Endovascular-first approach is not associated with worse amputation-free survival in appropriately selected patients with critical limb ischemia

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Objective: **Endovascular interventions for critical limb ischemia are associated with inferior limb salvage (LS) rates in most randomized trials and large series. This study examined the long-term outcomes of selective use of endovascular-first (endo-first) and open-first strategies in 302 patients from March 2007 to December 2010.**

Methods: **Endo-first was selected if (1) the patient had short (5-cm to 7-cm occlusions or stenoses in crural vessels); (2) the disease in the superficial femoral artery was limited to TransAtlantic Inter-Society Consensus II A, B, or C; and (3) no impending limb loss. Endo-first was performed in 187 (62%), open-first in 105 (35%), and 10 (3%) had hybrid procedures.**

Results: **The endo-first group was older, with more diabetes and tissue loss. Bypass was used more to infrapopliteal targets (70% vs 50%, $P = .031$). The 5-year mortality was similar (open, 48%; endo, 42%; $P = .107$). Secondary procedures (endo or open) were more common after open-first (open, 71 of 105 [68%] vs endo, 102 of 187 [55%]; $P = .029$). Compared with open-first, the 5-year LS rate for endo-first was 85% vs 83% ($P = .586$), and amputation-free survival (AFS) was 45% vs 50% ($P = .785$). Predictors of death were age >75 years (hazard ratio [HR], 3.3; 95% confidence interval [CI], 1.7-6.6; $P = .0007$), end-stage renal disease (ESRD) (HR, 3.4; 95% CI, 2.1-5.6; $P < .0001$), and prior stroke (HR, 1.6; 95% CI, 1.03-2.3; $P = .036$). Predictors of limb loss were ESRD (HR, 2.5; 95% CI, 1.2-5.4; $P = .015$) and below-the-knee intervention ($P = .041$). Predictors of worse AFS were older age (HR, 2.03; 95% CI, 1.13-3.7; $P = .018$), ESRD (HR, 3.2; 95% CI, 2.1-5.11; $P < .0001$), prior stroke ($P = .0054$), and gangrene ($P = .024$).**

Conclusions: **At 5 years, endo-first and open-first revascularization strategies had equivalent LS rates and AFS in patients with critical limb ischemia when properly selected. A patient-centered approach with close surveillance improves long-term outcomes for both open and endo approaches. (J Vasc Surg 2014;59:392-9.)**

Endovascular interventions for critical limb ischemia (CLI) are viewed as an inferior long-term alternative to open revascularization, especially when autologous saphenous vein is available.[1,2] Open bypass, however, can be detrimental to those with reduced life expectancy from severe comorbidities or with diminished quality of life.[3] Furthermore, patients undergoing open revascularization are at significant risk for perioperative morbidity and mortality.[4]

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The technological growth during the past few years has led to wide adoption of complex endovascular approaches (eg, infrapopliteal stenting, tibial atherectomy, retrograde tibial access) by most interventionalists, including vascular surgeons.[5-9] Selecting the appropriate method of revascularization should be based on the individual characteristics of each patient (anatomy, comorbidities, extent of tissue loss, expected benefits in functional status), operator skill level, and institutional algorithms.

We use an endovascular-first (endo-first) approach based on patient-centered criteria. Patients with CLI were offered revascularization based on lesion characteristics and distribution as well as medical comorbidities, with a preference for endo-first interventions. The goal of this study was to determine predictors and 5-year rates of survival, limb salvage (LS), and amputations-free survival (AFS) between endo-first patients and open-first patients within our institution since the patient-centered approach was incorporated.

METHODS

The New York University School of Medicine Institutional Review Board approved this study.

Study sample and data collection. From March 2007 to December 2010, endo-first was selected if (1) the patient had short (5-cm to 7-cm occlusions or stenoses in crural vessels); (2) the disease in the superficial femoral artery (SFA) was limited to TransAtlantic Inter-Society Consensus (TASC) II A, B, or C; and (3) no impending limb loss. Patients with significant medical comorbidities were also offered endo-first, particularly those with TASC II B and selected C lesions. Endo-first was not used for TASC II D lesions. Patients with long-segment occlusions (ie, TASC II C and D lesions) with acceptable perioperative risk were offered open revascularization.

Demographics, comorbidities, Rutherford classification, prior procedures, secondary open or endovascular interventions, and the most distal target for revascularization were analyzed. All patients met the criteria for chronic CLI, defined as rest pain, ulceration, or gangrene. Rest pain was defined as Rutherford class IV disease, tissue loss as class V disease, and gangrene as class VI.

The procedures analyzed for primary and secondary interventions were one or a combination of the following: percutaneous transluminal angioplasty, with or without atherectomy/stenting, infrainguinal bypass grafting, and open bypass thrombectomy. If patients presented with a prior procedure performed at another facility, it must have occurred within the timeframe of the study for the patient to be considered. Excluded from the study were patients who underwent primary amputation, hybrid procedures, or those with acute limb ischemia. Amputation was defined as a below-knee or above-knee amputation.

Study end points. The 5-year rates of survival, LS, and AFS between the two groups were compared.

Technique for endovascular and open procedures. Patients typically received 100 U/kg of heparin after sheath placement. Clopidogrel bisulfate (300 mg) was started in the recovery room and maintained (75 mg daily) for 6 weeks. Lifelong enteric-coated acetylsalicylic acid (81 mg) was also given.

The lesions were crossed using Glidewire (Terumo Medical Corp, Somerset, NJ) and catheters without intentionally using a subintimal approach. Routine nitinol-based stenting was used in SFA occlusions >5 cm; however, selective stenting was used for TASC II A lesions. A prolonged inflation time, between 30 seconds and 1 minute, was used for infrapopliteal lesions, with selective off-label use of balloon-expandable, drug-eluting coronary stenting for flow-limiting dissections or significant recoil after angioplasty. For patients with SFA disease or more proximal disease with concurrent infrapopliteal disease, initial treatment was directed toward improving inflow. Debulking (Foxhollow, Plymouth, Minn) was used as an adjunctive procedure initially and became more mainstream, especially in recent years in the infrapopliteal distribution. Similarly, complex tibial interventions (retrograde pedal access, buddy wire techniques with multiple infrapopliteal vessel recanalization) were used increasingly in later years.

Above-knee femoropopliteal bypasses were preferentially performed using prosthetic grafts. All infrageniculate bypasses were preferentially performed using autologous veins, and all patients underwent vein mapping.

Table I. Demographics, comorbidities, and Rutherford classification of the study population (N = 292) by initial open or endovascular (*endo*) procedure

Variable	*Initial open (n = 105)*	*Initial endo (n = 187)*	P
Age, years			
Mean ± SD	74.1 ± 11.5	75.5 ± 11.6	.301[a]
Range	32-94	42-97	
Sex			
Male	59 (56)	85 (45)	.078[b]
Female	46 (44)	102 (55)	
Smoker	14 (13)	25 (13)	.993[b]
Type 2 diabetes	54 (54)	134 (72)	.0027[b]
Hypertension	77 (73)	146 (78)	.360[b]
CAD	51 (49)	88 (47)	.804[b]
ESRD	16 (15)	27 (14)	.853[b]
CVA	29 (28)	61 (33)	.375[b]
Previous CABG	27 (26)	37 (20)	.240[b]
Rest pain	59 (56)	68 (36)	.0010[b]
Ulcer	52 (50)	127 (68)	.0020[b]
Gangrene	39 (27)	94 (50)	.031[b]
Above-knee intervention	32 (30)	107 (57)	<.0001[b]

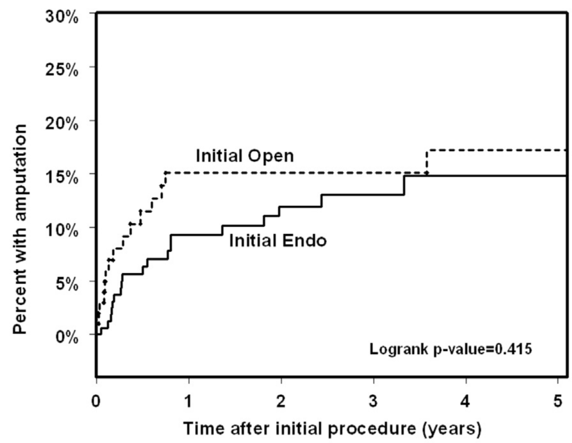
CABG, Coronary artery bypass grafting; *CAD,* coronary artery disease; *CVA,* cerebrovascular accident; *ESRD,* end-stage renal disease; *SD,* standard deviation.
Data are presented as number (%) unless otherwise indicated.
[a]Determined by two-sample *t*-test.
[b]Determined by χ^2 test.

All patients were followed up postoperatively, and at 3 months, 6 months, and every 6 months thereafter for ankle-brachial index measurements, graft or stent velocities, and duplex imaging.

Statistical analysis. Descriptive statistics, such as the calculation of means with standard deviations and percentages, were used to summarize the study population. The percentage of patients with each type of procedure (including the various combinations of initial and secondary procedures) was calculated. Patient characteristics, including demographics, comorbidities, and Rutherford classification, were compared between patients who had an initial open procedure and patients who had an initial endovascular procedure. The rate of each outcome (LS, amputation, AFS, and death) was calculated for the study population. The association between procedure type and LS was analyzed using χ^2 tests and multiple logistic regression analysis. For amputation, AFS, and death, Kaplan-Meier with log-rank tests and Cox regression were used to account for differential length of follow-up. Similar analyses were conducted to determine if demographics, comorbidities, or Rutherford classification, alone or combined, were associated with outcomes. All tests were two-sided, and values of $P < .05$ were considered significant. SAS 9.3 software (SAS Institute, Cary, NC) was used for statistical analysis.

RESULTS

Demographics. During the study period, 302 patients underwent infrainguinal revascularization and were included



Kaplan-Meier estimates and 95% confidence intervals for time until amputation after initial procedure between patients with Initial Open (n=102) and patients with Initial Endo (n=170)

	Time after initial procedure (years)				
	1	2	3	4	5
Initial Open (n=102)					
% with amputation	15%	15%	15%	17%	17%
95% CI	[8%-22%]	[8%-22%]	[8%-22%]	[9%-25%]	[9%-25%]
N at risk	69	64	45	32	13
Initial Endo (n=170)					
% with amputation	9%	12%	13%	15%	15%
95% CI	[5%-14%]	[7%-17%]	[7%-19%]	[8%-21%]	[8%-21%]
N at risk	115	98	55	31	11

Logrank p-value=0.415

Fig 1. Kaplan-Meier analysis shows time until amputation in patients after an initial open procedure (n = 102) compared with patients after an initial endovascular (*endo*) procedure (n = 170). *CI,* Confidence interval.

in this analysis. A total of 187 patients (62%) underwent endo-first, and 105 (35%) had initial open procedures. Ten patients (3%) had combined (hybrid) procedures and were excluded from our analysis. Patients in the endo-first group were more likely to be diabetic (77% vs 54%; $P = .0041$) and to present with ulcer (70% vs 50%; $P = .011$) or gangrene (50% vs 27%; $P = .031$). Patients in the initial open group were more likely to present with rest pain (56% vs 36%; $P = .001$). Patients in the endo-first group were more likely to receive above-knee interventions (57% vs 30%; $P \le .0001$). No difference was found between two groups with respect to age, sex, active smoking status, hypertension, coronary artery disease, end-stage renal disease (ESRD), cerebrovascular accident (CVA), and previous coronary artery bypass grafting (Table I). No patients died in the perioperative period.

LS. At 5 years, no difference was found in LS between endo-first (85%; 95% confidence interval [CI], 79%-92%) and initial open (83%; 95% CI, 75%-91%; Fig 1). In the unadjusted Cox regression model, procedure type was not associated with LS ($P = .415$). After controlling for ESRD and Rutherford classification, procedure type was still not associated with LS ($P = .586$).

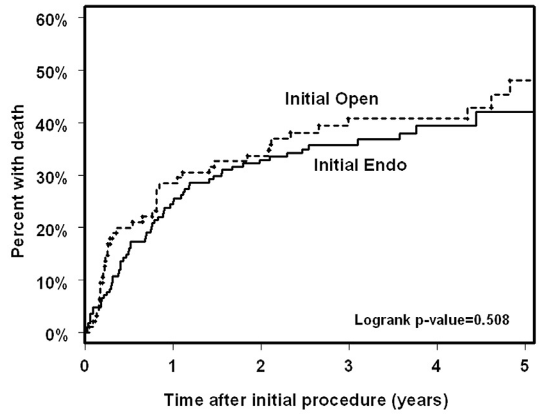
Survival. At 5 years, no difference was found in survival rates between endo-first (58%; 95% CI, 49%-67%) and initial open (52%; 95% CI, 40%-64%; Fig 2). In the unadjusted Cox regression model, procedure type was not associated with survival ($P = .508$). After controlling for age, ESRD, CVA, and Rutherford classification, endo-first demonstrated a trend toward improved survival benefit; however, this finding was not statistically significant (odds ratio, 1.40; 95% CI, 0.93-2.09; $P = .107$).

AFS. At 5 years, no difference was found between endo-first (55%; 95% CI, 44%-66%) and initial open (50%; 95% CI, 39%-62%; Fig 3). In the unadjusted Cox regression model, procedure type was not associated with AFS ($P = .548$). After controlling for age, ESRD, CVA, and Rutherford classification, procedure type was still not statistically significant ($P = .785$).

Independent predictors of survival, LS, and AFS. ESRD was a predictor of worse LS (odds ratio, 2.5; $P = .028$), survival (hazard ratio [HR], 3.5; $P < .0001$), and AFS (HR, 3.26; $P < .0001$). Age predicted worse survival in those aged 75 to 84 years (HR, 3.30; $P = .0007$) and ≥85 years (HR, 5.34; $P < .0001$). Similarly, ages 75 to 84 (HR, 2.03; $P = .018$) and ≥85 (HR, 4.35; $P < .0001$) predicted worse AFS. Prior stroke predicted worse survival (HR, 1.55; $P = .036$). Patients undergoing above-knee interventions were more likely to have LS (HR, 2.17; $P = .041$; Tables II-VI).

DISCUSSION

By individualizing open revascularization and endovascular therapy based on patient and lesion characteristics,

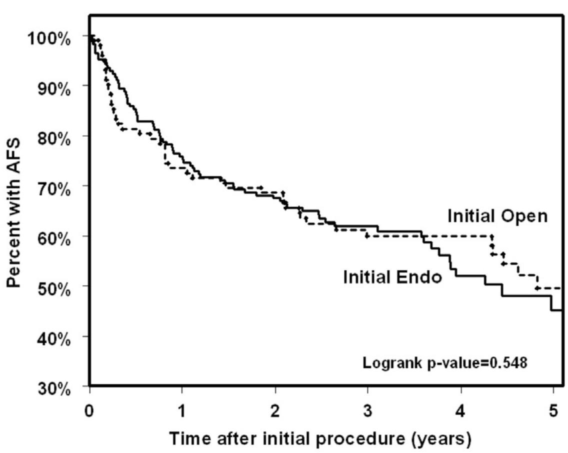


Kaplan-Meier estimates and 95% confidence intervals for time until death after initial procedure between patients with Initial Open (n=95) and patients with Initial Endo (n=168)

	Time after initial procedure (years)				
	1	2	3	4	5
Initial Open (n=95) % with death 95% CI N at risk	28% [19%-37%] 68	34% [24%-43%] 63	41% [31%-51%] 43	41% [31%-51%] 32	48% [36%-60%] 14
Initial Endo (n=168) % with death 95% CI N at risk	25% [18%-32%] 126	33% [26%-40%] 110	36% [28%-43%] 63	39% [31%-48%] 36	42% [33%-51%] 15

Logrank p-value=0.508

Fig 2. Kaplan-Meier analysis shows time until death in patients after an initial open procedure (n = 95) compared with patients after an initial endovascular (*endo*) procedure (n = 168). *CI,* Confidence interval.



Kaplan-Meier estimates and 95% confidence intervals for time with AFS after initial procedure between patients with Initial Open (n=102) and patients with Initial Endo (n=170)

	Time after initial procedure (years)				
	1	2	3	4	5
Initial Open (n=102) % with AFS 95% CI N at risk	74% [65%-82%] 75	69% [60%-78%] 70	60% [50%-70%] 47	60% [50%-70%] 35	50% [38%-61%] 14
Initial Endo (n=170) % with AFS 95% CI N at risk	75% [69%-82%] 128	68% [60%-75%] 112	62% [54%-69%] 65	52% [43%-61%] 37	45% [34%-56%] 15

Logrank p-value=0.548

Fig 3. Kaplan-Meier analysis shows time with amputation-free survival (*AFS*) in patients after an initial open procedure (n = 102) compared with patients after an initial endovascular (*endo*) procedure (n = 170). *CI,* Confidence interval.

Table II. Bivariate association of demographics, comorbidities, Rutherford classification, and procedure type with outcomes limited to those with an initial open or initial endovascular (*endo*) procedure (N = 292[a])

		LS		*Amputation*		*Death*			*AFS*		
Variable	*No.*	*%*	P	*1-year, %*	P	*1-year, %*	*3-year, %*	P	*1-year, %*	*3-year, %*	P
Age, years											
<65	52	83	.408[b]	17	.417[d]	17	24	<.0001[d]	84	79	<.0001[d]
65-74	75	85		13		14	22		86	79	
75-84	105	91		9		27	43		74	68	
≥85	60	87		8		50	63		51	42	
Sex											
Male	144	85	.333[b]	14	.164[d]	29	38	.918[d]	72	67	.740[d]
Female	148	89		8		24	38		77	69	
Smoker											
Yes	39	92	.440[c]	3	.387[d]	25	33	.666[d]	75	67	.565[d]
No	253	87		13		26	38		75	68	
Type 2 diabetes											
Yes	191	86	.506[b]	12	.554[d]	27	38	.810[d]	75	69	.967[d]
No	101	89		10		26	38		75	66	
Hypertension											
Yes	223	88	.602[b]	10	.433[d]	27	39	.379[d]	74	67	.530[d]
No	69	86		15		25	34		77	70	
CAD											
Yes	139	88	.829[b]	11	.777[d]	28	42	.340[d]	74	67	.799[d]
No	153	87		12		25	34		76	69	
ESRD											
Yes	43	77	.024[b]	23	.0040[d]	49	69	.0001[d]	55	45	<.0001[d]
No	249	89		10		22	33		78	72	
CVA											
Yes	90	88	.878[b]	12	.743[d]	39	53	.0015[d]	63	55	.0054[d]
No	202	87		11		21	31		80	74	
Previous CABG											
Yes	64	84	.422[b]	11	.339[d]	25	35	.676[d]	77	70	.530[d]
No	228	88		12		27	39		74	67	
Rest pain											
Yes	127	86	.499[b]	14	.369[d]	27	35	.598[d]	74	69	.640[d]
No	165	88		9		26	40		75	68	
Ulcer											
Yes	179	88	.806[b]	10	.932[d]	26	39	.641[d]	74	67	.440[d]
No	113	87		14		26	35		75	70	
Gangrene											
Yes	133	84	.143[b]	15	.094[d]	33	44	.068[d]	69	62	.024[d]
No	159	90		9		21	33		79	73	
Above-knee intervention											
Yes	139	91	.048[b]	7	.017[d]	30	41	.433[d]	70	64	.674[d]
No	153	84		16		22	35		79	72	

AFS, Amputation-free survival; *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *CVA,* cerebrovascular accident; *ESRD,* end-stage renal disease; *LS,* limb salvage.
[a]Overall n = 272 for the analysis of amputation, overall n = 263 for the mortality analysis, and overall n = 272 for the AFS analysis.
[b]Determined by χ^2 test.
[c]Determined by the Fisher exact test.
[d]Determined by log-rank test.

we were able to achieve favorable outcomes in the two treatment groups at 5 years for overall survival, LS, and AFS. The two patient groups were different at baseline, with a higher prevalence of diabetes and above-knee interventions in the endo-first cohort. Indications for intervention differed, with a higher prevalence of rest pain in the open-first cohort, and a higher prevalence of ulcer or gangrene in the endo-first group. An endo-first approach was preferentially used to treat short-segment lesions in the femoropopliteal segments and crural vessels. At 5 years, the primary end points were similar between the two patient cohorts. A comparison of patients undergoing endo-first vs an open-first approach found overall survival was 58% vs 52%, respectively; LS was 85% vs 82%, respectively; and AFS was 55% vs 50%, respectively. ESRD was a predictor of limb loss and death. Older patients had a lower AFS, whereas above-knee interventions were associated with a higher LS rate. The two groups were dissimilar owing to our patient-centered approach, making it unfair to draw outright comparisons; however, our

Table III. Independent predictors of limb salvage (LS)

Predictor	*OR (95% CI)*	*P*
ESRD		
Yes	0.40 (0.18-0.90)	.028
No	Reference	

CI, Confidence interval; *ESRD,* end-stage renal disease; *OR,* odds ratio.

Table IV. Independent predictors of time until amputation

Predictor	*HR (95% CI)*	*P*
ESRD		
Yes	2.54 (1.20-5.39)	.015
No	Reference	
Above-knee intervention		
Yes	0.46 (0.22-0.97)	.041
No	Reference	

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

outcomes are comparable with other studies reported in the literature.

Dosluoglu et al[10] undertook a methodical approach similar to ours. They reported 514 limbs in 433 patients in Veterans Affairs hospital spanning 8 years. At 5 years, the LS rate was 78% in both cohorts, with no difference in AFS or overall survival. Although there was no difference in 5-year primary patency, the assisted primary patency and secondary patency were improved in the endovascular group compared with the open group: 70% vs 59% (P = .037) and 73% vs 64% (P = .022), respectively. The authors concluded that the endovascular group consisted of medically higher-risk patients whereas the bypass group had complex multilevel disease that required more infrapopliteal interventions. Overall, by individualizing treatment based on patient characteristics, the authors were able to achieve comparable outcomes with acceptable LS.

Kudo et al[9] reported a 12-year experience with CLI. They used an open-first and endo-first in a complementary fashion, guided by a patient-centered approach. Despite a significant shift toward endovascular interventions, they noted no difference in long-term outcomes. Similarly, Soga et al[11] reported their outcomes from a retrospective registry consisting of 460 limbs with CLI with de novo infrainguinal lesions. Patients were grouped by those undergoing bypass surgery or endovascular therapy. At 3 years, they reported no difference in AFS, LS, or overall survival.[11]

Conrad et al[12] identified 447 limbs in 409 patients who underwent interventions for CLI, of which 16% were limited to crural vessels, 38% had multilevel interventions, and the SFA was treated in 56% of limbs. Their mean follow-up was 28 months (range, 8-83 months). At 5 years, they reported a primary patency of 31%, assisted patency of 75%, overall survival of 39%, and LS of 74%.[12] On multivariate analysis, female gender, poor runoff, and dialysis

Table V. Independent predictors of time until death

Predictor	*HR (95% CI)*	*P*
Age, years		
<65	Reference	
65-74	1.30 (0.60-2.83)	.506
75-84	3.30 (1.65-6.61)	.0007
≥85	5.34 (2.60-10.99)	<.0001
ESRD		
Yes	3.43 (2.09-5.64)	<.0001
No	Reference	
CVA		
Yes	1.55 (1.03-2.32)	.036
No	Reference	

CI, Confidence interval; *CVA,* cerebrovascular accident; *ESRD,* end-stage renal disease; *HR,* hazard ratio.

Table VI. Independent predictors of time with amputation-free survival (AFS)

Predictor	*HR (95% CI)*	*P*
Age, years		
<65	Reference	
65-74	1.18 (0.63-2.24)	.602
75-84	2.03 (1.13-3.66)	.018
85+	4.35 (2.37-7.96)	<.0001
ESRD		
Yes	3.26 (2.08-5.11)	<.0001
No	Reference	

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

dependence were associated with increased risk of limb loss. They conclude that despite a low primary patency, excellent LS rates can be achieved with close follow-up and secondary interventions, lending further support for an endo-first approach in appropriately selected patients.

An important predictor of treatment outcomes is lesion characteristics. Using TASC II, Giles et al[13] justified an endo-first approach for CLI with close follow-up. They reported an excellent LS rate of 84% at 3 years, with poorer technical success in treating TASC D lesions of 75% vs 100% for TASC A, B, or C ($P < .001$).[13] In a follow-up study from the same institution, unsuitability for bypass and TASC D lesions were associated with increased risk of amputation, whereas TASC A, B, and C lesions can safely be treated using an endo-first approach.[14]

Although the aforementioned single-institution studies report promising results, the only randomized study to date, the Bypass vs Angioplasty in Severe Ischaemia of the Leg (BASIL) trial, found that at 2 years, the primary outcomes of death and amputation between the two treatment groups were comparable.[15] However, among patients surviving >2 years, those undergoing a bypass had superior overall survival and a trend toward improved AFS.[16] The AFS rate was >50% in both groups at the study end point. Outcomes from the BASIL trial suggest the superiority of open surgery for CLI and have influenced contemporary guidelines in approaching CLI; however, treatment strategies are best individualized when managing this group of patients.

Comorbid conditions have a significant affect on LS and mortality. Our findings corroborate other studies that have demonstrated poor outcomes in patients with ESRD.[17-20] In addition, the level of intervention affects LS rates, with significantly higher limb loss associated with infrapopliteal interventions than with above-knee interventions.[21,22]

Our study has the limitations associated with being a single-institution retrospective study. The two groups were different by design, with differences in comorbidities as well as in characteristics, thus making it difficult to directly compare the two groups. A well-designed randomized study would best address the efficacy of an endovascular or open approach to treating CLI, but the difficulty remains in the design of such a trial. Patients with CLI have significant comorbidities and variable distribution of disease, making randomization of two similar cohorts an arduous if not impossible task. Furthermore, as suggested by recent studies, there may be merit in individualizing treatment strategies rather than in using a single approach.

CONCLUSIONS

CLI arises in a sick cohort of patients with multiple medical comorbidities who, despite adequate therapy, remain at a high risk for limb loss and poor overall survival.[23,24] Deciding the appropriate treatment approach in such a population is critical to minimizing morbidity while optimizing outcomes. Although endovascular interventions have gained widespread acceptance in treating CLI, we believe they have been used indiscriminately at times. This may have led to poorer outcomes when compared head-to-head with open bypass, especially in case-cohort studies. Our experience adds to the growing body of literature in support of an endo-first approach in appropriately selected patients.

AUTHOR CONTRIBUTIONS

Conception and design: FV, FM
Analysis and interpretation: KG, FM, MA, CB, TM
Data collection: PK, RM
Writing the article: KG, FM, FV, PK, RM
Critical revision of the article: KG, FM, FV, CR, MA, TM
Final approval of the article: KG, FM, PK, RM, CB, MA, TM, FV
Statistical analysis: KG, FM
Obtained funding: FM
Overall responsibility: FM
PK and RM contributed equally to the manuscript.

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