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Outcomes of chronic limb-threatening ischemia revascularization in patients with chronic kidney disease in the BEST-CLI trial

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ABSTRACT

Background: Chronic limb-threatening ischemia (CLTI) in patients with chronic kidney disease (CKD) has a high risk of poor outcomes. We aimed to compare the outcomes of lower extremity revascularization in patients with CLTI stratified by CKD severity in patients enrolled in the prospective, randomized Best Endovascular vs Best Surgical Therapy in Patients with CLTI (BEST-CLI) trial.

Methods: The BEST-CLI trial dataset was queried to categorize patients into three groups according to CKD stage. Group A includes non-CKD and CKD stages <3; group B includes stage 3 and stage 4 CKD patients; and group C includes stage 5 CKD and dialysis-dependent patients. Furthermore, spline modeling was performed across the range of estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) observed in study participants to identify a threshold eGFR that impacted the primary trial outcomes: major adverse limb events (MALEs; defined as above-ankle amputation or major reintervention) or all-cause mortality, by surgical or endovascular revascularization (as-treated analysis). Kaplan-Meier and multivariate Cox regression analyses were used to assess association of CKD risk groups with the outcomes.

Results: A total of 1797 patients were included. Group C patients had double the risk of amputation (hazard ratio [HR], 2.13; $P < .001$), MALE, or all-cause mortality (HR, 2.05; $P < .001$) and more than triple the risk of all-cause mortality (HR, 3.40; $P < .001$) compared with group A. In dialysis-dependent patients, endovascular therapy was associated with better survival, but twice the risk of reintervention compared with surgical revascularization. According to spline model analysis, hazard of MALE or all-cause mortality increased sharply at eGFR <30. The hazard ratios for eGFR <30 vs ≥60 were 2.03 (95% confidence interval [CI], 1.68-2.43; $P < .001$) and 3.46 (95% CI, 2.80-4.27; $P < .001$) for MALE and mortality, respectively. At eGFR <30, there was no difference in the primary outcome by treatment received (surgical or endovascular revascularization).

Conclusions: The progressive nature of renal impairment in patients with CLTI threatens their survival and limb salvage and may reduce the relative benefit of open vs endovascular revascularization seen in the overall BEST-CLI trial population. In dialysis-dependent patients, endovascular therapy was associated with lower mortality but increased reintervention rate. (J Vasc Surg 2025;■:1-12.)

Keywords: Bypass; Endovascular; Dialysis; Chronic Kidney Disease; Amputation; BEST-CLI

Chronic kidney disease (CKD) is one of the predominant medical comorbidities in patients with peripheral arterial disease, especially those presenting with chronic limb-threatening ischemia (CLTI), characterized by ischemic rest pain or tissue loss, where the disease is prevalent in almost one quarter of this patient cohort.[1,2] Although revascularization generally improves the prognosis of patients with CLTI, concomitant CKD in patients undergoing revascularization has been associated with an increased risk of amputations, reintervention, mortality, and other perioperative complications; this is especially true for those with end-stage renal disease.[3-6] Several explanations for the higher morbidity and mortality in CKD patients with CLTI are described in the literature. Compared with those without CKD, CLTI in patients with CKD more often presents with tissue loss, ulcerations, and gangrene, as well as having severely heavily calcified arteries and a predilection for more distal disease.[7] These patients are also at twice the risk for postoperative infection and sepsis and their decreased kidney function is a risk factor for cardiovascular events leading to myocardial infarction, stroke, and mortality.[8-10]

According to Kidney Disease Improving Global Outcomes, kidney function is considered impaired when it advances to CKD stage ≥3 for ≥3 months.[11] The Society for Vascular Surgery recommends revascularization whenever feasible for patients with CLTI, either by surgical bypass or endovascular therapy (ET).[2] Several clinical trials have investigated the best revascularization strategy for patients with CLTI, including the recent Best Endovascular vs Best Surgical Therapy in Patients with CLTI (BEST-CLI) trial comparing open bypass with ET. Results from the BEST-CLI trial indicated that bypass with single segment great saphenous vein (SSGSV) was associated with a lower hazard of major adverse limb events (MALEs; defined as above ankle amputation or major reintervention) or all-cause mortality compared with ET.[12]

For patients with differing CKD severity, the optimal revascularization method is unclear and offering amputation instead of attempting to revascularize is associated with worse survival outcomes.[13] In a systematic review and meta-analysis by Narayanan et al,[14] patients with CKD or kidney failure treated by dialysis undergoing ET had higher rates of reintervention compared with open bypass. In another study by Chen et al,[15] ET was found to have lower risk of amputation or mortality compared with open bypass despite higher reintervention rates in CKD patients. Other studies suggest open bypass has worse amputation-free survival compared with ET.[16] Work by Cheng et al,[17] in contrast, showed kidney failure, defined in the study as and estimated glomerular filtration rate (eGFR) of <15 mL/min/1.73 m^2), but not CKD (eGFR 15-59 mL/min/1.73 m^2), was associated with higher perioperative and long-term mortality after lower extremity bypass for CLTI.

ARTICLE HIGHLIGHTS

- **Type of Research:** Analysis of prospectively collected data from the BEST-CLI multicenter, randomized, controlled trial
- **Key Findings:** In this post hoc analysis of 1797 patients enrolled in the Best Endovascular vs Best Surgical Therapy in Patients with CLTI (BEST-CLI) trial, spline model analysis revealed an estimated glomerular filtration rate of <30 mL/min/1.73 m^2 was found to be the threshold below which patients had a significantly higher hazard of mortality or major adverse limb events, with no difference by treatment received (surgical or endovascular revascularization). In dialysis-dependent patients, endovascular therapy was associated with lower mortality but increased reintervention.
- **Take Home Message:** The progressive nature of renal impairment in chronic limb-threatening ischemia patients threatens their survival and limb salvage and may reduce the relative benefit of open vs endovascular revascularization seen in the overall BEST-CLI trial population.

In this study, we aimed to investigate the impact of CKD severity on the outcomes of lower extremity infrainguinal revascularization (including open bypass and endovascular procedures) in patients presenting with CLTI using data from the BEST-CLI trial.

METHODS

The BEST-CLI trial was a multispecialty, multicenter, pragmatic prospective, randomized, controlled trial designed to compare the outcomes of best endovascular vs best open surgical revascularization in patients with CLTI who were candidates for either revascularization strategy. Further details of the study design and variable definitions have been previously reported (Clinical trial registration: https://www.clinicaltrials.gov/Unique identifier: NCT02060630).[18] CKD is classified according to eGFR values into stage 1, ≥90 mL/min/1.73 m^2 (with other signs of kidney damage such as proteinuria or albuminuria); stage 2, 60-89 mL/min/1.73 m^2; stage 3, 30-59 mL/min/1.73 m^2; stage 4, 15-29 mL/min/1.73 m^2; and stage 5, <15 mL/min/1.73 m^2. Patients in our study were categorized into three groups according to CKD stage. Group A includes non-CKD and CKD stages 1 and 2; group B includes stage 3 and stage 4 CKD patients; and group C includes stage 5 CKD and dialysis dependent patients. We stratified the patients into those three main groups with group A representing patients with normal renal function and mild renal impairment, group B representing moderate renal impairment, and group C representing end-stage renal disease.

Outcomes. The primary outcome of our study was the composition of MALE or all-cause mortality. MALE is defined as above-ankle amputation of the index limb or a major index-limb reintervention (new bypass, interposition graft revision, thrombectomy, or thrombolysis). Secondary outcomes include above-ankle amputation (hip disarticulation, above-knee, or below-knee amputation), MALE or all-cause mortality, amputation or all-cause mortality, major reintervention (new bypass graft, jump/interposition graft revision, thrombectomy, or thrombolysis), any reintervention (major reintervention or surgical patch angioplasty, balloon angioplasty, atherectomy, laser treatment, stent placement, or stent graft placement), and major adverse cardiovascular event (MACE defined as myocardial infarction, stroke, or death from any cause).

Statistical analysis. Continuous variables were presented as means ± standard deviation, and categorical variables were shown as frequencies and percentages. Differences between groups were examined by analysis of variance, F-test, and χ^2 tests for categorical variables. Univariate and multivariate Cox regression analyses were used to estimate the association between independent variables and outcomes. Variables entered in the multivariate models were CKD risk group, age, sex, race, ethnicity, antiplatelet use, type of surgery (as-treated analysis of open vs endovascular), coronary artery disease, diabetes, and hypertension. The selected variables included in the regression models were chosen according to statistical significance as well as clinical relevance based on similar studies published in the literature, and outcomes in the final regression models were adjusted to the aforementioned covariates.

Restricted cubic splines were used to examine the moderating effect of eGFR on the association of surgery type on MALE/death. We used restricted-cubic-spline plots fitting a restricted-cubic-spline function with five knots located at the observed quintiles. Based on our restricted cubic spline plots for the primary outcome and the results of previous analyses we selected a level of eGFR of 30 as the reference value. All analyses were conducted with SAS software, version 9.4 (SAS Institute, Cary, NC). No adjustment was performed to account for multiple testing. A two-sided P value of <.05 was considered statistically significant in all analyses.

RESULTS

Of the 1830 subjects included in the BEST-CLI trial, 12 subjects with missing CKD grade status and 21 patients with functioning renal transplant were excluded. A total of 1797 patients were included in our study. When grouped according to CKD stage, three-quarters of the patients belonged to group A (patients with normal kidney function and CKD stage <3) (1327 [73.8%]), while 14.7% and 11.5% of the patients were in group B (CKD stages 3-4)

and group C (stage 5 CKD and dialysis-dependent patients), respectively. More than two-thirds of the patients were male across the three groups (A, 71.2%; B, 74.6%; C, 69.9%). Group C patients were more likely to be non-White (45.3%) and Hispanic (21.4%) compared with A (24.7%; 12.4%) and B (31.6%; 11.0%) ($P < .001$). Even though patients in group C were relatively younger and less likely to have a smoking history, they were more likely to be hypertensive, diabetic, with congestive heart failure, have experienced a prior stroke, and have the lowest albumin level compared with patients in groups A and B (Table I).

More than 70% of patients in each group were receiving a statin and at least one antiplatelet agent, with group B patients being more likely to have been on a statin preoperatively (B, 79.2% vs A, 70.5% and C, 72.8%; $P = .017$). There were no intergroup differences with regards to antiplatelet utilization ($P = .235$). A dose-response-like relationship is demonstrated with regards to Wound, Ischemia, foot Infection wound, grade ≥1 and CKD severity among the groups (A, 78.8% vs B, 82.6% vs C, 89.1%; $P < .001$) as well as a trend of lowest toe pressure measurements with the most advanced CKD stage (A, 34.9 mm Hg vs B, 38.5 mm Hg vs C, 31.2 mm Hg; $P = .097$).

For patients who underwent open surgical bypass, femoral to tibial/pedal was the most common anatomical configuration in each CKD group. There were no intergroup differences regarding the anatomical locations of the bypass procedures except in those who underwent femoral to above-knee popliteal bypass (A, 9.8% vs B, 6.6% vs C, 2.5%; $P = .001$). Tibial/pedal arteries were more commonly the anatomical site of intervention of group C (36.7%) compared with A (23.8%) and B (27.6%) patients who underwent ET ($P < .001$). Furthermore, atherectomy use in group C (12.6%) was double that of group A (6.1%) and 25% higher than group B (10.1%) patients ($P < .001$).

Table II demonstrates results of multivariable Cox regression analysis of outcomes of group B and C patients in reference to group A after adjusting for the following covariates: age, type of intervention (open vs endovascular), diabetes, infrapopliteal disease, history of prior infrainguinal revascularization, and Wound, Ischemia, foot Infection wound grade. Patients in group B had similar hazard of amputation and MALE compared with group A; however, group C was associated with more than double the hazard of amputation (hazard ratio [HR], 2.13; 95% confidence interval [CI], 1.49-3.05; $P < .001$) and a >50% higher risk of MALE (HR, 1.53; 95% CI, 1.15-2.03; $P = .003$). All-cause mortality was 50% higher in group B (HR, 1.50; 95% CI, 1.18-1.90; $P = .001$) and more than three times higher in group C (HR, 3.40; 95% CI, 2.69-4.30; $P < .001$). Group B had slightly higher risk of MALE or all-cause mortality (HR, 1.28; 95% CI, 1.05-1.56; $P = .015$), whereas group C had double that hazard (HR, 2.05; 95% CI, 1.67-2.52; $P < .001$) compared

Table I. Baseline characteristics of patients by CKD group

	Overall (n = 1797)	Group A (n = 1327)	Group B (n = 264)	Group C (n = 206)	P value
Demographics					
Age, years	67.3 ± 9.7	67.0 ± 9.4	70.8 ± 9.8	64.5 ± 10.4	**<.001**
Gender					.456
Male	71.6 (1286/1797)	71.2 (945/1327)	74.6 (197/264)	69.9 (144/206)	
Female	28.4 (511/1797)	28.8 (382/1327)	25.4 (67/264)	30.1 (62/206)	
Hispanic	13.3 (238/1796)	12.4 (165/1327)	11.0 (29/263)	21.4 (44/206)	**.001**
Race					**<.001**
White	72.0 (1281/1780)	75.3 (990/1314)	68.4 (180/263)	54.7 (111/203)	
Black	20.4 (363/1780)	18.7 (246/1314)	19.0 (50/263)	33.0 (67/203)	
Other	7.6 (136/1780)	5.9 (78/1314)	12.5 (33/263)	12.3 (25/203)	
Body weight, kg	82.6 ± 19.5 (1736)	81.7 ± 19.7 (1279)	85.5 ± 18.7 (258)	84.7 ± 18.7 (199)	**.005**
BMI, kg/m^2	27.9 ± 6.0 (1724)	27.6 ± 5.9 (1272)	28.8 ± 6.2 (254)	29.2 ± 6.0 (198)	**<.001**
Systolic blood pressure[b]	139.3 ± 21.9 (1762)	139.1 ± 21.0 (1300)	139.4 ± 22.7 (259)	140.0 ± 26.4 (203)	.871
Diastolic blood pressure[b]	72.0 ± 12.0 (1762)	73.0 ± 11.8 (1300)	69.3 ± 11.5 (259)	69.1 ± 13.0 (203)	**<.001**
eGFR, mL/min/1.73 m^2	72.3 ± 38.2 (1772)	87.2 ± 31.2 (1305)	46.7 ± 15.9 (263)	10.3 ± 5.8 (204)	**<.001**
Serum creatinine, mg/dL	1.8 ± 2.2 (1772)	1.0 ± 0.7 (1305)	1.7 ± 0.7 (263)	6.9 ± 2.8 (204)	**<.001**
HbA1C	8.4 ± 5.6 (912)	8.4 ± 5.0 (650)	8.3 ± 2.1 (150)	8.7 ± 10.4 (112)	.834
Comorbidities					
Obese (BMI ≥30 kg/m^2)	32.8 (565/1724)	30.9 (393/1272)	35.0 (89/254)	41.9 (83/198)	**.006**
Diabetes	69.1 (1242/1797)	64.4 (854/1327)	79.2 (209/264)	86.9 (179/206)	**<.001**
Hypertension	87.3 (1568/1797)	84.4 (1120/1327)	93.6 (247/264)	97.6 (201/206)	**<.001**
Previous MI	50.1 (404/807)	49.5 (268/541)	55.6 (80/144)	45.9 (56/122)	.267
Prior CABG/PCI	73.9 (598/809)	72.5 (393/542)	77.9 (113/145)	75.4 (92/122)	.385
Congestive heart failure	5.8 (104/1795)	4.1 (54/1326)	9.5 (25/263)	12.1 (25/206)	**<.001**
Chronic obstructive pulmonary disease	15.3 (275/1797)	14.1 (187/1327)	22.3 (59/264)	14.1 (29/206)	**.003**
Stroke	13.9 (250/1797)	12.2 (162/1327)	16.3 (43/264)	21.8 (45/206)	**<.001**
Transient ischemic attack	4.8 (87/1797)	4.1 (55/1327)	8.7 (23/264)	4.4 (9/206)	**.006**
Clinical characteristics					
Smoking status					**<.001**
Never	21.9 (393/1797)	19.0 (252/1327)	23.9 (63/264)	37.9 (78/206)	
Prior (>1 year)	33.8 (607/1797)	29.9 (397/1327)	48.1 (127/264)	40.3 (83/206)	
Current or <1 year prior	44.4 (797/1797)	51.1 (678/1327)	28.0 (74/264)	21.8 (45/206)	
Ambulatory status					**<.001**
Ambulatory without assistance	54.0 (970/1796)	58.4 (775/1326)	46.2 (122/264)	35.4 (73/206)	
Ambulatory with assistance	32.8 (589/1796)	30.3 (402/1326)	34.8 (92/264)	46.1 (95/206)	
Uses wheelchair or bed bound	13.2 (237/1796)	11.2 (149/1326)	18.9 (50/264)	18.4 (38/206)	
Living home	94.1 (1690/1796)	95.2 (1263/1326)	90.5 (239/264)	91.3 (188/206)	**.002**
Albumin[a]	3.5 ± 0.6 (962)	3.6 ± 0.6 (690)	3.4 ± 0.7 (147)	3.3 ± 0.6 (125)	**<.001**
Medications					
Statin	72.1 (1293/1794)	70.5 (934/1324)	79.2 (209/264)	72.8 (150/206)	**.017**
Antiplatelet					.235
None	27.0 (485/1794)	27.6 (365/1324)	22.7 (60/264)	29.1 (60/206)	
Any single	54.8 (983/1794)	54.3 (719/1324)	60.6 (160/264)	50.5 (104/206)	
DAPT	18.2 (326/1794)	18.1 (240/1324)	16.7 (44/264)	20.4 (42/206)	
Anticoagulant	11.0 (198/1794)	9.0 (119/1324)	20.1 (53/264)	12.6 (26/206)	**<.001**

Table I. Continued.

	Overall (n = 1797)	Group A (n = 1327)	Group B (n = 264)	Group C (n = 206)	P value
Limb details					
Infrainguinal revascularization of index limb	6.4 (114/1792)	6.0 (79/1323)	8.7 (23/263)	5.8 (12/206)	.229
WIfI wound grade					**<.001**
0	21.2 (369/1737)	23.6 (303/1283)	17.4 (44/253)	10.9 (22/201)	
1	42.9 (746/1737)	42.7 (548/1283)	45.8 (116/253)	40.8 (82/201)	
2	29.8 (518/1737)	28.4 (365/1283)	26.9 (68/253)	42.3 (85/201)	
3	6.0 (104/1737)	5.2 (67/1283)	9.9 (25/253)	6.0 (12/201)	
WIfI stage					**.002**
1	6.4 (99/1552)	6.9 (80/1156)	5.7 (13/227)	3.6 (6/169)	
2	28.7 (446/1152)	30.4 (351/1156)	26.9 (61/227)	20.1 (34/169)	
3	29.5 (458/1552)	30.2 (349/1156)	25.1 (57/227)	30.8 (52/169)	
4	35.4 (549/1552)	32.5 (376/1156)	42.3 (96/227)	45.6 (77/169)	
ABI in index limb[b]	0.6 ± 0.3 (1243)	0.6 ± 0.3 (963)	0.6 ± 0.3 (178)	0.7 ± 0.4 (102)	**<.001**
Toe pressure[b]	35.0 ± 25.0 (768)	34.9 ± 23.4 (549)	38.5 ± 27.9 (127)	31.2 ± 29.5 (92)	.097
Surgical bypass details					
Location					
Above-the-knee femoropopliteal	8.5 (149/1756)	9.8 (127/1300)	6.6 (17/257)	2.5 (5/199)	**.001**
Below-the-knee femoropopliteal	12.1 (213/1756)	12.5 (163/1300)	9.7 (25/257)	12.6 (25/199)	.443
Femoral- tibial/pedal	17.9 (315/1756)	17.8 (231/1300)	19.5 (50/257)	17.1 (34/199)	.769
Popliteal- tibial/pedal	7.0 (123/1756)	6.2 (81/1300)	10.1 (26/257)	8.0 (16/199)	.069
Technique					
Bypass using SSGSV	34.9 (612/1755)	35.5 (461/1300)	37.0 (95/257)	28.3 (56/198)	.106
Bypass using alternative vein	4.1 (72/1755)	4.6 (60/1300)	1.9 (5/257)	3.5 (7/198)	.131
Bypass using composite vein	2.2 (38/1756)	2.5 (32/1300)	0.0 (0/257)	3.0 (6/199)	**.032**
Bypass using prosthetic conduit	8.2 (144/1755)	7.8 (101/1300)	7.8 (20/257)	11.6 (23/198)	.178
Endovascular therapy details					
Location					
Superficial femoral artery	34.9 (612/1756)	35.2 (458/1300)	34.2 (88/257)	33.2 (66/199)	.830
Popliteal artery	27.8 (488/1756)	26.7 (347/1300)	30.7 (79/257)	31.2 (62/199)	.221
Tibial/pedal arteries	25.9 (454/1756)	23.8 (310/1300)	27.6 (71/257)	36.7 (73/199)	**<.001**
Technique					
Atherectomy	7.4 (130/1756)	6.1 (79/1300)	10.1 (26/257)	12.6 (25/199)	**<.001**
Angioplasty alone	27.4 (481/1756)	25.5 (332/1300)	31.1 (80/257)	34.7 (69/199)	**.009**
Drug-coated balloon angioplasty	14.3 (251/1756)	14.5 (189/1300)	12.1 (31/257)	15.6 (31/199)	.503
Bare metal stents	23.3 (410/1756)	24.2 (314/1300)	20.6 (53/257)	21.6 (43/199)	.392
Drug-eluting stents	12.3 (216/1756)	12.8 (166/1300)	10.9 (28/257)	11.1 (22/199)	.600
Stent grafts	5.6 (98/1756)	6.0 (78/1300)	4.3 (11/257)	4.5 (9/199)	.431

ABI, Anke-brachial index; *BMI*, body mass index; *CABG*, coronary artery bypass graft; *DAPT*, dual antiplatelet therapy; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *SSGSV*, single segment great saphenous vein; *WIfI*, Wound, Ischemia, foot Infection.
Boldface entries indicate statistical significance.
Values are mean ± standard deviation or percent (n/N).
[a]Albumin measured in g/dL.
[b]Pressure recorded in mm Hg.

Table II. Multivariate Cox regression analysis of outcomes with reference to group A

	Group B HR (95% CI)[a]	*P* Value	Group C HR (95% CI)[a]	*P* Value
Above-ankle amputation[b]	1.10 (0.73-1.65)	.653	2.13 (1.49-3.05)	**<.001**
All-cause mortality	1.50 (1.18-1.90)	**.001**	3.40 (2.69-4.30)	**<.001**
Amputation or all-cause mortality	1.45 (1.16-1.80)	**.001**	2.76 (2.22-3.44)	**<.001**
MALE[c]	1.04 (0.78-1.39)	.773	1.53 (1.15-2.03)	**.003**
MALE or all-cause mortality	1.28 (1.05-1.56)	**.015**	2.05 (1.67-2.52)	**<.001**
Major reintervention[d]	0.86 (0.59-1.26)	.444	0.88 (0.57-1.34)	.543
Any reintervention[e]	1.01 (0.79-1.28)	.955	0.99 (0.75-1.30)	.925
MACE[f]	1.39 (1.11-1.74)	**.003**	2.97 (2.38-3.71)	**<.001**

CI, Confidence interval; *HR*, hazard ratio.
Boldface entries indicate statistical significance.
[a]HR adjusted for age, type of surgery (open vs endovascular), diabetes, infrapopliteal disease, history of prior infrainguinal revascularization, and WIfI grade.
[b]Above-ankle amputation includes hip disarticulation, above-knee (transfemoral), or below-knee (transtibial) amputation.
[c]Major adverse limb events (*MALE*) defined as above-ankle amputation of the index limb or a major index-limb reintervention (new bypass, interposition graft revision, thrombectomy, or thrombolysis).
[d]Major reintervention is defined as a new bypass graft, jump/interposition graft revision, thrombectomy, or thrombolysis reintervention.
[e]Any reintervention defined as major reintervention or surgical patch angioplasty, balloon angioplasty, atherectomy, laser treatment, stent placement, or stent graft placement.
[f]Major adverse cardiovascular events (*MACE*) defined as a composite of myocardial infarction, stroke, or death from any cause.

with A. Furthermore, group C had triple the hazard of MACE (HR, 2.97; 95% CI, 2.38-3.71; *P* < .001), whereas the risk of MACE in group B patients was 39% higher (HR, 1.39; 95% CI, 1.11-1.74; *P* = .003) compared with group A. There was no significant difference in the hazard of reintervention among the three CKD groups. Fig 1 illustrates the Kaplan-Meier curves of group A vs group B vs group C with regards to MALE or all-cause mortality, showing the outcome exceeding 70% before the 3-year mark in group C patients.

Spline analysis. A restricted spline model analysis was then performed on all the patients to identify the eGFR value at which the hazard of MALE or all-cause mortality became significantly different between the two treatment modalities. In the spline model, we identified eGFR 30 mL/min/1.73 m^2 as the knot at which the primary outcome becomes statistically significant (Fig 2). Patients eGFR values of <60 mL/min/1.73 m^2 did not exhibit significant differences in the primary outcome of MALE or all-cause death based on treatment type. In contrast, open bypass was associated with a trend toward lower hazard of MALE or all-cause mortality when the eGFR exceeds 60 mL/min/1.73 m^2 (Fig 3). Based on the prior findings, we subsequently reordered the patients into three groups according to the GFR cutoff value based on our own spline model: eGFR <30 mL/min/1.73 m^2; 30 ≤ eGFR <60 mL/min/1.73 m^2; and eGFR ≥60 mL/min/1.73 m^2 (baseline characteristics by eGFR demonstrated in Supplementary Table I, online only).

After adjusting to the following covariates—age, sex, race, ethnicity, antiplatelet agent use, type of surgery (open vs endovascular), coronary artery disease, diabetes, and hypertension—patients with 30 ≤ eGFR < 60 mL/

min/1.73 m^2 had a 31% higher hazard of all-cause mortality (HR, 1.31; 95% CI, 1.07-1.62; *P* = .011) but 32% lower risk of major reintervention (HR, 0.68; 95% CI, 0.49-0.95; *P* = .022) compared with patients with eGFR f ≥60 mL/min/1.73 m^2 (Table III). In contrast, patients with eGFR <30 mL/min/1.73 m^2 had 88% higher hazard of above-ankle amputation (HR, 1.88; 95% CI, 1.34-2.64; *P* < .001), more than double the risk of MALE or death (HR, 2.03; 95% CI, 1.68-2.43; *P* < .001), amputation or death (HR, 2.63; 95% CI, 2.16-3.21; *P* < .001), and MACE (HR, 2.80; 95% CI, 2.30-3.42; *P* < .001) and more than three times the hazard of dying from any cause (HR, 3.46; 95% CI, 2.80-4.27; *P* < .001). In subgroup analysis of MALE, the only significant interaction was antiplatelet agent use with nonusers at increased risk (HR, 2.58, 1.71-3.89; *P* < .001) vs no significant increase in risk among users (interaction *P* = .006) (Supplementary Table II, online only). We ran a separate subanalysis after excluding dialysis-dependent patients in order to exclusively investigate the impact of eGFR. Our results show that although nondialysis-dependent, patients with eGFR <30 had significantly higher hazard of all-cause mortality, amputation/death, MALE/death, and MACE compared with those with eGFR >60 (Table IV).

Outcomes in dialysis-dependent patients. Patients on hemodialysis have historically experienced notably concerning high rates of morbidity and mortality. Therefore, we decided to analyze the outcomes looking exclusively at dialysis-dependent patients. Going from 1 year to 3 years after revascularization, there was a close to 5% increase in above-ankle amputation (18.52% vs 23.28%) and MALE (30.16% vs 35.45%), whereas overall mortality (28.57% to 56.61%) and MACE (31.75% to 62.43%) were
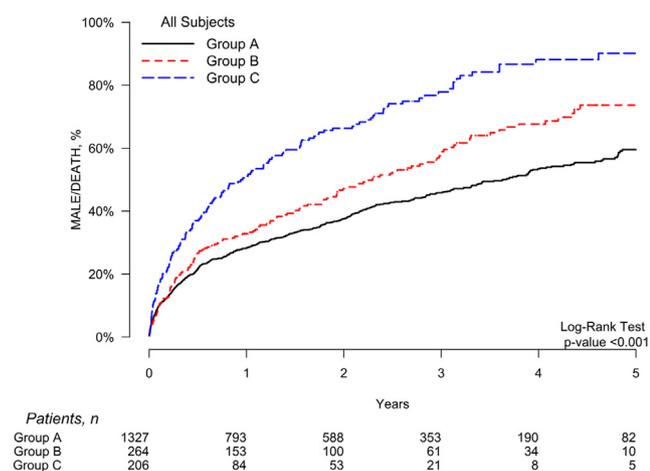
Fig 1. Kaplan-Meier analysis of MALE/death by CKD group A: non-CKD and CKD stage <3. Group B: stage 3 CKD and stage 4 CKD. Group C: stage 5 CKD and dialysis-dependent. The x-axis displays number of years after revascularization. The y axis displays Kaplan-Meier estimates for MALE or death. *CKD*, chronic kidney disease; *MALE*, major adverse limb events defined as above-ankle amputation of the index limb or a major index-limb reintervention (new bypass, interposition graft revision, thrombectomy, or thrombolysis).
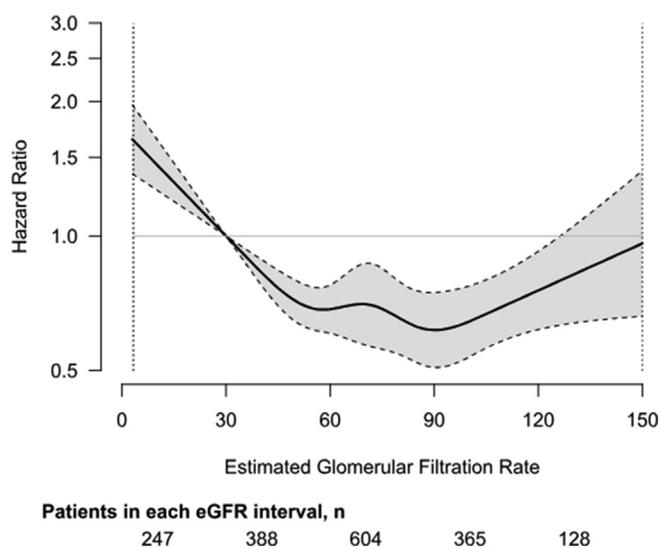

Fig 2. Spline model analysis of effect of eGFR on time to first MALE/death inflection point is at eGFR of 30 mL/min/1.73 m². The x axis displays the eGFR measured in mL/min/1.73 m². The y axis displays the hazard ratio for MALE or death. Shading indicates 95% confidence interval. *eGFR*, estimated glomerular filtration rate; *MALE*, major adverse limb events defined as above-ankle amputation of the index limb or a major index-limb reintervention (new bypass, interposition graft revision, thrombectomy, or thrombolysis).

doubled (Supplementary Table III, online only). The primary outcome of MALE/death was experienced in almost two-thirds of the patients on hemodialysis

regardless of the treatment modality (open SSGSV, 76.36% vs open alternative conduit, 66.67% vs ET, 65.42%). More than 50% of the patients on hemodialysis were dead after 3 years postrevascularization with the higher mortality rates belonging to patients who underwent revascularization by open bypass (open SSGSV, 67.27% vs open alternative conduit, 59.26% vs ET, 50.47%). After adjusting to confounders, there was no significance difference in any of the outcomes between bypass with alternative conduit and bypass with SSGSV in dialysis-dependent patients (Table V). However, when compared with SSGSV bypass, ET was associated with a 41% lower hazard of all-cause mortality (HR, 0.59; 95% CI, 0.37-0.94; P = .026), but double the hazard of any reintervention (HR, 2.07; 95% CI, 1.06-4.05; P = .034). There was also a trend of higher MALE with ET (HR, 1.79; 95% CI, 0.94-3.42; P = .076).

Long-term outcomes. Our analysis also exhibits a relationship between CKD severity and MALE/death outcomes. Two phenomena are observed with each added year after revascularization: (1) the of rate of MALE/death increase over the years within each CKD group, and (2) the more advanced the CKD stage, the higher the rate of the primary outcome. Both phenomena are illustrated in Fig 1, where patients who experienced MALE/death increase from around 25% at 1 year to almost 60% at 5 years in group A, approximately 30% to approximately 70% in group B, and approximately 50% to >80% in group C. After regrouping patients according to the cutoff of eGFR 30 mL/min/1.73 m² based on our spline model analysis, the difference in MALE/death is more clearly evident with the eGFR <30 mL/min/1.73 m² group compared with 30 ≤ eGFR < 60 mL/min/1.73 m² and eGFR ≥60 mL/min/1.73 m² groups (Fig 4). Similar findings were found when investigating other outcomes such as above-ankle amputation, all-cause mortality, and amputation-free survival (Figs 5-7, respectively).

DISCUSSION

Advanced CKD substantially increased the risk of worse outcomes after revascularization by either endovascular or surgical intervention in patients with CLTI. Compared with patients without CKD or less advanced CKD, those with CKD stages 3 and 4 had a nearly 50% higher risk of major amputation or all-cause mortality after revascularization Moreover, stage 5 CKD and dialysis dependence were associated with triple the risk of overall mortality and MACE, as well as more than double the hazard of amputation, amputation or death, and MALE or death. Looking at dialysis dependent patients in particular, our analysis showed high rates of all-cause mortality and MALE plus all-cause mortality exceeding 50% and 65%, respectively, at 3 years (Supplementary Table III, online only). The only significant differences observed between open bypass (with SSGSV) and ET in
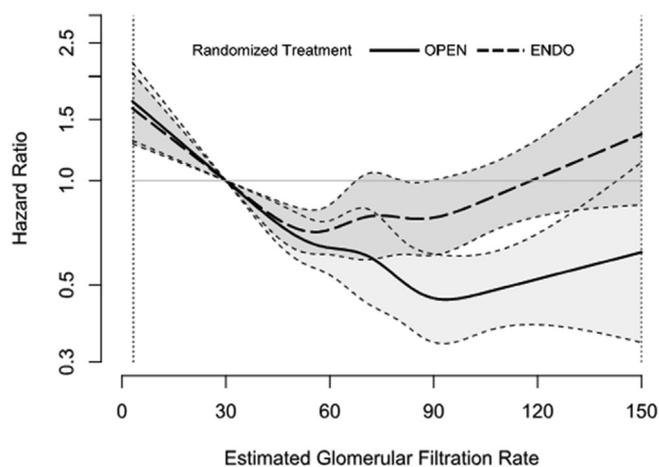
Fig 3. Spline model analysis of effect of eGFR on time to first MALE/death by randomized treatment (open bypass vs endovascular therapy [ET]). The x axis displays the eGFR measured in mL/min/1.73 m². The y axis displays the hazard ratio for MALE or death. Shading indicates 95% confidence interval. Inflection point at an eGFR of 30 mL/min/1.73 m². *eGFR*, estimated glomerular filtration rate; *ENDO*, endovascular therapy (including atherectomy, balloon angioplasty, stents, stent grafts); *OPEN*, open surgical bypass (including single segment saphenous vein graft or alternative conduit); *MALE*, major adverse limb events defined as above-ankle amputation of the index limb or a major index-limb reintervention (new bypass, interposition graft revision, thrombectomy, or thrombolysis).

patients with CLTI on dialysis is double the risk of reintervention, but a 40% lower mortality with ET. Although not statistically significant on multivariable analysis, our unadjusted Kaplan-Meier analysis shows that patients who survived to 3 years after revascularization had better limb salvage and lower MALE with surgical bypass (SSGSV or alternative conduit) compared with ET with approximately 10% and 20% difference in crude rates of major amputation and MALE, respectively. Prior studies used categorical CKD stages to assess outcomes of different procedures. Because these cutoffs were not necessarily aligned to CTLI risks, we also used restricted spline modeling to identify a GFR threshold for worsened outcomes and when these outcomes differ between open and ET in patients with CLTI. Our spline model shows that an eGFR of 30 mL/min/1.73 m² is the statistically significant level below which clinical outcomes are significantly worse (higher hazard of amputation, amputation/death, overall mortality, MALE, MALE/death, and MACE) with no apparent difference between revascularization modalities in the trial population.

Evidence for associations between reduced kidney function and worsened outcomes after revascularization has been previously observed. Affecting one-quarter of the population, peripheral arterial disease, CKD, and particularly kidney failure treated by dialysis, reduce likelihood of limb salvage and survival for patients with CLTI. Prolonged exposure to uremic toxins, disruption of calcium-phosphate regulation, and long standing oxidative stress may contribute to accelerated progression of atherosclerosis and calcification leading to rapid disease progression.[19-21] Patients with advanced CKD are more likely to have distal lower extremity disease as well as calcified vessels leading to more challenging revascularization attempts and lower durability compared with patients without CKD.[22,23]

Other studies have reported that patients with CKD or kidney failure treated by dialysis have double the risk of major amputation and mortality compared with those without CKD.[14] Additionally, no differences in reintervention rates were observed by CKD status except when a stratified by procedure type. ET was found to have higher reintervention rates compared with open bypass mirroring our own findings. Although we found CKD stage ≥3 predicted mortality, another study showed conflicting results as they identified only kidney failure (eGFR <15 mL/min/1.73 m²), but not less severe CKD (eGFR 15-59 mL/min/1.73 m²) was associated with higher 3-year mortality compared with patients with CLTI without CKD undergoing infrainguinal bypass.[17] A study of ET in advanced CKD (eGFR <15-30 mL/min/1.73 m²) showed higher amputation and mortality at 21 months compared with those with higher eGFR.[24] Grouping patients by Kidney Disease Improving Global Outcomes eGFR categories to classify CKD has produced inconsistent results for CTLI outcomes and responses to revascularization.[17,25-27] Taken together, these findings stimulated our decision to run the spline model analysis to identify a more objective eGFR threshold for CTLI risks and treatment outcomes. At eGFR ≤30 mL/min/1.73 m², risks of MALE and death increased sharply with no difference in these outcomes by endovascular or surgical intervention.[11]

Among patients with CLTI on dialysis, more than one-half died after 3 years. Numerous comorbidities such as diabetes and extensive cardiovascular disease contribute to the poor survival among this population, which raises concerns of whether a revascularization attempt is appropriate or not.[28] Recent studies looking at survival of patients with CLTI after revascularization report 3-year survival rates of 24.7%, 48.0%, 58.3%, and 72.0% showing a wide range of published post-revascularization survival (possibly reflecting the large variation in sample sizes in these studies). In contrast, in the present trial 73% of surviving dialysis patients at 3 years had their treated limb intact. These results reinforce the need for fully informed, shared decision-making regarding revascularization vs primary amputation or palliative wound care in this high-risk population.[13,17,24,29]

Table III. Multivariate Cox Regression analysis of outcomes with reference to patients with and eGFR of ≥60

	30 ≤ eGFR <60 HR (95% CI)[a]	P Value	eGFR <30 HR (95% CI)[a]	P Value
Above-ankle amputation[b]	1.10 (0.77-1.57)	.608	1.88 (1.34-2.64)	**<.001**
All-cause mortality	1.31 (1.07-1.62)	**.011**	3.46 (2.80-4.27)	**<.001**
Amputation or all-cause mortality	1.18 (0.97-1.44)	.094	2.63 (2.16-3.21)	**<.001**
MALE[c]	0.92 (0.72-1.18)	.516	1.41 (1.09-1.83)	**.010**
MALE or all-cause mortality	1.08 (0.91-1.29)	.389	2.03 (1.68-2.43)	**<.001**
Major reintervention[d]	0.68 (0.49-0.95)	**.022**	0.87 (0.61-1.26)	.468
Any reintervention[e]	0.82 (0.67-1.01)	.061	1.02 (0.80-1.29)	.868
MACE[f]	1.20 (0.99-1.46)	.063	2.80 (2.30-3.42)	**<.001**

CI, Confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
Boldface entries indicate statistical significance.
[a]HR adjusted for age, sex, race, ethnicity, Antiplatelet use, type of surgery (open vs endovascular), coronary artery disease, diabetes, and hypertension.
[b]Above-ankle amputation include hip disarticulation, above-knee (transfemoral), or below-knee (transtibial) amputation.
[c]Major adverse limb events (MALE) defined as above-ankle amputation of the index limb or a major index-limb reintervention (new bypass, interposition graft revision, thrombectomy, or thrombolysis).
[d]Major reintervention is defined as a new bypass graft, jump/interposition graft revision, thrombectomy, or thrombolysis reintervention.
[e]Any reintervention defined as major reintervention or surgical patch angioplasty, balloon angioplasty, atherectomy, laser treatment, stent placement, or stent graft placement.
[f]Major adverse cardiovascular events (MACE) defined as a composite of myocardial infarction, stroke, or death from any cause.

Table IV. Outcomes of Non-dialysis dependent patients with an eGFR of <30 compared with patients with an eGFR of ≥60

	Nondialysis-dependent with an eGFR of <30 HR[a] (95% CI)	P Value
Above-ankle amputation	1.13 (0.55-2.34)	.732
All-cause mortality	2.41 (1.66-2.51)	**<.001**
Amputation or all-cause mortality	1.79 (1.25-2.56)	**.002**
MALE	0.98 (0.58-1.66)	.947
MALE or all-cause mortality	1.48 (1.06-2.07)	**.021**
Major reintervention	0.75 (0.36-1.53)	.422
Any reintervention	0.89 (0.57-1.39)	.603
MACE	1.84 (1.27-2.66)	**.001**

CI, Confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MACE, major adverse cardiac events; MALE, major adverse limb event.
Boldface entries indicate statistical significance.
[a]HR adjusted for age, sex, race, ethnicity, antiplatelet, statin, type of surgery (open vs endovascular), coronary artery disease, diabetes, and hypertension.

Prior literature has demonstrated high mortality rates in dialysis-dependent patients undergoing lower extremity revascularization with several factors impacting the survival of those medically compromised patients. For instance, in a study comparing autogenous vs synthetic bypass conduits in patients on hemodialysis, patient survival was greater for patients who received autogenous bypasses (HR, 1.10; 95% CI, 1.02-1.19; P = .01). The survival rates were 59% vs 55% at 1 year, 43% vs 37% at 2 years, 31% vs 28% at 3 years, 23% vs 21% at 4 years, and 20% vs 18% at 5 years (P < .001), respectively.[30] Another study on 9305 infrainguinal bypasses showed the impact of race and ethnicity on long-term survival with the survival rates at 4 years being 15% in White patients vs 30% in Black patients vs 33% in Hispanics (HR for Blacks, 0.65 [P <.001] and Hispanics, 0.67 [P <. 001] compared with Whites).[31] Furthermore, in a single institutional study of 146 dialysis-dependent patients who underwent lower extremity bypass, the survival rates at 1, 3, and 5 years were 60%, 18%, and 5%, respectively. The study also showed that the number of years on dialysis as well as age and hypertension were independent negative predictors of survival after infrainguinal revascularization.[32] Renal transplantation was also found to promote survival as dialysis dependence was associated with a 2.4-fold increase in mortality after lower extremity bypass compared with the renal transplantation group (HR, 2.42; 95% CI, 2.17-2.71; P <.001). Kaplan-Meier survival estimates of patients on hemodialysis compared with after renal transplantation were 57.6% vs 77.8% at 1 year, 40.5% vs 68.9% at 2 years, 29.7% vs 59.9% at 3 years, 21.9% vs 52.1% at 4 years, and 19.2% vs 48.2% at 5 years (P < .001).[33]

The impact of the surgical approach on limb and survival outcomes varies by CKD severity.[34] Overall MALE and death outcomes were worse with eGFR <30 mL/min/1.73 m^2 with either open or endovascular revascularization. However, ET was associated with better survival compared with open bypass in patients treated by dialysis. Similar findings of higher mortality with open bypass has been previously reported in this population.[35,36]

LIMITATIONS

This post hoc study has notable limitations. Although the data were derived from a randomized controlled trial, participants were not stratified by CKD severity at

Table V. Multivariate Cox regression analysis of outcomes of bypass with alternative conduit and endovascular therapy (ET) with reference to bypass with SSGSV in dialysis-dependent patients

	Bypass with alternative conduit HR (95% CI)	P value	Endovascular therapy HR (95% CI)	P value
Above-ankle amputation[a]	1.47 (0.44-4.92)	.531	2.10 (0.86-5.09)	.101
All-cause mortality	0.71 (0.37-1.40)	.327	0.59 (0.37-0.94)	**.026**
Amputation or all-cause mortality	0.68 (0.36-1.28)	.233	0.68 (0.44-1.05)	.085
MALE[b]	0.69 (0.24-1.97)	.483	1.79 (0.94-3.42)	.076
MALE or all-cause mortality	0.62 (0.34-1.16)	.138	0.89 (0.59-1.36)	.600
Major reintervention[c]	0.30 (0.04-2.55)	.273	1.54 (0.61-3.89)	.364
Any reintervention[d]	1.64 (0.65-4.13)	.293	2.07 (1.06-4.05)	**.034**
MACE[e]	0.65 (0.34-1.25)	.198	0.72 (0.47-1.12)	.144

CI, Confidence interval; *eGFR,* estimated glomerular filtration rate; *HR,* hazard ratio; *MACE,* major adverse cardiac events; *MALE,* major adverse limb event.
Boldface entries indicate statistical significance.
[a]Above-ankle amputation includes hip disarticulation, above-knee (transfemoral), or below-knee (transtibial) amputation.
[b]MALE defined as above-ankle amputation of the index limb or a major index-limb reintervention (new bypass, interposition graft revision, thrombectomy, or thrombolysis).
[c]Major reintervention is defined as a new bypass graft, jump/interposition graft revision, thrombectomy, or thrombolysis reintervention.
[d]Any reintervention defined as major reintervention or surgical patch angioplasty, balloon angioplasty, atherectomy, laser treatment, stent placement, or stent graft placement.
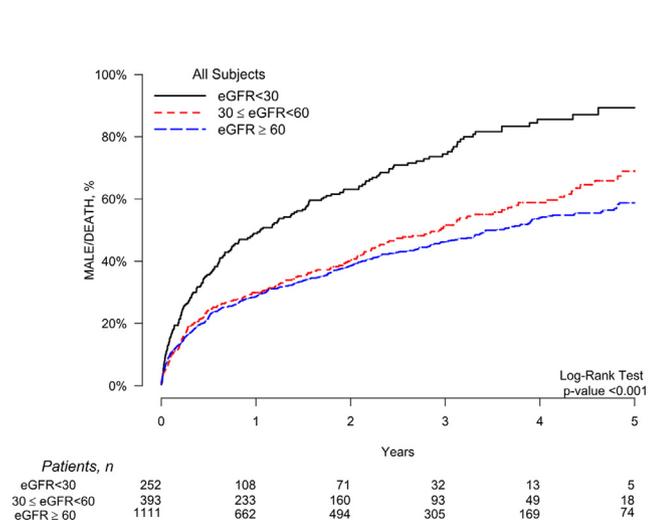[e]MACE defined as a composite of myocardial infarction, stroke, or death from any cause.

Fig 4. Kaplan-Meier analysis of MALE/death by eGFR groups. The *x* axis displays the number of years after revascularization. The *y* axis displays the Kaplan-Meier estimates for MALE or death. *eGFR,* estimated glomerular filtration rate (mL/min/1.73 m^2); *MALE,* major adverse limb events defined as above-ankle amputation of the index limb or a major index-limb reintervention (new bypass, interposition graft revision, thrombectomy, or thrombolysis).

Fig 5. Kaplan-Meier analysis of above-ankle amputation by eGFR groups. *eGFR,* estimated glomerular filtration rate.

Fig 6. Kaplan-Meier analysis of all-cause mortality by eGFR groups. *eGFR,* estimated glomerular filtration rate.

randomization. Subgroup analyses comparing open bypass vs ET in patients with CLTI could be underpowered owing to the small sample size. Furthermore, potential confounders such as degree of vascular calcification, dialysis vintage, and many medications were not available to be analyzed. In this study we did not examine whether renal impairment influenced quality of life changes after revascularization, an important goal of treatment in patients with CLTI. Finally, our
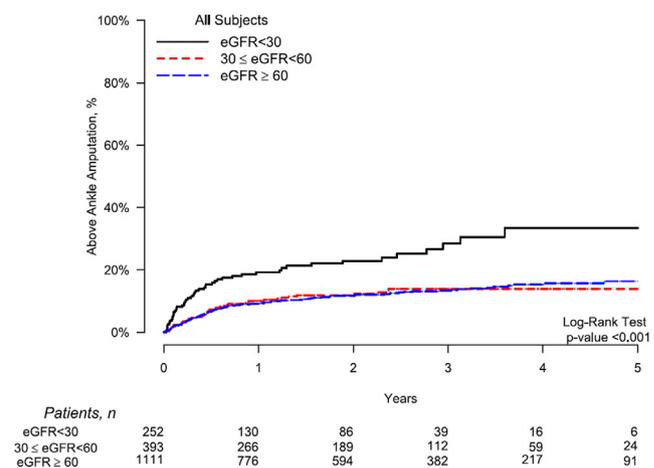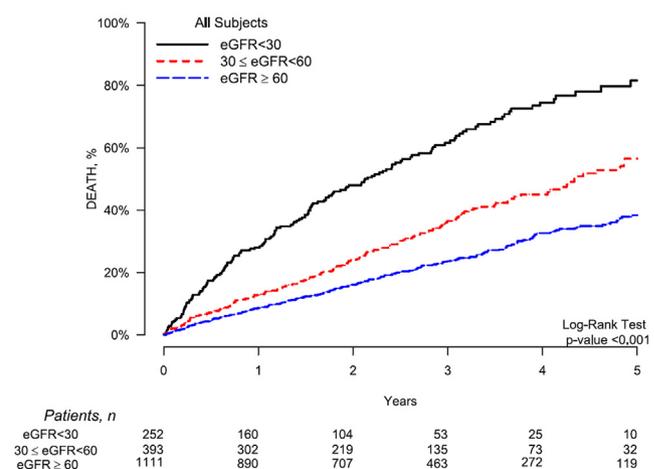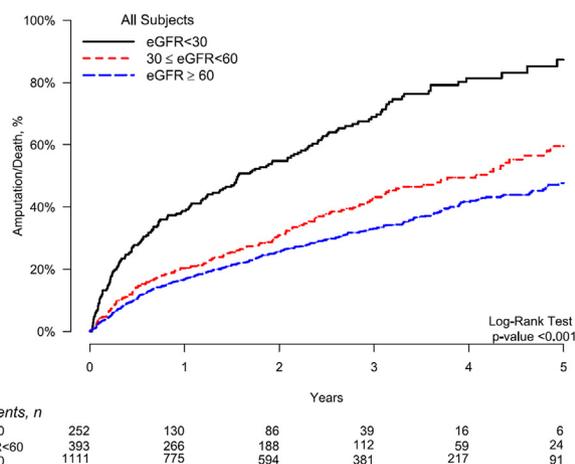
Fig 7. Kaplan-Meier analysis of amputation-free survival by eGFR groups. *eGFR*, estimated glomerular filtration rate.

findings need to be confirmed by prospective randomized analyses to draw more valid and reliable conclusions, therefore the results must be interpreted cautiously and as mainly hypothesis generating.

CONCLUSIONS

Patients with CLTI and CKD in the BEST-CLI trial, especially those who are dialysis dependent, had poor outcomes in terms of limb loss and MALE along with higher risks of death and MACE. The severity of CKD in patients with CLTI threatens both their overall survival and limb salvage. At eGFR <30 mL/min/1.73 m^2, risks of MALE and death increased sharply with no apparent difference in the primary outcome by surgical or endovascular revascularization. In dialysis dependent patients, ET was associated with lower mortality but increased rates of reintervention. Finally, unlike other studies in the literature that stratify CKD patients by arbitrary eGFR estimates, our spline model analysis is the first to provide an evidence based eGFR value of 30 mL/min/1.73 m^2 as the cutoff below which patients with CLTI experience significantly worse outcomes after revascularization regardless of treatment method.

AUTHOR CONTRIBUTIONS

Conception and design: MBM, MH, AF, MTM, MC, MBS, GD, KT
Analysis and interpretation: MBM, MH, AF, MTM, MC, KR, MBS, GD, RP, CM, WG, MLS, SA, KS, MD, JR, KT
Data collection: NA
Writing the article: MBM, MH, KT
Critical revision of the article: MBM, MH, AF, MTM, MC, KR, MBS, GD, RP, CM, WG, MLS, SA, KS, MD, JR, KT
Final approval of the article: MBM, MH, AF, MTM, MC, KR, MBS, GD, RP, CM, WG, MLS, SA, KS, MD, JR, KT
Statistical analysis: MBM, MH, GD
Obtained funding: Not applicable
Overall responsibility: MBM

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Supplementary Table I (online only). Baseline characteristics of patients by estimated glomerular filtration rate (*eGFR*)

	eGFR < 30 (n = 252)	30 ≤ eGFR < 60 (n = 393)	eGFR ≥ 60 (n = 1111)	*P* value
Demographics				
Age, years	65.1 ± 10.2	71.6 ± 9.4	66.5 ± 9.3	**<.001**
Gender				**<.001**
Male	70.2%	62.6%	75.0%	
Female	29.8%	37.4%	25.0%	
Hispanic	19.5%	11.2%	12.3%	**.004**
Race				**<.001**
White	55.4%	76.7%	74.9%	
Black	31.7%	14.0%	19.7%	
Other	12.9%	9.3%	5.3%	
BMI (kg/m^2)	29.0 ± 6.2	29.0 ± 6.1	27.4 ± 5.8	
Comorbidities				
Dialysis dependent	80.6%	0.8%	0.0%	**<.001**
Obese (BMI ≥30 kg/m^2)	40.9%	35.5%	30.0%	**.002**
Diabetes	86.5%	76.8%	63.2%	**<.001**
Hypertension	96.8%	93.1%	83.6%	
Previous MI	45.1%	52.2%	50.2%	.418
Prior CABG/PCI	74.5%	76.2%	73.0%	.678
Congestive heart failure	12.3%	7.9%	3.6%	**<.001**
Chronic obstructive pulmonary disease	14.7%	17.6%	14.4%	.310
Stroke	20.2%	11.5%	13.3%	**.005**
Transient ischemic attack	5.6%	6.9%	4.1%	.072
Clinical characteristics				
Smoking status				**<.001**
Never	36.5%	25.5%	18.0%	
Prior (>1 year)	40.9%	42.6%	29.9%	
Current or <1 year prior	22.6%	31.9%	52.1%	
Ambulatory status				**<.001**
Ambulatory without assistance	39.3%	45.4%	60.9%	
Ambulatory with assistance	43.3%	39.8%	28.0%	
Uses wheelchair or bed bound	17.5%	14.8%	11.2%	
Living home	92.1%	93.6%	95.1%	.127
Albumin[a]	3.3 ± 0.7	3.5 ± 0.6	3.6 ± 0.6	**<.001**
Medications				
Statin	74.6%	73.7%	71.5%	.487
Antiplatelet				.893
None	27.8%	26.3%	26.5%	
Any single	52.4%	55.6%	55.8%	
DAPT	19.8%	18.1%	17.7%	
Anticoagulant	13.1%	16.1%	9.2%	**<.001**
Limb details				
Infrainguinal revascularization of index limb	6.0%	7.4%	6.4%	.724
WIfI wound grade				**<.001**
0	12.2%	17.5%	24.6%	
1	41.2%	45.8%	42.0%	

Supplementary Table I (online only). Continued.

	eGFR < 30 (n = 252)	30 ≤ eGFR < 60 (n = 393)	eGFR ≥ 60 (n = 1111)	*P* value
2	38.8%	29.6%	27.7%	
3	7.8%	7.1%	5.7%	
ABI in index limb[b]	0.7 ± 0.4	0.6 ± 0.3	0.6 ± 0.3	**<.001**
Toe pressure[b]	32.0 ± 28.0	39.3 ± 24.7	34.1 ± 21.9	**.020**

ABI, Anke-brachial index; *BMI*, body mass index; *CABG*, coronary artery bypass graft; *DAPT*, dual antiplatelet therapy; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *WIfI*, Wound, Ischemia, foot Infection.
Boldface entries indicate statistical significance. Values are mean ± standard deviation unless otherwise indicated.
[a]Albumin measured in g/dL.
[b]Pressure recorded in mm Hg.

Supplementary Table II (online only). Subgroup analysis of major adverse limb events (*MALE*) with reference to an estimated glomerular filtration rate (*eGFR*) of >60

Subgroup analyzed	eGFR<30 vs eGFR>60 HR (95% CI)	30 ≤ eGFR<60 vs eGFR>60 HR (95% CI)	*P* value for interaction
Age ≤65	1.79 (1.28-2.51); *P* ≤ .001	1.04 (0.69-1.56); *P* = .858	.307
Age >65	1.22 (0.85-1.74); *P* = .285	0.81 (0.60-1.09); *P* = .158	
Male gender	1.57 (1.18-2.09); *P* = .002	1.00 (0.76-1.32); *P* = .994	.316
Female gender	1.31 (0.81-2.12); *P* = .270	0.66 (0.42-1.04); *P* = .074	
Non-White	1.44 (0.97-2.13); *P* = .073	0.83 (0.51-1.35); *P* = .461	.974
White	1.53 (1.11-2.10); *P* = .010	0.87 (0.66-1.14); *P* = .318	
Non-Hispanic	1.50 (1.15-1.96); *P* = .003	0.82 (0.63-1.06); *P* = .124	.486
Hispanic	1.57 (0.85-2.90); *P* = .151	1.23 (0.63-2.39); *P* = .539	
No hypertension	1.26 (0.30-5.19); *P* = .751	1.15 (0.52-2.56); *P* = .725	.732
Hypertension	1.46 (1.13-1.87); *P* = .004	0.83 (0.65-1.07); *P* = .152	
No diabetes	1.66 (0.89-3.10); *P* = .111	0.94 (0.59-1.51); *P* = .806	.760
Diabetes	1.41 (1.07-1.85); *P* = .014	0.82 (0.62-1.09); *P* = .166	
No smoking history	1.17 (0.72-1.91); *P* = .520	0.97 (0.59-1.60); *P* = .911	.351
Smoking history	1.67 (1.26-2.23); *P* ≤ .001	0.83 (0.63-1.09); *P* = .178	
No congestive heart failure	1.45 (1.11-1.88); *P* = .006	0.89 (0.70-1.14); *P* = .363	.379
Congestive heart failure	1.13 (0.53-2.43); *P* = .746	0.43 (0.16-1.18); *P* = .102	
No MI or stroke or PCI or CABG	1.38 (0.95-1.99); *P* = .088	0.81 (0.58-1.15); *P* = .242	.886
MI or stroke or PCI or CABG	1.52 (1.09-2.12); *P* = .014	0.89 (0.63-1.24); *P* = .473	
Albumin <3.5 g/dL	1.08 (0.68-1.71); *P* = .752	0.55 (0.32-0.95); *P* = .031	.098
Albumin ≥3.5 g/dL	1.71 (1.10-2.67); *P* = .018	1.08 (0.72-1.62); *P* = .712	
No statin	1.39 (0.84-2.32); *P* = .203	0.72 (0.44-1.17); *P* = .185	.677
Statin	1.51 (1.14-2.01); *P* = .004	0.92 (0.70-1.20); *P* = .530	
No antiplatelet	2.58 (1.71-3.89); *P* ≤ .001	0.85 (0.53-1.36); *P* = .499	**.006**
Antiplatelet	1.14 (0.84-1.56); *P* = .405	0.86 (0.65-1.13); *P* = .286	

CABG, Coronary artery bypass graft; *CI*, confidence interval; *HR*, hazard ratio; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention.
Boldface entries indicate statistical significance.
Hazard ratios and *P* values are calculated from a Cox proportional hazards model.

Supplementary Table III (online only). Univariate 1-year and 3-year outcomes in dialysis-dependent patients

	All patients (n = 189)	Open SSGSV (n = 55)	Open alternative conduit (n = 27)	Endovascular therapy (n = 107)
	No. (%)	No. (%)	No. (%)	No. (%)
Above-ankle amputation[a]				
1 Year	35 (18.52)	7 (12.7)	3 (11.11)	25 (23.36)
3 Years	44 (23.28)	9 (16.36)	5 (18.52)	30 (28.04)
All-cause mortality				
1 Year	54 (28.57)	20 (36.36)	9 (33.33)	25 (23.36)
3 Years	107 (56.61)	37 (67.27)	16 (59.26)	54 (50.47)
Amputation or all-cause mortality				
1 Year	75 (39.68)	25 (45.45)	11 (40.74)	39 (36.45)
3 Years	120 (63.49)	41 (74.55)	18 (66.67)	61 (57.01)
MALE[b]				
1 Year	57 (30.16)	12 (21.82)	4 (14.81)	41 (38.32)
3 Years	67 (35.45)	15 (27.27)	6 (22.22)	46 (42.99)
MALE or all-cause mortality				
1 Year	92 (48.68)	28 (50.91)	11 (40.74)	53 (49.53)
3 Years	130 (68.78)	42 (76.36)	18 (66.67)	70 (65.42)
Major reintervention[c]				
1 Year	27 (14.29)	6 (10.91)	2 (7.41)	19 (17.76)
3 Years	29 (15.34)	7 (12.73)	2 (7.41)	20 (18.69)
Any reintervention[d]				
1 Year	63 (33.33)	13 (23.64)	9 (33.33)	41 (38.32)
3 Years	71 (37.57)	16 (29.09)	11 (40.74)	44 (41.12)
MACE[e]				
1 Year	60 (31.75)	23 (41.82)	9 (33.33)	28 (26.17)
3 Years	118 (62.43)	41 (74.55)	17 (62.96)	60 (56.07)

SSGSV, Single segment great saphenous vein.
[a]Above-ankle amputation include hip disarticulation, above-knee (transfemoral), or below-knee (transtibial) amputation.
[b]Major adverse limb events (*MALE*) defined as above-ankle amputation of the index limb or a major index-limb reintervention (new bypass, interposition graft revision, thrombectomy, or thrombolysis).
[c]Major reintervention is defined as a new bypass graft, jump/interposition graft revision, thrombectomy, or thrombolysis reintervention.
[d]Any reintervention defined as major reintervention or surgical patch angioplasty, balloon angioplasty, atherectomy, laser treatment, stent placement, or stent graft placement.
[e]Major adverse cardiovascular events (*MACE*) defined as a composite of myocardial infarction, stroke, or death from any cause.