.663
eGFR, mean $\pm$ SD	68.07 $\pm$ 38.66 (1215)	72.53 $\pm$ 41.62 (390)	65.96 $\pm$ 37.02 (825)	.008
Albumin, mean $\pm$ SD	3.44 $\pm$ 0.64 (686)	3.54 $\pm$ 0.64 (214)	3.40 $\pm$ 0.64 (472)	.008
Total cholesterol, mean $\pm$ SD	149.80 $\pm$ 47.33 (408)	145.74 $\pm$ 45.64 (131)	151.72 $\pm$ 48.07 (277)	.234
LDL, mean $\pm$ SD	80.01 $\pm$ 38.15 (400)	78.65 $\pm$ 39.03 (129)	80.66 $\pm$ 37.78 (271)	.623
HDL, mean $\pm$ SD	39.53 $\pm$ 15.29 (407)	39.54 $\pm$ 13.67 (130)	39.53 $\pm$ 16.02 (277)	.994
Triglycerides, mean $\pm$ SD	165.39 $\pm$ 115.56 (394)	150.99 $\pm$ 94.11 (126)	172.16 $\pm$ 123.96 (268)	.062
HbA1c, mean $\pm$ SD	8.90 $\pm$ 5.82 (756)	8.11 $\pm$ 5.02 (232)	9.25 $\pm$ 6.11 (524)	.007
HbA1c groups, % (No.)				<.001
HbA1c <7	26.8 (203)	44.0 (102)	19.2 (101)	
HbA1c ≥ 7	73.2 (554)	56.0 (130)	80.8 (424)	
Glucose control at 12 months				
HbA1c, mean $\pm$ SD	8.11 $\pm$ 2.07 (299)	7.33 $\pm$ 1.71 (88)	8.44 $\pm$ 2.12 (211)	<.001
HbA1c groups, % (No.)				<.001
HbA1c <7	32.8 (98)	51.1 (45)	25.1 (53)	
HbA1c ≥ 7	67.2 (201)	48.9 (43)	74.9 (158)	
Glucose control at 24 months				
HbA1c at 24 months, mean $\pm$ SD	7.99 $\pm$ 1.95 (276)	7.36 $\pm$ 1.73 (79)	8.24 $\pm$ 1.98 (197)	<.001
HbA1c group, % (No.)				.004
HbA1c <7	37.3 (103)	50.6 (40)	32.0 (63)	
HbA1c ≥ 7	62.7 (173)	49.4 (39)	68.0 (134)	

eGFR, Estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IRDM, insulin-requiring diabetes; LDL, low-density lipoprotein; NIRDm, non-insulin-requiring diabetes; SD, standard deviation.

Boldface P values represent statistical significance.

N at 12 and 24 months reflects the number of patients in each group with available laboratory values.

Table III. Presentation and procedural characteristics in patients with diabetes mellitus (DM) stratified by insulin requirement in the BEST-CLI trial

Characteristics	Overall (N = 1229)	NIRDM (N = 397)	IRDM (N = 832)	P value
Presentation				
Ankle-brachial index in index limb, mean $\pm$ SD	0.61 $\pm$ 0.33 (824)	0.58 $\pm$ 0.34 (274)	0.63 $\pm$ 0.33 (550)	.044
Ankle pressure, mean $\pm$ SD	91.4 $\pm$ 51.1 (851)	88.7 $\pm$ 55.2 (284)	92.8 $\pm$ 48.9 (567)	.296
Toe pressure, mean $\pm$ SD	37.5 $\pm$ 25.4 (545)	37.7 $\pm$ 26.9 (173)	37.4 $\pm$ 24.7 (372)	.903
Wlfl wound grade, % (No.)				.005
0	12.5 (148/1188)	15.5 (60/386)	11.0 (88/802)	
1	44.6 (530/1188)	48.4 (187/386)	42.8 (343/802)	
2	35.2 (418/1188)	29.8 (115/386)	37.8 (303/802)	
3	7.7 (92/1188)	6.2 (24/386)	8.5 (68/802)	
Wlfl ischemia grade, % (No.)				.741
1	16.6 (175/1054)	17.2 (59/344)	16.3 (116/710)	
2	30.9 (326/1054)	29.4 (101/344)	31.7 (225/710)	
3	52.5 (553/1054)	53.5 (184/344)	52.0 (369/710)	
Wlfl infection grade, % (No.)				.171
0	49.7 (596/1200)	54.0 (210/389)	47.6 (386/811)	
1	21.2 (254/1200)	20.6 (80/389)	21.5 (174/811)	
2	26.3 (316/1200)	22.9 (89/389)	28.0 (227/811)	
3	2.8 (34/1200)	2.6 (10/389)	3.0 (24/811)	
Wlfl stage, % (No.)				.004
1	5.5 (58/1053)	6.4 (22/346)	5.1 (36/707)	
2	20.8 (219/1053)	26.0 (90/346)	18.2 (129/707)	
3	30.1 (317/1053)	30.9 (107/346)	29.7 (210/707)	
4	43.6 (459/1053)	36.7 (127/346)	47.0 (332/707)	
Wlfl stage grouped, % (No.)				.002
Early stages 1/2	26.3 (277/1053)	32.4 (112/346)	23.3 (165/707)	
Advanced stages 3/4	73.7 (776/1053)	67.6 (234/346)	76.7 (542/707)	
Type of revascularization, % (No.)				
Bypass using SSGSV	36.0 (442/1229)	35.5 (141/397)	36.2 (301/832)	.821
Bypass using alternative conduits	13.8 (170/1229)	14.3 (57/397)	13.6 (113/832)	.79
Endovascular therapy	50.2 (617/1229)	50.1 (199/397)	50.2 (418/832)	.992
Infrapopliteal disease	57.3 (704/1229)	49.1 (195/397)	61.2 (509/832)	<.001

IRDM, Insulin-requiring diabetes; NIRDM, non-insulin-requiring diabetes; SD, standard deviation; SSGSV, single segment great saphenous vein; Wlfl, Wound, ischemia, and Foot Infection. Boldface P values represent statistical significance.

differences in estimated rates of all-cause death (35.8% vs 31.3%; $P = .153$) between the two groups (Fig. B). The rates of the composite end point of MALE or all-cause death (54.7% vs 51%; $P = .141$) and amputation or all-cause death (45.8% vs 40.8%; $P = .142$) were also comparable between the groups (Fig. C and D, respectively). There were no differences in estimated rates of above-ankle amputation (18.8% vs 15.6%; $P = .181$) and major reinterventions (19.5% vs 17.5%; $P = .644$) between the IRDM and NIRDM groups (Supplementary Table III, online only).

Multivariable Cox regression analysis. In the multivariable Cox regression models, insulin requirement was

independently associated with a lower risk of CLTI resolution (HR = 0.86 [0.75-0.99]). The presence of infrapopliteal disease was also significantly associated with a decreased risk of CLTI resolution (HR = 0.81 [0.70-0.93]). Compared with endovascular treatment, open revascularization was associated with a significantly lower risk of major reintervention (HR = 0.41 [0.30-0.56]), above-ankle amputation (HR = 0.65 [0.48-0.88]), and MALE or death (HR = 0.78 [0.66-0.91]). No significant differences were observed between open and endovascular approaches for amputations or all-cause death, CLTI resolution, or all-cause death.

CKD was associated with a higher risk of MALE or all-cause death (HR = 1.56 [1.33-1.84]), above-ankle

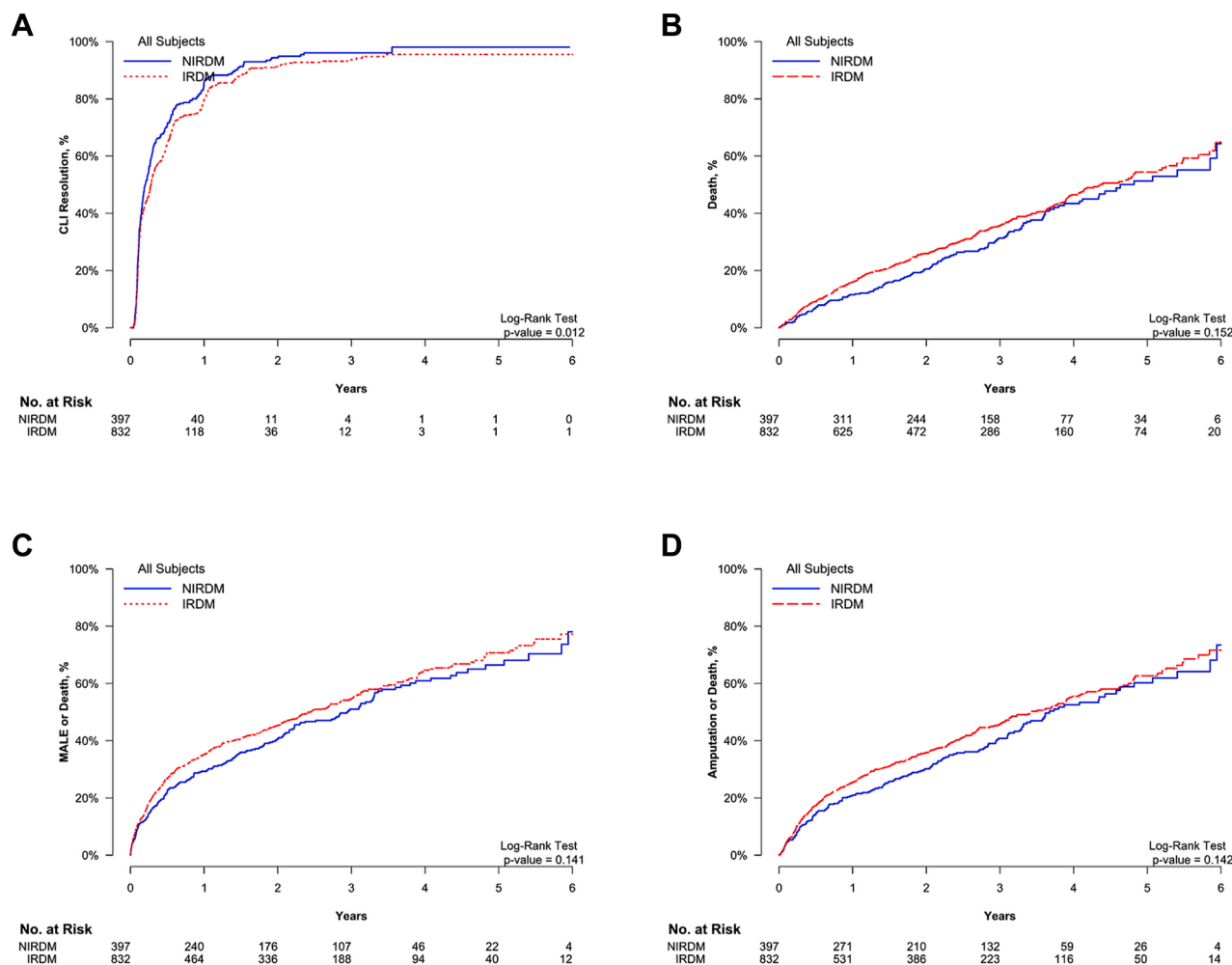


Fig. Kaplan-Meier survival analysis comparing non-insulin-requiring diabetes mellitus (NIRDM) vs insulin-requiring diabetes mellitus (IRDM) across clinical outcomes: **(A)** CLI resolution, **(B)** death, **(C)** male or death, **(D)** amputation of death. CLI, Chronic limb-threatening ischemia; MALE, major adverse limb events.

amputation (HR = 1.62 [1.20-2.19]), all-cause death (HR = 2.06 [1.71-2.49]), and amputations or all-cause death (HR = 1.82 [1.53-2.16]). Recent smoking history (within 2 weeks to 1 year) was also associated with increased risk of all-cause death (HR = 1.80 [1.23-2.64]) and MALE or death (HR = 1.41 [1.03-1.94]) (Table IV).

A spline model demonstrated that open revascularization was associated with a lower HR of MALE or death compared with endovascular regardless of the HbA1c level (Supplementary Fig, online only). Similarly, stratified analysis by insulin requirement confirmed that open revascularization was associated with lower HR of MALE or death in patients with NIRDM (HR = 0.75 [0.56-0.99]) as well as patients with IRDM (HR = 0.79 [0.65-0.95]) (Table V).

DISCUSSION

This study showed that among patients with DM undergoing infrainguinal LER for CLTI, insulin requirement

was associated with decreased likelihood of resolution of CLTI, but there was not a statistically significant association between insulin use and other major outcomes. Open surgery was independently associated with decreased likelihood of reintervention, above-ankle amputation, as well as major amputation or death regardless of insulin requirement or glucose control. Overall, most patients had poor glucose control before revascularization with 73.2% of the sample exhibiting baseline HbA1c ≥ 7 . The use of contemporary DM medications such as GLP-1 agonists and SGLT-2 inhibitors was very low, reflective of the enrollment years of the BEST-CLI trial (2014-2019).

In this cohort, patients with IRDM had significantly lower rates of resolution of CLTI compared with those with NIRDM, consistent with prior data suggesting that insulin requirement is a surrogate for more advanced or poorly controlled DM, which is associated with worse PAD outcomes.¹³ A retrospective study involving 8887 patients

undergoing interventions for CLTI demonstrated that IRDM was associated with lower rates of complete wound healing at 6 months compared with NIRDM.¹⁴ Another retrospective study using data from the American College of Surgeons' National Surgical Quality Improvement Program, involving 8022 patients undergoing infrainguinal endovascular interventions, showed that IRDM significantly increased the risk of 30-day postprocedural amputation compared with NIRDM.⁵

The lower rates of CLTI resolution in patients with IRDM could also be explained by the higher HbA1c levels in patients with IRDM compared with those with NIRDM. At baseline and throughout follow-up after 24 months, patients with IRDM had a higher percentage of HbA1c >7. These findings highlight the challenge of achieving effective glycemic control in patients with DM, particularly among those with IRDM, undergoing LER for CLTI.

Prior literature has shown that persistently elevated HbA1c levels are associated with impaired wound healing, chronic inflammation, and adverse tissue remodeling, all of which impact the outcomes of revascularization.¹⁵ A retrospective study demonstrated that patients with an HbA1c level >7% undergoing popliteal and infrapopliteal revascularization for CLTI had a significant increase in reintervention rate compared with patients with HbA1c <7%.¹⁶ In a retrospective study of 304 patients with DM treated for ischemic foot ulcers with endovascular revascularization, elevated HbA1c levels were independently associated with a higher risk of CLTI relapse.¹⁷ This highlights the importance of glycemic optimization in patients with DM as an integral component of CLTI treatment.

This study demonstrates that open revascularization was associated with superior outcomes compared with

Table IV. Multivariable Cox regression models for the outcomes of revascularization

Variables	CLTI resolution	Major reintervention	Above-ankle amputation	All-cause death	MALE or death
IRDM vs NIRDM	0.86 [0.75-0.99]	0.92 [0.67-1.25]	1.12 [0.80-1.56]	1.19 [0.97-1.47]	1.12 [0.95-1.34]
Open vs endovascular treatment	1.11 [0.98-1.26]	0.41 [0.30-0.56]	0.65 [0.48-0.88]	1.10 [0.91-1.32]	0.78 [0.66-0.91]
Infrapopliteal disease	0.81 [0.70-0.93]	0.94 [0.69-1.29]	1.59 [1.12-2.27]	1.25 [1.00-1.55]	1.17 [0.98-1.39]
Age	1.00 [0.99-1.01]	0.99 [0.97-1.00]	0.98 [0.96-0.99]	1.03 [1.02-1.04]	1.01 [1.00-1.02]
CKD	0.97 [0.85-1.11]	0.93 [0.68-1.28]	1.62 [1.20-2.19]	2.06 [1.71-2.49]	1.56 [1.33-1.84]
Prior infrainguinal revascularization	1.23 [0.95-1.58]	1.42 [0.83-2.41]	1.03 [0.57-1.87]	0.79 [0.53-1.19]	1.06 [0.78-1.44]
Smoking history					
Prior (>1 year) vs never	1.13 [0.97-1.33]	1.21 [0.82-1.77]	1.06 [0.73-1.55]	1.08 [0.86-1.36]	1.02 [0.84-1.25]
Prior (2 weeks to 1 year) vs never	1.05 [0.80-1.37]	1.64 [0.94-2.87]	1.55 [0.88-2.71]	1.80 [1.23-2.64]	1.41 [1.03-1.94]
Current vs never	1.06 [0.89-1.27]	1.20 [0.79-1.83]	1.17 [0.77-1.78]	1.06 [0.80-1.40]	1.07 [0.85-1.34]
Cohort 2 vs 1	1.07 [0.91-1.26]	1.21 [0.84-1.75]	1.24 [0.85-1.82]	1.12 [0.86-1.46]	1.06 [0.86-1.31]

CKD, Chronic kidney disease; CLTI, chronic limb-threatening ischemia; IRDM, insulin-requiring diabetes; MALE, major adverse limb events; NIRDM, non-insulin-requiring diabetes. Bold values denote statistical significance.

Table V. Multivariable Cox regression for open revascularization compared with endovascular revascularization stratified by diabetes status

Open vs endovascular	NIRDM	IRDM
End point	HR [95% CI]	HR [95% CI]
CLTI resolution	1.12 [0.9-1.39]	1.11 [0.95-1.29]
Above-ankle amputation	0.64 [0.36-1.12]	0.65 [0.46-0.93]
All reinterventions	0.66 [0.48-0.90]	0.7 [0.55-0.87]
Death	0.92 [0.65-1.29]	1.19 [0.95-1.48]
MALE or death	0.75 [0.56-0.99]	0.79 [0.65-0.95]

CI, Confidence interval; CLTI, chronic limb-threatening ischemia; HR, hazard ratio; IRDM, insulin-requiring diabetes; MALE, major adverse limb events; NIRDM, non-insulin-requiring diabetes. Bold values denote statistical significance.

endovascular therapy, regardless of insulin requirement or glucose control. Patients who underwent open bypass had a significantly lower risk of any reintervention, and the composite outcome of MALE or death relative to those treated with endovascular techniques. These associations were consistent across the IRDM and NIRDM subgroups and remained significant irrespective of the HbA1c level, as demonstrated in spline modeling. Multiple prior studies have demonstrated that surgical bypass is superior to endovascular therapy for patients with CLTI, including those with DM and IRDM. The BEST-CLI trial demonstrated that open bypass significantly reduced the risk of MALE or death compared with endovascular treatment in patients with or without DM.¹⁰ In a retrospective study with 580 patients with IRDM undergoing first-time infrainguinal revascularization for CLTI, open bypass-first treatment was associated with significantly better long-term restenosis and reintervention outcomes compared with endovascular therapy.¹⁸

Several limitations of this study require consideration. The trial was not originally designed to compare outcomes by DM or insulin status, and the observational nature of subgroup analyses introduces the potential for selection bias. It is also possible that patients with IRDM, who may have had more advanced peripheral neuropathy, experienced ongoing neuropathic pain despite wound healing. In such cases, pain may have been misclassified as persistent ischemic rest pain, potentially underestimating CLTI resolution in this subgroup. Regardless, patients with DM achieved more than 90% CLTI resolution with revascularization irrespective of insulin requirement. Moreover, unmeasured confounders such as duration of diabetes, time frame of insulin use, and medication adherence could not be accounted for. Socioeconomic status, lifestyle modification, and access to wound care were not captured. The use of contemporary medications such as GLP-1 agonists and SGLT-2 inhibitors was very low, and it is unclear how the adoption of those medications can impact the outcomes of patients undergoing revascularization for CLTI. HbA1c data were only available for approximately 62% of patients, which limited the ability to adjust for glycemic control in multivariable analyses. Moreover, the as-treated approach does not preserve randomization and may be confounded by selection bias related to the revascularization strategy. These limitations highlight the need for future studies specifically powered to evaluate the impact of DM severity and glucose control on revascularization outcomes.

CONCLUSIONS

Patients with IRDM undergoing LER for CLTI present with worse glucose control and a more advanced CLTI stage compared with those with NIRDM. Insulin requirement is associated with a lower rate of CLTI resolution in

this population. Open revascularization is superior to endovascular therapy in patients with DM regardless of insulin therapy or the HbA1c level.

AUTHOR CONTRIBUTIONS

Conception and design: DA, MH, GD, MC, KR, MS, M Menard, AF, AH, M Malas, CC

Analysis and interpretation: DA, MH, GD, M Malas, CC

Data collection: M Menard, AF, AH

Writing the article: DA, MH, M Malas, CC

Critical revision of the article: DA, MH, GD, MC, KR, MS, M Menard, AF, AH, M Malas, CC

Final approval of the article: DA, MH, GD, MC, KR, MS, M Menard, AF, AH, M Malas, CC

Statistical analysis: GD

Obtained funding: Not applicable

Overall responsibility: CC

DA and MH contributed equally to the article.

M Malas and CC contributed equally to the article.

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). These include Physician Societies: Vascular InterVentional Advances, Society for Vascular Surgery, New England Society for Vascular Surgery, Western Vascular Society, Eastern Vascular Society, Midwest Vascular Surgery Society, Southern Association of Vascular Surgeons, Canadian Society for Vascular Surgery, Society for Clinical Vascular Surgery, Society of Interventional Radiology, Vascular and Endovascular Surgery Society, 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

A.F. is a grant recipient from the Novo Nordisk Foundation; serves as a consultant for Sanifit, LeMaitre, and BioGenCell; and is a member of the advisory board for Dialysis-X and iThera Medical. C.I.O.C. is a consultant for SVS-PSO and EnVeno Medical; has IP of patent U.S.S.N. 10,524,89; and has received research support from the Yale Department of Surgery, SVS, AVF, CT Innovation, VSCNE, NIH, Boston Scientific, Medtronic, EnVeno Medical, and Inari Medical. M. Malas is a consultant for Bard. M. T.M. is an advisor for Janssen. M.S.C. receives research grants from BioGenCell and Medistim. K.R. receives income as a consultant or member of a scientific advisory board for the following entities: Abbott Vascular,

Angiodynamics, Boston Scientific, Contego, Innova Vascular, Inspire MD, Janssen/Johnson & Johnson, MedAlliance, Medtronic, Neptune Medical, Philips, Thrombolex, Vasorum, and Vumedi. He owns equity or stock options in the following entities: Access Vascular, Contego, Endo-span, Imperative Care/Truvis, Innova Vascular, InspireMD, JanaCare, Magneto, MedAlliance, Neptune Medical, Orchestra, Skydance, Summa Therapeutics, Thrombolex, Vasorum, and Vumedi. He or his institution (on his behalf) receives research grants from the following entities: Boston Scientific, Novo Nordisk Foundation, and Penumbra. He serves as a member of the Board of Directors of the National PERT Consortium. The remaining authors report no conflicts.

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Submitted Jun 12, 2025; accepted Aug 22, 2025.

Additional material for this article may be found online at www.jvascsurg.org.

Supplementary Table I (online only). Revascularization techniques and operators in patients with diabetes mellitus (DM) stratified by insulin requirement in the BEST-CLI trial

Characteristics	Overall (N = 1229)	NIRDM (N = 397)	IRDM (N = 832)	P value
Surgical bypass details, % (No.)				
Bypass using SSGSV	36.0 (442/1229)	35.5 (141/397)	36.2 (301/832)	.821
Bypass using alternative vein	4.0 (49/1229)	3.5 (14/397)	4.2 (35/832)	.569
Bypass using composite vein	2.1 (26/1229)	1.8 (7/397)	2.3 (19/832)	.553
Bypass using prosthetic conduit	7.7 (95/1229)	9.1 (36/397)	7.1 (59/832)	.225
Femoropopliteal bypass	17.9 (220/1229)	20.4 (81/397)	16.7 (139/832)	.114
Above-knee femoropopliteal bypass	7.2 (89/1229)	8.3 (33/397)	6.7 (56/832)	.317
Below-knee femoropopliteal bypass	10.7 (131/1229)	12.1 (48/397)	10.0 (83/832)	.261
Femoral-tibial/pedal bypass	19.0 (233/1229)	16.1 (64/397)	20.3 (169/832)	.080
Popliteal-tibial/pedal bypass	9.4 (115/1229)	9.3 (37/397)	9.4 (78/832)	.975
Endovascular therapy details, % (No.)				
Location				
Superficial femoral artery	32.8 (403/1229)	35.3 (140/397)	31.6 (263/832)	.202
Popliteal artery	27.4 (337/1229)	26.7 (106/397)	27.8 (231/832)	.696
Tibial/pedal arteries	29.0 (356/1229)	23.7 (94/397)	31.5 (262/832)	.005
Technique				
Atherectomy	7.2 (88/1229)	8.8 (35/397)	6.4 (53/832)	.120
Angioplasty alone	29.6 (364/1229)	25.7 (102/397)	31.5 (262/832)	.037
Drug-coated balloon angioplasty	14.0 (172/1229)	12.6 (50/397)	14.7 (122/832)	.328
Bare metal stents	20.7 (255/1229)	22.4 (89/397)	20.0 (166/832)	.319
Drug-eluting stents	12.9 (158/1229)	11.6 (46/397)	13.5 (112/832)	.359
Stent grafts	4.6 (57/1229)	6.0 (24/397)	4.0 (33/832)	.105
Superficial femoral artery (N = 403), % (No.)				
Atherectomy	11.7 (47/403)	14.3 (20/140)	10.3 (27/263)	.125
Angioplasty alone	22.1 (89/403)	20.0 (28/140)	23.2 (61/263)	.860
Drug-coated balloon angioplasty	28.5 (115/403)	22.1 (31/140)	31.9 (84/263)	.198
Bare metal stents	41.2 (166/403)	41.4 (58/140)	41.1 (108/263)	.435
Drug-eluting stents	25.8 (104/403)	27.1 (38/140)	25.1 (66/263)	.334
Stent grafts	9.2 (37/403)	12.9 (18/140)	7.2 (19/263)	.031
Popliteal artery (N = 337), % (No.)				
Atherectomy	13.1 (44/337)	17.0 (18/106)	11.3 (26/231)	.214
Angioplasty alone	31.5 (106/337)	23.6 (25/106)	35.1 (81/231)	.045
Drug-coated balloon angioplasty	31.5 (106/337)	30.2 (32/106)	32.0 (74/231)	.626
Bare metal stents	27.9 (94/337)	30.2 (32/106)	26.8 (62/231)	.707
Drug-eluting stents	13.4 (45/337)	15.1 (16/106)	12.6 (29/231)	.634
Stent grafts	6.5 (22/337)	8.5 (9/106)	5.6 (13/231)	.384
Tibial/pedal arteries (N = 356), % (No.)				
Atherectomy	11.8 (42/356)	19.1 (18/94)	9.2 (24/262)	.137
Angioplasty alone	80.1 (285/356)	79.8 (75/94)	80.2 (210/262)	.014
Drug-coated balloon angioplasty	6.7 (24/356)	9.6 (9/94)	5.7 (15/262)	.582
Bare metal stents	3.9 (14/356)	2.1 (2/94)	4.6 (12/262)	.147
Drug-eluting stents	18.3 (65/356)	13.8 (13/94)	19.8 (52/262)	.029
Stent grafts	0.6 (2/356)	0.0 (0/94)	0.8 (2/262)	.328

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Supplementary Table I (online only). Continued.

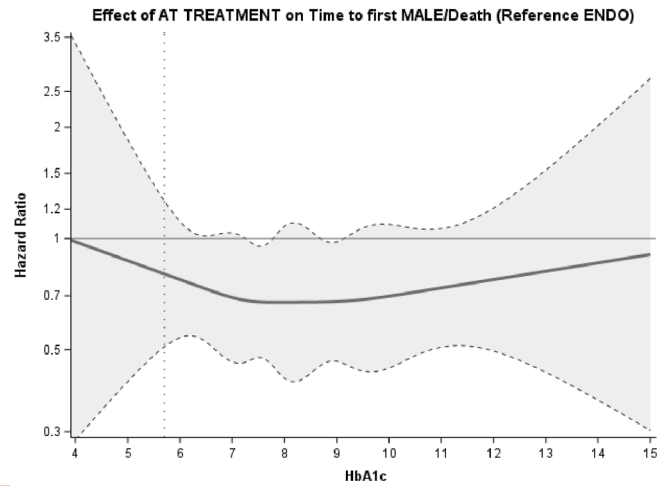
Characteristics	Overall (N = 1229)	NIRDM (N = 397)	IRDM (N = 832)	P value
Operator specialty, % (No.)				
Vascular surgeons	86.5 (1063/1229)	85.9 (341/397)	86.8 (722/832)	.671
Interventional cardiologists	7.4 (91/1229)	6.0 (24/397)	8.1 (67/832)	.209
Interventional radiologists	6.6 (81/1229)	8.1 (32/397)	5.9 (49/832)	.151
Vascular medicine specialists	0.5 (6/1229)	0.8 (3/397)	0.4 (3/832)	.353
IRDM, Insulin-requiring diabetes; NIRDM, non-insulin-requiring diabetes; SSCV, single saphenous vein graft. Boldface P values represent statistical significance.				

Supplementary Table II (online only). Analysis of perioperative end points based on insulin status

30-day end points	All patients (N = 1229)		NIRDM (N = 397)		IRDM (N = 832)		Hazard ratio (95% CI) (IRDM vs NIRDM)
	Patients with events, No. (%)	KM% at 30 days	Patients with events, No. (%)	KM% at 30 days	Patients with events, No. (%)	KM% at 30 days	
Above-ankle amputation	21 (1.71)	1.74	8 (2.02)	2.05	13 (1.56)	1.59	0.78 (0.32, 1.89), <i>P</i> = .585
Death	22 (1.79)	100.00	6 (1.51)	—	16 (1.92)	100.00	1.19 (0.46, 3.08), <i>P</i> = .714
MI	33 (2.69)	2.71	9 (2.27)	2.28	24 (2.88)	2.91	1.28 (0.60, 2.76), <i>P</i> = .522
Stroke	8 (0.65)	0.66	2 (0.50)	0.51	6 (0.72)	0.73	1.44 (0.29, 7.14), <i>P</i> = .655
CI, Confidence interval; IRDM, insulin-requiring diabetes; KM, Kaplan-Meier; MI, myocardial infarction; NIRDM, non-insulin-requiring diabetes.							

Supplementary Table III (online only). Kaplan-Meier estimates of outcomes in insulin-requiring diabetes mellitus (IRDM) and non-insulin-requiring diabetes mellitus (NIRDM) at 3 years after lower extremity revascularization in the BEST-CLI trial

Outcomes	All patients (N = 1229), %	NIRDM (N = 397), %	IRDM (N = 832), %	P value
Above-ankle amputation	17.8	15.6	18.8	.181
Minor ipsilateral reintervention	37.4	40.5	35.7	.273
Major ipsilateral reintervention	18.15	19.5	17.5	.644
All reinterventions	43.9	47.1	42.3	.413
CLTI resolution	94.5	96.1	93.7	.012
Amputation or all-cause death	44.2	40.8	45.8	.142
All-cause death	34.3	31.3	35.8	.153
MALE or all-cause death	53.5	51	54.7	.141
IRDM, Insulin-requiring diabetes; CLTI, chronic limb-threatening ischemia; MALE, major adverse limb events; NIRDM, non-insulin-requiring diabetes. Boldface P value represents statistical significance.				



Supplementary Fig (online only). Spline model demonstrating the effect of open surgical treatment compared with endovascular at various hemoglobin A1c (HbA1c) levels. *MALE*, Major adverse limb events.