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Factors associated with lower preoperative quality of life in patients with chronic limb-threatening ischemia in the BEST-CLI trial

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ABSTRACT

Objectives: There are few contemporary data regarding health-related quality of life (HRQOL) measures in patients with chronic limb-threatening ischemia (CLI).

Methods: The Best Endovascular versus Best Surgical Therapy in Patients with CLI (BEST-CLI) trial is an ongoing, National Institutes of Health-sponsored, multicenter, randomized, controlled trial comparing revascularization strategies in patients with CLI. BEST-CLI baseline HRQOL measures were evaluated for patient-specific variables that were associated with poor HRQOL and then compared with published outcomes. The HRQOL measures Vascular Quality of Life Questionnaire (VascQOL), European Quality of Life 5D (EQ-5D), and the Short Form 12 (SF-12) Index score, physical component score (PCS) and mental component score (MCS) were aggregated from preoperative questionnaires completed by trial patients at baseline visits. Multivariable linear regression models were fit to determine which baseline characteristics were associated with poor HRQOL.

Results: We randomized 1830 patients into BEST-CLI. The majority (94.9%, 95.8%, and 95.8%) completed the VascQOL, EQ-5D, and SF-12 instruments at baseline, respectively. In the VascQOL, female sex, smoking history, opioid use, and nonindependent ambulation predicted lower HRQOL scores. Overall, VascuQOL scores were similar to those of participants in the Bypass versus Angioplasty in Severe Ischemia of the Leg (mean, 3.07 ± 1.2 vs mean, 2.9 ± 1.1 ; $P = .07$). In EQ-5D, nonindependent ambulation predicted lower HRQOL scores. In the SF-12, female sex, opioid use, nonindependent ambulation, and a history of smoking predicted lower HRQOL scores. The mean SF-12 PCS for all patients in the study was 33.0 ± 8.5 and for the MCS was 46.4 ± 12.0 , significantly lower than the national SF-12 scores for US population ages more than 60 years, which is a PCS of 46.5 ± 11.4 and an MCS of 52.9 ± 8.7 .

Conclusions: Patients with CLI entering the BEST-CLI trial have very low HRQOL scores, comparable with patients suffering from other chronic conditions characterized by physical limitations and chronic pain. A history of smoking, impaired ambulation, opioid use, and female sex predicted lower HRQOL in patients with CLI, using multiple HRQOL measurement tools. (*J Vasc Surg* 2022;76:1642-50.)

Keywords: Critical limb ischemia; PAD; HRQOL

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When compared with the general population, chronic limb-threatening ischemia (CLI) is associated with multiple comorbidities, a high 5-year mortality rate, and significant disability and results in poor health-related quality of life (HRQOL).¹⁻⁴ Previous studies in patients with CLI, including the Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) and a multicenter, randomized trial of Edifoligide for the Prevention of Vein Graft Failure in Lower Extremity Bypass Surgery (PREVENT III) trials have examined the impact of revascularization on HRQOL.^{3,5} In general, revascularization has been shown to improve HRQOL in such patients. However, there has been minimal work examining the impact of patient presentation and associated comorbidities on HRQOL in patients with CLI. For instance, it is unclear what role, if any, patient-specific factors such as sex, age, diabetes, presence of tissue loss, and ambulatory status among others have on HRQOL at presentation. These data may be important to assist the physician in identifying high-risk patients who may gain the most improvement in HRQOL through addressing modifiable risk factors and various open or endovascular (EVT) interventions. As overall medical therapy has improved with time, it is possible that patients with CLI could have experienced improvement in their HRQOL owing to factors such as improved wound care, more aggressive lipid management, and better smoking cessation programs. As such, there is a need for a contemporary assessment of HRQOL measures in patients presenting with CLI.

The Best Endovascular versus Best Surgical Therapy in Patients with CLI (BEST-CLI) Trial is a randomized multi-institutional trial that compares EVT therapy with open surgical bypass in patients with CLI.⁶ This multispecialty trial includes participation of cardiologists, interventional radiologists, vascular medicine, and vascular surgeons.⁷ At baseline entry into the trial various HRQOL measures were obtained. The purpose of this report is to use data from this large randomized trial to provide a contemporary assessment of HRQOL in patients with CLI and to identify predictors of poor HRQOL at presentation.

METHODS

The institutional review board of each participating institution approved the protocol and informed consent. All patients gave informed consent before participating in the BEST-CLI Trial. The BEST-CLI Trial is a multicenter, randomized, controlled trial of best EVT or best open surgical (OPEN) revascularization in patients with CLI owing to infrainguinal arterial occlusive disease who are candidates for both open and EVT treatment ([ClinicalTrials.gov NCT02060630](https://clinicaltrials.gov/ct2/show/study/NCT02060630)). The trial protocol has been described previously.⁶ Briefly the trial has a superiority design and its primary aim is to compare the primary endpoint event rates of major adverse limb event-free survival in patients with CLI randomized to best EVT revascularization with rates in those randomized to best OPEN. Best revascularization, whether EVT or OPEN, was defined as the technique

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter prospective randomized study
- **Key Findings:** The health-related quality of life (HRQOL) was measured using the Vascular Quality of Life Questionnaire, Short Form-12, and EuroHRQOL 5D in 1830 patients with chronic limb-threatening ischemia (CLI) before intervention. Self-reported female sex, impaired mobility, smoking history and opioid use were all associated with significantly worse HRQOL scores at baseline.
- **Take Home Message:** Patients with CLI entering the Best Endovascular versus Best Surgical Therapy in Patients with CLI trial have very low HRQOL scores, comparable with patients suffering from other chronic conditions characterized by physical limitations and chronic pain. A history of smoking, impaired ambulation, opioid use, and female sex predicted lower HRQOL in patients with CLI, using multiple HRQOL measurement tools.

deemed most appropriate for the patient by the operator(s), with respect to the index limb. Treatment comparisons (EVT vs OPEN) were made in two cohorts: (1) patients with an available single segment great saphenous vein and (2) patients without a single segment great saphenous vein (ie, alternative conduit to be used if randomized to OPEN).

As a secondary end point, HRQOL was assessed with questionnaires. Currently, there are no patient-reported outcome measures that specifically address HRQOL in patients with CLI.⁸ As such, three different patient-reported QOL measures were used. These included the Vascular Quality of Life Questionnaire (VascuQOL),⁹ the European Quality of Life 5D (EQ-5D),¹⁰ and the Short Form 12 (SF-12). These are standard, validated instruments and available in Spanish and English. The EQ-5D and SF-12 are complementary assessment tools that comprehensively gauge global health related HRQOL/function, and the VascuQOL is a peripheral vascular disease-specific questionnaire that better allows one to detect subtle changes in vascular disease severity.

Questionnaires were administered at various time points throughout the study. In the current study, only the results from the questionnaires administered after patients signed consent and enrolled into the study but before any form of revascularization were analyzed. Subsequent reports from BEST-CLI will examine improvements in QOL after intervention. The current data will serve as a useful benchmark for measuring HRQOL in CLI using numerous patient-reported outcome measures with more than 95% of patients responding. Information in this article should be useful to physicians interested in addressing specific modifiable risk factors that can help to improve QOL in their patients with CLI.

Statistical analyses. Baseline characteristics are summarized as mean \pm standard deviation for continuous variables and proportions for categorical variables. Mean VascuQoL was compared between studies using *t* test statistics. Potential correlations of baseline demographics and patient-specific variables with HRQOL measures were assessed using multipredictor regression model. The models were adjusted for race, age (≥ 80 years), gender, heart failure, above-ankle amputation of the nonindex limb, bilateral CLI, chronic obstructive pulmonary disease, smoking status, end-stage renal disease, hyperlipidemia, diabetes, hypertension, tissue loss, opiate use, comorbidity index, ambulatory status and living home. Parameter estimates with 95% confidence intervals (CI) are presented. SAS EG version 8.3 (SAS Institute, Cary, NC) software was used to conduct the statistical analyses.

RESULTS

A total of 1830 patients were enrolled into the BEST-CLI Trial. The demographics of the study population are shown in Table I. Completion of the HRQOL questionnaires occurred in the majority of patients. The Vascular Quality of Life Questionnaire (VASCQOL) was completed by 95% of patients and the EQ-5D and SF-12 were completed by 96%.

VASCQOL. The peripheral vascular disease-specific HRQOL assessment tool demonstrated that female sex, history of smoking, opioid use, and impaired ambulatory status were associated with significantly worse VASCQOL scores at presentation into the trial (Table II). Because all patients in BEST-CLI were suitable for surgery, comparing these populations at entry with surgical arms of the previous randomized CLI trials BASIL and PREVENT III was performed. The patients in BEST-CLI tended to have less severe VASCQOL scores (Table III). In the BASIL Trial, which randomized patients with CLI to open surgery versus EVT therapy, the baseline VASCQOL score for the surgical arm was 2.9 ± 1.1 , which trended lower than in the BEST-CLI trial, in which it was 3.1 ± 1.3 ($P = .07$).¹¹ However, patients in the surgical control arm of the PREVENT III trial presented with a mean score of 2.8 ± 1.1 , which was significantly lower compared with patients enrolled into BEST-CLI ($P < .001$).³

SF-12. The analysis of the more nonspecific health status measurement tool SF-12 demonstrated similar findings compared with the VASCQOL. The SF-12 cumulative index measurement, Short-form Six-Dimension health index-R2 (SF6DR-2), scores were significantly lower at presentation for female sex, history of smoking, opioid use, and impaired ambulation status (Table IV). Patients with previous contralateral major leg amputation (amputation at or above the ankle) actually had improved SF6DR scores. The SF6DR-2 is a composite index comprised of the physical health composite score (PCS) and the mental health composite score (MCS). When examined individually, the MCS was significantly

Table I. Demographic baseline characteristics – Best Endovascular versus Best Surgical Therapy in Patients with CLI (BEST-CLI)

Characteristic	Overall (n = 1830)
Age, years	67.3 \pm 9.8
Female	519 (28)
Non-Caucasian race	510 (28)
Ischemic rest pain alone	410 (22)
Tissue loss	1420 (78)
Bilateral CLI	290 (16)
Current/past year smoking	800 (44)
Major amputation nonindex leg	129 (7)
Prior intervention index leg	254 (14)
Diabetes	1261 (69)
End-stage renal disease	196 (11)

CLI, Chronic limb-threatening ischemia.
Values are mean \pm standard deviation or number (%).

lower for younger age, female sex, history of or active smoking and opioid use, and ambulatory status (Table V). The PCS was not significantly different for age or sex, but was significantly improved for Black race compared with White and significantly worse for smoking history, opioid use, and nonindependent ambulatory status (Table VI).

EQ-5D. Patients with bilateral CLI, a history of or active smoking, or impaired ambulatory status had worse EQ-5D scores (Table VII). There was no difference in EQ-5D based on patient sex.

DISCUSSION

CLI is characterized by severe pain and disability, as well as a limited life expectancy. Therapies typically revolve around revascularization using open, EVT, or hybrid approaches with associated wound care procedures for tissue loss. In the past, the success of such procedures has been measured using physician-centered outcomes, such as graft patency, limb salvage, and major adverse limb events. However, the goals of therapy are not just limb salvage, but also improvement in patient HRQOL to the greatest degree possible. Thus, patient-centered assessments of HRQOL are crucial to accurately determine the severity of symptoms important to patients and how various therapies can effectively address such symptoms.^{1,8} The importance of quantifying the patient's perception of their disease process and treatment is emphasized in The Global Vascular Guidelines on the Management of Chronic Limb-threatening Ischemia, which strongly recommend incorporating HRQOL instruments and patient-reported outcome measures into trial design.¹² The current study, BEST-CLI, not only uses the SF-12, but also the disease-specific VASCQOL and the generalized EQ-5D, both of which are also used in the Bypass vs Angioplasty in Severe Ischemia of the Leg

Table II. Multipredictor regression of overall vascular quality of life (VascQoL)

Predictors	Estimate	95% CI	P value
Race			
Black	0.18	(0.03 to 0.33)	.02
All other races	−0.36	(−0.57 to −0.14)	.001
White	Ref.		
Age ≥80 years	0.19	(−0.01 to 0.40)	.06
Male	0.18	(0.05 to 0.31)	.01
Heart failure	0.03	(−0.24 to 0.29)	.85
Above-ankle amp of nonindex limb	0.43	(0.19 to 0.67)	<.001
Bilateral CLI	−0.12	(−0.28 to 0.03)	.12
COPD	−0.12	(−0.30 to 0.06)	.18
Smoking			
Current or within past year	−0.63	(−0.79 to −0.46)	<.001
>1 year ago	−0.18	(−0.34 to −0.01)	.03
Never	Ref.		
ESRD	0.07	(−0.13 to 0.26)	.5
Hyperlipidemia	0.05	(−0.09 to 0.19)	.45
Diabetes	−0.12	(−0.27 to 0.04)	.14
Hypertension	−0.16	(−0.36 to 0.04)	.12
Tissue loss	0.01	(−0.13 to 0.16)	.89
Opiate use	−0.33	(−0.46 to −0.20)	<.001
Comorbidity index ^a	0.02	(−0.04 to 0.08)	.56
Ambulatory status			
Uses wheelchair/bed bound	−0.70	(−0.89 to −0.50)	<.001
Ambulatory with assistance	−0.49	(−0.63 to −0.36)	<.001
Ambulatory without assistance	Ref.		
Living home ^b	−0.15	(−0.40 to 0.10)	.23

CI, Confidence interval; CLI, chronic limb-threatening ischemia; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease. Parameter estimates of greater than 0 means higher Vascular Quality of Life Questionnaire score. Boldface entries indicate statistical significance.
^aComorbidity index was the sum of baseline diabetes, COPD, congestive heart failure, myocardial infarction, CAD, carotid artery disease, hypertension, stroke, transient ischemic attack, and peripheral artery disease.
^bPre-enrollment living status was categorized as living home versus all others (assisted living, nursing home, homeless, or hospital inpatient for a prolonged period).

Table III. *t* Test statistics comparing the mean difference of Best Endovascular versus Best Surgical Therapy in Patients with CLI (BEST-CLI) and Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL), and BEST-CLI and Prevention of Vein Graft Failure in Lower Extremity Bypass Surgery (PREVENT III)

	Mean	STD	No.	Mean difference	SE	<i>t</i> Test	DF	P value
BEST-CLI vs BASIL								
BEST-CLI	3.07	1.26	1735	0.170	0.092	1.846	1937	.07
BASIL	2.9	1.1	204	—	—	—	—	—
BEST-CLI vs PREVENT III								
BEST-CLI	3.07	1.26	1735	0.270	0.044	6.158	3029	<.001
PREVENT III	2.8	1.1	1296	—	—	—	—	—

(BASIL-2) and the Balloon vs Stenting in Severe Ischemia of the Leg (BASIL-3) Trials.¹²

Previous HRQOL work focused primarily on impact of revascularization procedures on improvement in HRQOL scores in patients with CLI.^{3,13,14} There is a considerably

smaller contemporary body of work identifying which patient characteristics predict poor HRQOL at presentation. It is clear that patients with CLI have a markedly impaired quality of life. In the current study, SF-12 scores were up to two standard deviations lower than the

Table IV. Multipredictor regression of utility index score (Short-form Six-Dimension health index-R2 [SF6D-R2])

Predictors	Estimate	95% CI	P value
Race			.003
Black	0.02	(0.00 to 0.03)	.02
All other races	−0.02	(−0.05 to −0.00)	.04
White	Ref.		
Age ≥80 years	0.02	(0.00 to 0.05)	.03
Male	0.03	(0.01 to 0.04)	<.001
Heart failure	−0.001	(−0.03 to 0.03)	.93
Above-ankle amp of nonindex limb	0.04	(0.01 to 0.06)	.003
Bilateral CLI	−0.01	(−0.03 to 0.01)	.28
COPD	−0.01	(−0.03 to 0.01)	.30
Smoking			<.001
Current or within past year	−0.05	(−0.07 to −0.03)	<.001
>1 year ago	−0.01	(−0.03 to 0.01)	.25
Never	Ref.		
ESRD	0.01	(−0.01 to 0.03)	.22
Hyperlipidemia	0.01	(−0.01 to 0.02)	.22
Diabetes	−0.003	(−0.02 to 0.01)	.73
Hypertension	−0.01	(−0.03 to 0.02)	.62
Tissue loss	0.01	(−0.01 to 0.02)	.44
Opiate use	−0.03	(−0.05 to −0.02)	<.001
Comorbidity index ^a	−0.002	(−0.01 to 0.00)	.57
Ambulatory status			<.001
Uses wheelchair/bed bound	−0.08	(−0.10 to −0.06)	<.001
Ambulatory with assistance	−0.05	(−0.07 to −0.04)	<.001
Ambulatory without assistance	Ref.		
Living home ^b	−0.0006	(−0.03 to 0.03)	.96

CI, Confidence interval; CLI, chronic limb-threatening ischemia; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease. Parameter estimates greater than 0 means higher SF6D-R2 score. Boldface entries indicate statistical significance.

^aComorbidity index was the sum of baseline diabetes, COPD, congestive heart failure, myocardial infarction, CAD, carotid artery disease; hypertension, stroke, transient ischemic attack, and peripheral artery disease.

^bPre-enrollment living status was categorized as living home vs all others (assisted living, nursing home, homeless, or hospital inpatient for prolonged period).

general US population.¹⁵ SF-12 scores in patients with CLI have been shown to be similar to patients suffering from cancer with multiple associated comorbidities.¹⁶ To put these findings into context the mean PCS score for the normal US population ages more than 60 years in 2018 was 46.5 ± 11.4 compared with 33.0 ± 8.5 for the entire cohort of patients enrolled in BEST-CLI. Similarly, the MCS score for the population aged more than 60 years was 52.9 ± 8.7 compared with 46.4 ± 12.0 in BEST-CLI.

Two large randomized CLI trials have examined the impact of CLI on HRQOL measures. PREVENT III was a large (1404 patients), multicenter, double-blind, randomized clinical trial evaluating the efficacy of intraoperative treatment of vein grafts with edifoligide to prevent vein graft failure in patients undergoing infrainguinal arterial reconstruction with vein grafts for CLI.³ The second trial is the UK-based, multicenter BASIL trial, was a randomized trial comparing the clinical usefulness and cost-

effectiveness of bypass surgery first with a balloon angioplasty-first revascularization strategy for CLI caused by infrainguinal disease.⁵ Both trials focused on the impact of revascularization on HRQOL measures and did not focus on patient characteristics that predicted lower HRQOL scores at baseline. The only HRQOL measure that was used in both studies was the VASCQOL. Patients enrolled in both BASIL and PREVENT III tended to have significantly lower baseline HRQOL scores as measured by the VASCQOL compared with patients enrolled in BEST-CLI (Table III). The reasons for the higher baseline HRQOL score in the BEST-CLI patients is unclear; all trials had similar inclusion and exclusion criteria. This improvement could be related to other factors, such as recent improvements in wound care, pain control, and medical management.

Important findings in the current study have identified numerous patient-specific characteristics that predict a

Table V. Multipredictor regression of the Short Form-12 (SF-12) mental health composite scale score (MCS)

Predictors	Estimate	95% CI	P value
Race			.10
Black	0.34	(−1.09 to 1.77)	.64
All other races	−2.14	(−4.24 to −0.04)	.05
White	Ref.		
Age ≥80 years	3.46	(1.48 to 5.43)	<.001
Male	2.95	(1.69 to 4.21)	<.001
Heart failure	0.40	(−2.15 to 2.96)	.76
Above-ankle amp of nonindex limb	2.62	(0.27 to 4.97)	.03
Bilateral CLI	−1.14	(−2.65 to 0.37)	.14
COPD	−0.76	(−2.51 to 0.98)	.39
Smoking			.002
Current or within past year	−2.74	(−4.34 to −1.13)	<.001
>1 year ago	−0.92	(−2.50 to 0.65)	.25
Never	Ref.		
ESRD	0.98	(−0.91 to 2.87)	.31
Hyperlipidemia	0.88	(−0.48 to 2.23)	.20
Diabetes	0.26	(−1.23 to 1.75)	.74
Hypertension	−1.14	(−3.08 to 0.80)	.25
Tissue loss	−0.49	(−1.90 to 0.93)	.50
Opiate use	−2.89	(−4.18 to −1.59)	<.001
Comorbidity index ^a	−0.20	(−0.82 to 0.41)	.52
Ambulatory status			<.001
Uses wheelchair/bed bound	−4.41	(−6.31 to −2.52)	<.001
Ambulatory with assistance	−2.99	(−4.28 to −1.71)	<.001
Ambulatory without assistance	Ref.		
Living home ^b	0.10	(−2.35 to 2.55)	.94

CI, Confidence interval; CLI, chronic limb-threatening ischemia; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease. Parameter estimates greater than 0 means higher SF-12 score. Boldface entries indicate statistical significance.
^aComorbidity index was the sum of baseline diabetes, COPD, congestive heart failure, myocardial infarction, CAD, carotid artery disease, hypertension, stroke, transient ischemic attack, and peripheral artery disease.
^bPre-enrollment living status was categorized as living home vs all others (assisted living, nursing home, homeless, or hospital inpatient for prolonged period).

significant negative impact of CLI on patients HRQOL at presentation that were found in two or more of the surveys conducted in the trial. These factors include female sex, history of smoking, and opioid use, which were identified in both the vascular disease-specific VASCQOL and the generic SF-12 as having significantly worse scores at enrollment into the trial. Additionally, impaired ambulation was associated with worse scores in all three instruments used to measure HRQOL. Interestingly, although patients with contralateral CLI had worse HRQOL scores as measured by EQ-5D, patients with previous contralateral major leg amputation (amputation at or above the ankle) actually had improved HRQOL as measured by both the VASCQOL and the SF6DR-2. The cause for this finding is unclear and warrants further investigation. The association of HRQOL measures with hemodynamic such as the ankle-brachial index, toe-brachial index, pulse volume recordings, and transcutaneous partial

pressure of oxygen is difficult to determine owing to the heterogeneity of studies used to confirm CLI in a real-world study such as BEST-CLI.

Previous work has shown that female sex is associated with worse quality-of-life scores at presentation with CLI.⁴ This finding was also confirmed in the current study in which female sex was associated with lower VASCQOL and SF-12 scores. The SF-12 is composed of a PCS and an MCS. In previous CLI Trials HRQOL measurements using either the SF-12 or SF-36, the PCS scores were typically lower owing to impaired walking ability, bodily pain, and wound-related issues. In the current study, of the patient characteristics identified with lower overall SF-12 scores, female sex was the only variable in which the PCS scores were not different and the lower SF-12 score was driven by a dramatic decrease in the MCS component. The MCS includes measurements of vitality, social functioning, and mental health. It is unclear whether

Table VI. Multipredictor regression of the Short Form 12 (SF-12) Physical Health Composite Scale Score (PCS)

Predictors	Estimate	95% CI	P value
Race			.01
Black	1.51	(0.49 to 2.52)	.004
All other races	−0.48	(−1.97 to 1.01)	.53
White	Ref.		
Age ≥80 years	0.29	(−1.11 to 1.69)	.68
Male	0.37	(−0.53 to 1.26)	.42
Heart failure	−0.62	(−2.43 to 1.19)	.50
Above-ankle amp of nonindex limb	1.03	(−0.63 to 2.70)	.22
Bilateral CLI	−0.48	(−1.56 to 0.59)	.38
COPD	−0.59	(−1.83 to 0.65)	.35
Smoking			<.001
Current or within past year	−2.61	(−3.75 to −1.47)	<.001
>1 year ago	−0.08	(−1.19 to 1.04)	.90
Never	Ref.		
ESRD	−0.32	(−1.66 to 1.02)	.64
Hyperlipidemia	−0.03	(−0.99 to 0.93)	.95
Diabetes	−0.92	(−1.97 to 0.14)	.09
Hypertension	−0.41	(−1.79 to 0.96)	.56
Tissue loss	0.73	(−0.28 to 1.73)	.16
Opiate use	−1.19	(−2.11 to −0.27)	.01
Comorbidity index ^a	−0.23	(−0.66 to 0.21)	.30
Ambulatory status			<.001
Uses wheelchair/bed bound	−4.54	(−5.88 to −3.19)	<.001
Ambulatory with assistance	−3.16	(−4.07 to −2.24)	<.001
Ambulatory without assistance	Ref.		
Living home ^b	0.56	(−1.19 to 2.30)	.53

CI, Confidence interval; CLI, chronic limb-threatening ischemia; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease. Parameter estimates greater than 0 means higher PCS score.

Boldface entries indicate statistical significance.

^aComorbidity index was the sum of baseline diabetes, COPD, congestive heart failure, myocardial infarction, CAD, carotid artery disease; hypertension, stroke, transient ischemic attack, and peripheral artery disease.

^bPre-enrollment living status was categorized as living home vs all others (assisted living, nursing home, homeless, or hospital inpatient for prolonged period).

the decrease in the VASCQOL and SF-12 scores associated with female sex is due to a more virulent form of CLI or could be related to presentation at a later stage of the disease process in women. Previous work in other disease processes has shown that elderly females frequently lack the family and social support mechanisms available to men and that they frequently seek medical attention at more advanced stages of disease.¹⁷ This concept is supported by data in the present trial, which show a decrease in the MCS of the SF-12 as the main driver of decreased HRQOL in women. Further studies need to be completed to focus on why female sex is associated with decreased HRQOL at presentation and in particular what strategies can be developed to improve the MCS scores in this patient population.

In the current study, patients with a previous history of smoking had lower HRQOL scores compared with never smokers. Previous work has shown that the magnitude

of the negative relationship between smoking and lower QOL is related to the number of cigarettes smoked. Smoking cessation has been shown to improve HRQOL significantly, regardless of socioeconomic class. Smoking is also associated with multiple comorbidities, including chronic obstructive pulmonary disease and several types of cancers that can affect QOL. Numerous smoking cessation strategies exist and should be used to treat this modifiable risk factor for poor HRQOL.

Patients with opiate use had significantly worse HRQOL scores at presentation. The use of opiates is likely a marker for the severity of CLI and may be associated with significant side effects, such as sedation, nausea, constipation, and physical dependence, all of which can impact QOL. Treatment strategies should be directed at minimizing opiate use through alternative pharmacologic pain management strategies as well as revascularization.

Table VII. Multipredictor Regression of European Quality of Life 5D (EQ-5D) health status

Predictors	Estimate	95% CI	P value
Race			.11
Black	2.37	(−0.25 to 4.98)	.08
All other races	−1.57	(−5.41 to 2.26)	.42
White	Ref.		
Age ≥80 years	2.94	(−0.68 to 6.55)	.11
Male	0.81	(−1.50 to 3.11)	.49
Heart failure	−2.61	(−7.27 to 2.06)	.27
Above-ankle amp of nonindex limb	3.06	(−1.20 to 7.33)	.16
Bilateral CLI	−3.96	(−6.74 to −1.18)	.01
COPD	−1.66	(−4.85 to 1.54)	.31
Smoking			.005
Current or within past year	−3.39	(−6.33 to −0.44)	.02
More than 1 year ago	0.55	(−2.34 to 3.44)	.71
Never	Ref.		
ESRD	−2.61	(−6.06 to 0.84)	.14
Hyperlipidemia	0.86	(−1.62 to 3.34)	.5
Diabetes	−0.99	(−3.71 to 1.74)	.48
Hypertension	−0.99	(−4.55 to 2.56)	.58
Tissue loss	−0.43	(−3.02 to 2.15)	.74
Opiate use	−2.67	(−5.05 to −0.30)	.03
Comorbidity index ^a	−1.20	(−2.32 to −0.07)	.04
Ambulatory status			<.001
Uses wheelchair/bed bound	−6.37	(−9.83 to −2.90)	<.001
Ambulatory with assistance	−3.25	(−5.60 to −0.90)	.01
Ambulatory without assistance	Ref.		
Living home ^b	3.10	(−1.41 to 7.60)	.18

CI, Confidence interval; CLI, chronic limb-threatening ischemia; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease. Parameter estimates greater than 0 means higher EQ-5D health status. Boldface entries indicate statistical significance.
^aComorbidity index was the sum of baseline diabetes, COPD, congestive heart failure, myocardial infarction, CAD, carotid artery disease, hypertension, stroke, transient ischemic attack, and peripheral artery disease.
^bPre-enrollment living status was categorized as living home vs all others (assisted living, nursing home, homeless, or hospital inpatient for prolonged period).

Factors related to independence (such as lack of independent ambulation) were associated with decreased HRQOL scores in all three instruments and were also associated with lower PCS and MCS scores. It is remarkable that the lack of independent ambulation predicted impaired HRQOL, whereas contralateral leg amputation and independent living status were not associated with lower HRQOL scores. Extent of tissue loss and frailty are two common causes of nonambulation in patients with CLI. Treatment options tailored to patients with foot wounds include wound off-loading and aggressive revascularization to expedite ambulation. Meeting the needs of this particular group of patients may result in the greatest HRQOL gains.

Subsequent reports from BEST-CLI will examine improvements in QOL after intervention. These articles will not have the same level of detail as the current study

regarding patient-specific factors that affect QOL in CLI. The current data will serve as a useful benchmark for HRQOL in CLI using numerous patient-reported outcome measures with more than 95% of patients responding. These data can be used to develop performance goals for future CLI trials and will be useful to investigators planning future CLI trials.

CONCLUSIONS

Patients with CLI entering the BEST-CLI trial have very low HRQOL scores. This finding is particularly true for female sex, as well as a history of smoking, opioid use, and nonindependent ambulatory status. These data are meant to serve as a contemporary baseline of HRQOL in CLI. In addition, by quantifying factors associated with worse HRQOL, physicians can focus on the management of identifiable risk factors, such as smoking,

nonindependent ambulation, and opiate use, as well as prioritize future research into the reasons certain risk factors such as female gender are associated with poor QOL.

AUTHOR CONTRIBUTIONS

Conception and design: RP, NC, MIC, MM, KR, AF

Analysis and interpretation: RP, NC, MIC, MC, KG, TH, MM, KR, VR, JS, MIS, MVO, MV, CW, AF

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