

One-Year Outcomes of Peripheral Endovascular Device Intervention in Critical Limb Ischemia Patients: Sub-Analysis of the LIBERTY 360 Study

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Background: High-risk patients with advanced peripheral artery disease (PAD), including critical limb ischemia (CLI), are often excluded from peripheral endovascular device intervention clinical trials, leading to difficulty in translating trial results into real-world practice. There is a need for prospectively assessed studies to evaluate peripheral endovascular device intervention outcomes in CLI patients.

Methods: LIBERTY 360 is a prospective, observational, multi-center study designed to evaluate the procedural and long-term clinical outcomes of peripheral endovascular device intervention in real-world patients with symptomatic lower-extremity PAD. One thousand two hundred and four patients were enrolled and stratified based on Rutherford Classification (RC): RC2-3 (N=501), RC4-5 (N=603), and RC6 (N=100). For this sub-analysis, RC5 and RC6 patients (RC5-6; N=404) were pooled and 1-year outcomes were assessed.

Results: Procedural complications rarely (1.7%) resulted in post-procedural hospitalization and 89.1% of RC5-6 patients were discharged to home. Considering the advanced disease state in RC5-6 patients, there was a high freedom from 1-year major adverse event rate of 65.5% (defined as target vessel revascularization, death to 30 days, and major target limb amputation). At 1 year, freedom from major amputation was 89.6%. Wounds identified at baseline on the target limb had completely healed in 172/243 (70.8%) of the RC5-6 subjects by 1 year. Additionally, the overall quality of life, as measured by VasuQoL, improved from baseline to 1 year.

Conclusion: LIBERTY investigated real-world PAD patients with independent oversight of outcomes. This analysis of LIBERTY RC5-6 patients demonstrates that peripheral endovascular device intervention can be successful in CLI patients, with low rates of major amputation and improvement in wound healing and quality of life through 1-year follow-up.

LIBERTY 360, <https://clinicaltrials.gov/ct2/show/NCT01855412>, ClinicalTrials.gov Identifier: NCT01855412.

Keywords: amputation, critical limb ischemia, CLI, endovascular therapy

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Introduction

Approximately 18 million Americans have peripheral artery disease (PAD) and 2 million of these patients suffer from critical limb ischemia (CLI),^{1,2} the end stage of PAD.³ CLI is highly prevalent in older patients with diabetes and/or end-stage renal disease⁴ and is associated with high risk of amputation and mortality.⁵ The results following lower extremity amputation can be devastating – 27% of these patients will have one or more re-amputation(s) within 1 year,⁶ 35% will have a higher level of limb loss,⁷ and 55% will have a contralateral limb amputation within 2–3 years.⁸ Furthermore, the mortality rates

after primary amputation are very high, with rates ranging from 9 to 33% at 1 year^{6,7,9,10} and 26 to 82% at 5 years.^{6,9–11} Despite such devastating outcomes, primary amputation remains a common treatment modality for CLI.

The 2016 AHA/ACC Guideline on the management of patients with lower extremity PAD now recommends an evaluation for revascularization options by an interdisciplinary care team before amputation in CLI patients (Class I).¹² Interestingly, recent studies demonstrate an increased utilization of endovascular intervention as a first-line approach for CLI patients in the US with a corresponding decrease of in-hospital death and major amputation.^{13–15}

CLI patients, in particular, Rutherford Class 5–6 (RC5–6) patients with ischemic ulcerations or gangrene, are often excluded or under-represented in endovascular intervention clinical trials given their multiple comorbidities and advanced PAD. To the best of our knowledge, no endovascular device clinical studies in the US have been conducted specifically for RC5–6 patients.

In this sub-analysis of the LIBERTY 360 study, we aimed to investigate outcomes through 1 year in CLI RC5–6 patients treated with endovascular intervention.

Materials and Methods

Study Design and Patient Selection

The LIBERTY 360 study design has been previously described.^{16,17} Briefly, patients were eligible for the study if they were at least 18 years old and had clinical evidence of PAD (Rutherford classification 2 to 6) that required endovascular interventions on one or both limbs that included a target lesion in a native vessel located within or extending into 10 cm above the medial epicondyle to the digital arteries. Patients were excluded from the study if (1) they required a conversion from endovascular intervention to a surgical bypass graft for any lesion in the target area, (2) had an in-stent restenosis in the target area, and this lesion was the only one requiring treatment, or (3) had an anticipated life span of less than 1 year. The study included any FDA-approved technology to treat claudication and CLI. A total of 1204 patients were enrolled at 51 US sites and divided into three groups based on Rutherford Classification (RC): RC2–3 (N=501), RC4–5 (N=603), and RC6 (N=100). The list of participating institutions is provided in [Supplementary Appendix 1](#). Sites were required to comply with the principles of Good Clinical Practices and meet the World Medical Association Declaration of Helsinki requirements. The study protocol was approved

by the Institutional Review Board at each participating institution, and all patients gave written informed consent. Patients were followed up in clinic at 30 days, 6 months, and 1 year. For this sub-analysis, RC5 and RC6 patients (N=404) were pooled and 1-year outcomes were assessed.

Endpoints

Procedural success was defined as a final post-procedural result of less than 50% residual stenosis for all treated lesions during index procedure without significant angiographic complications (flow-limiting dissection, perforation, distal embolization, acute vessel closure) as determined by the angiographic core laboratory (SynvaCor, Springfield, IL). Lesion success was defined as a final post-procedural result of less than 50% residual stenosis for a given lesion treated during the index procedure and without significant angiographic complications as determined by the angiographic core laboratory. Major adverse events were defined as a composite of (1) death within 30 days of index procedure, (2) unplanned major (above the ankle) amputation of the target limb, or (3) target vessel revascularization as assessed by the angiographic core laboratory when angiographic images were available. Changes in quality of life (QoL) from baseline were analyzed using the Vascular Quality of Life Questionnaire (VascuQoL, measures PAD related health status). Wounds and wound care visits were assessed on the target limb only; wound status (including wound healing) was collected in-office at 30 days, 6 months, and 12 months.

Statistical Analysis

Data analysis was performed with the SAS Software System (SAS Institute, Inc., Cary, NC). Data are reported as percentage or mean \pm standard deviation. For categorical responses, p-values were approximated using a Monte Carlo Approximation of the Fisher's Exact Test. For ordinal categorical or yes/no responses, p-values were calculated using McNemar's Test. For continuous variables, p-values were calculated using a paired *t*-test or ANOVA. Imputation of significant angiographic complications for procedural and lesion success of core lab identified lesions were performed by using site data when the core lab was unable to perform angiographic assessment. Kaplan–Meier method used to obtain estimate of survival rate. Greenwood's method used to obtain the 95% confidence interval for the estimate. The statistical significance was set at $p < 0.05$.

Results

Patient Characteristics

Patient demographics and baseline characteristics are included in [Table 1](#). Most patients were white males with high prevalence of hypertension, hyperlipidemia, and diabetes. Fifty-seven percent of patients had coronary artery disease and 14.6% had chronic kidney disease requiring hemodialysis.

Table 1 Demographics and Baseline Characteristics

	Rutherford 5–6 (N=404)
Age (years)	69.2 ± 11.6 69.0 [62.0, 78.0] (N=403)
Male sex	272 (67.3)
Race	
White	316 (78.2)
Black or African American	77 (19.1)
American Indian or Alaska Native	3 (0.7)
Asian	2 (0.5)
Other ^a	6 (1.5)
Body mass index (kg/m ²)	29.4 ± 6.6 28.3 [24.7, 33.4]
Current or former smoker	245 (60.6)
History of:	
Diabetes	315 (78.0)
Hyperlipidemia	326 (80.7)
Hypertension	372 (92.1)
Chronic renal disease	168 (41.6)
Coronary artery disease	229 (56.7)
Prior endovascular treatment of target limb	118/403 (29.3)
Previous amputation	N=404
Both limbs	23 (5.7)
Target limb	47 (11.6)
Non-target limb	57 (14.1)
None	277 (68.6)
Highest level of prior target limb amputation	N=70
Toe(s) only	66 (94.3)
Foot only	4 (5.7)
Highest level of prior contralateral limb amputation	N=80
Toe(s) only	39 (48.8)
Foot only	3 (3.8)
Below knee/above ankle	28 (35.0)
Above the knee	10 (12.5)

Notes: Data provided as mean ± standard deviation/median [IQR] or number (percentage) as appropriate. ^aOther race includes patients with more than one race category reported.

Almost half of the patients (47%) had previous drug therapy for PAD and 43.6% had previous lower-limb endovascular treatment for PAD. Patients with prior lower-limb endovascular treatments had a mean number of 1.3 ± 1.8 lower-limb procedures on their target limb in the prior 3 years. Thirty-one percent of the patients had previous amputations and 9.4% had previous major contralateral limb amputations.

Lesion Characteristics and Treatment

More than 76% of target lesions were located below-the-knee ([Supplementary Table 1](#)). On average, 1.4 ± 0.7 lesions were treated per subject. Approximately 60% of the lesions were calcified and 73.8% of calcified lesions were moderate to severely calcified per PARC definition.¹⁸ As shown in [Figure 1](#), balloon and/or atherectomy were the preferred devices. Percutaneous transluminal angioplasty and the orbital atherectomy system were the most frequently used devices in almost 79% and 48% of the lesions, respectively. Stents were used in 17% of the lesions but with minimal bailout stenting due to angiographic complications or suboptimal result (4.6%).

Procedural and Lesion Success

Procedural success was 76.0%; 83.6% of patients had less than 50% final residual stenosis in all target lesions treated and 88.8% had no severe angiographic complications. Lesion success is presented in [Supplementary Table 1](#).

Discharge Status and Medications

Procedural complications rarely (1.7%) resulted in post-procedural hospitalization and 89.1% of patients were discharged to home. Subjects were taking the following medications at the time of discharge: 91.6% antiplatelet therapy, 10.9% anti-coagulants, 74.8% anti-hyperlipidemic, and 88.4% anti-hypertensive.

Change in Rutherford Category and Quality of Life

RC5-6 patients showed a marked improvement from baseline to 12 months ([Supplementary Figure 1](#)). Quality of life improved significantly from baseline to 12 months, as measured by the total score and all subdomains of the VasuQoL ([Figure 2](#)) and EQ-5D ($p < 0.001$).

Major Adverse Events and Amputation Free Survival at 12 Months

Freedom from MAEs and amputation free survival is presented in [Figure 3](#) and [Table 2](#). Considering the advanced

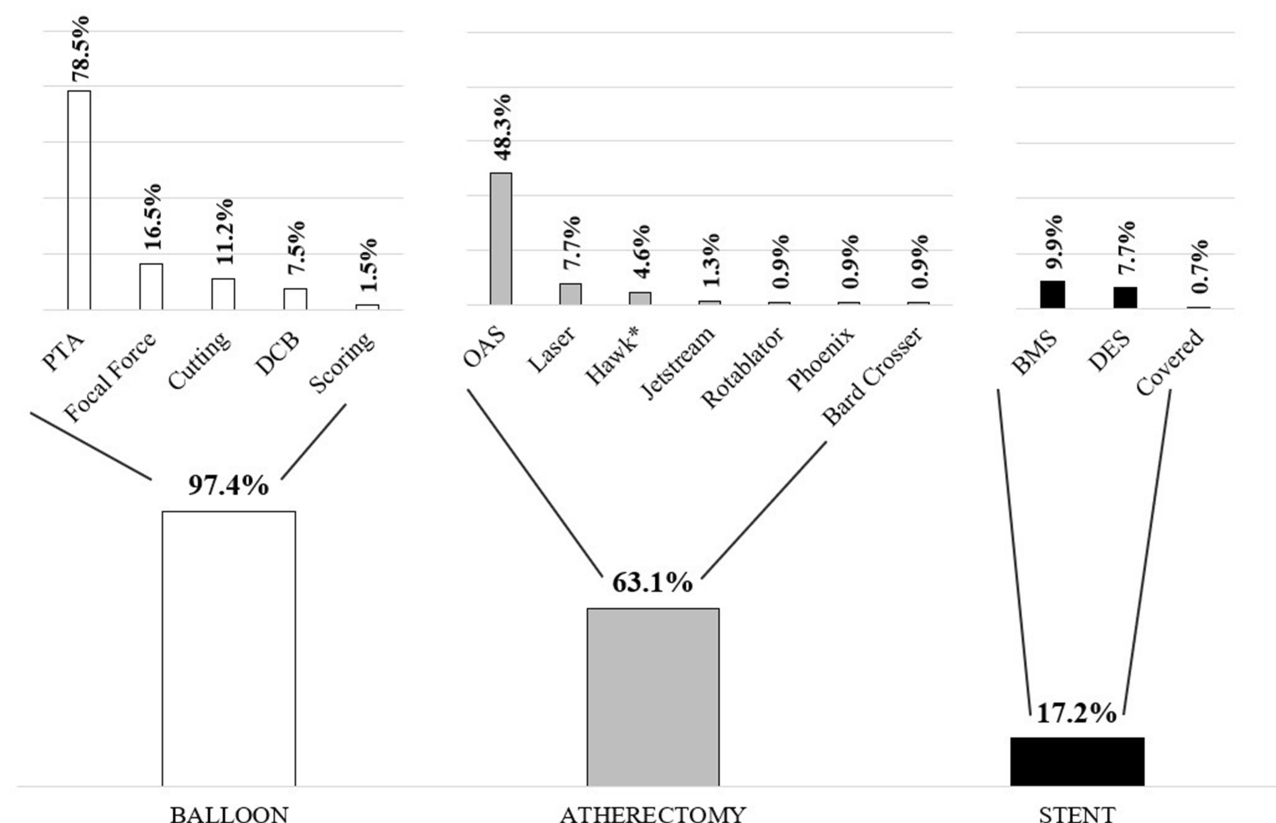


Figure 1 Device usage by lesion (N=558) assessed by angiographic core lab. *Hawk: Turbohawk, Silverhawk, Hawk One.

Abbreviations: BMS, bare-metal stent; DCB, drug-coated balloon; DES, drug-eluting stent; OAS, orbital atherectomy system; PTA, percutaneous transluminal angioplasty.

disease state in RC5-6 patients, there were high rates of 12-month amputation free survival (78.2%) and freedom from major target limb amputation (89.6%).

Wound Healing on Target Limb

Significant improvement was noted in the number of wounds from baseline to 12 months (Table 3). At 12 months, wounds identified at baseline on the target limb had completely healed in 172/243 (70.8%) of the RC5-6 subjects (RC5: 144/198 (72.7%); RC6: 28/45 (62.2%)). When assessing paired data, the percentage of subjects not seeing a wound care specialist improved significantly from 31.8% (N=69) at baseline to 66.4% (N=144) at 12 months; however, at 12 months 5.1% (N=11) began seeing a wound care specialist as compared to baseline. Of subjects seeing a wound care specialist at 12 months, 27.4% visited monthly, 20.5% once every 2 weeks, 39.7% weekly, and only 12.3% more than 2 times per week.

Discussion

CLI patients are under-represented in endovascular therapy clinical trials for multiple reasons: they are challenging to

treat due to their comorbidities and long-term follow-up of this challenging population is near impossible because of their high mortality rate. In addition, treatment of CLI patients has not yet been standardized, and primary amputation was the first-line therapy for 22 to 67% of these patients until the mid-2010s,^{5,19} although less than 5% of the CLI patients should have primary amputation due to the severity of their disease.²⁰

A recent meta-analysis of six trials that compared bypass surgery with angioplasty found no evidence to favor bypass surgery over angioplasty in terms of the effect on death, improvement of symptoms, amputation rate, need for further procedure, or long-term mortality.²¹ However, that study showed that angioplasty was associated with decreased procedural complications and shorter hospital stay compared with bypass surgery and concluded that endovascular treatment should be used in patients with CLI as they are high-risk surgical candidates.²¹ Mustapha et al²² found the same in their population-based cohort study using Medicare data of CLI patients treated with endovascular- or surgical revascularization or primary major amputation. Long-term survival and healthcare cost were comparable between the revascularization

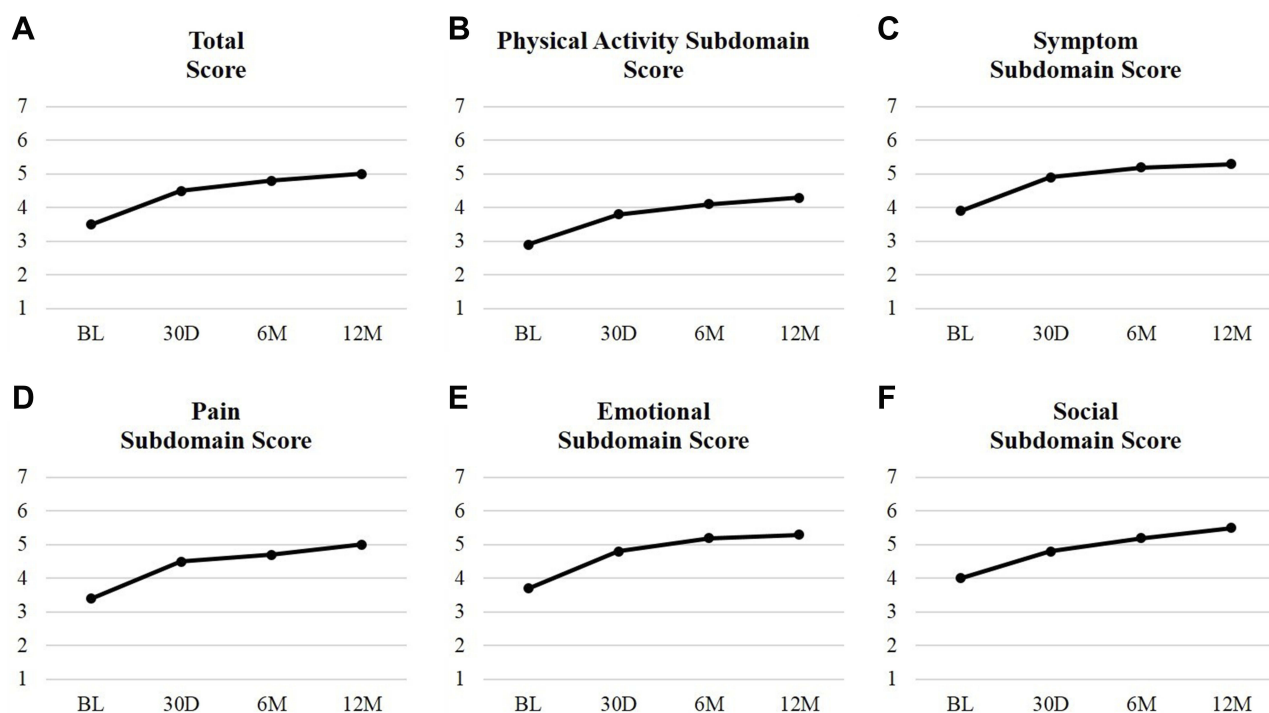


Figure 2 Changes in quality of life from baseline to 12 months (VasculoQoL). Vascular Quality of Life Questionnaire: **(A)** Total score; **(B)** Physical activity subdomain score; **(C)** Symptom subdomain score; **(D)** Pain subdomain score; **(E)** Emotional subdomain score; and **(F)** Social subdomain score. Higher subdomain scores indicate better rating of health. Value presented as mean as recorded at each follow-up visit.

Abbreviations: BL, baseline; 30D, 30 days; 6M, 6 months; 12M, 12 months.

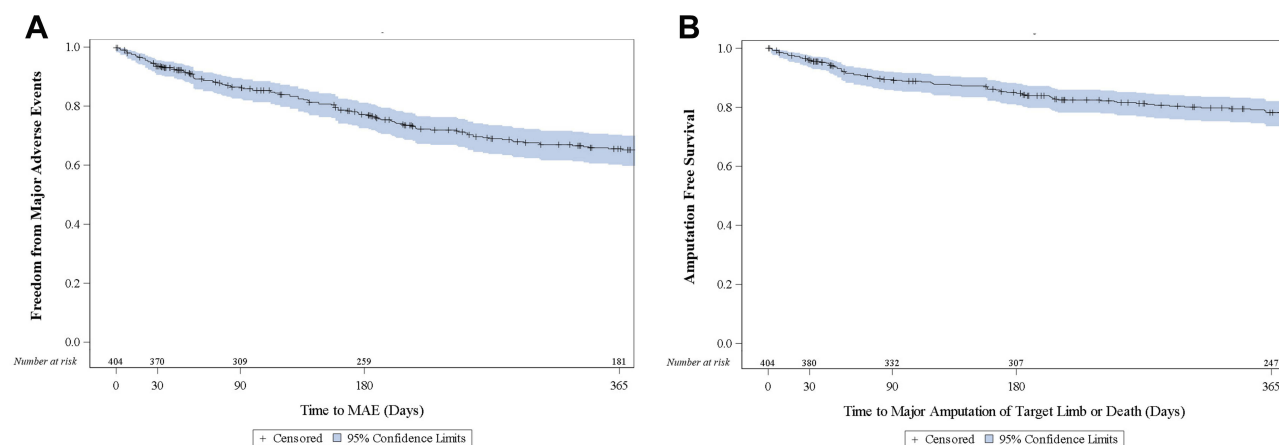


Figure 3 Kaplan–Meier curves for freedom from major adverse events **(A)** and amputation free survival **(B)** with number of subjects at risk.

Abbreviation: MAE, major adverse events.

techniques but with lower major amputation rates following endovascular therapy. In addition, primary major amputation was associated with shorter survival time, higher risk of subsequent amputation, and higher costs compared with revascularization techniques.

Despite the evidence-based preventive effect of revascularization on limb amputation in CLI patients, recent studies reported that 13.5%²³ and 23%¹⁵ of CLI patients

were still managed with major amputation and minor amputation or conservative therapy, respectively, instead of endovascular revascularization.

Not all CLI patients are the same. CLI is a broad definition and includes patients with Rutherford classification 4 to 6, where RC4 is characterized by ischemic rest pain, RC5 with minor tissue loss, and RC6 with major tissue loss – ulcer, gangrene.²⁴ Previous studies found that

Table 2 Freedom from Major Adverse Events and Amputation Free Survival at 30 Days, 6 Months, and 12 Months

	30 Days	6 Months	12 Months
Freedom from MAE	93.5 (91.1, 95.9)	77.2 (72.9, 81.5)	65.5 (60.4, 70.6)
Freedom from death*	98.5 (97.3, 99.7)	91.2 (88.3, 94.1)	86.7 (83.2, 90.2)
Freedom from major amputation	97.2 (95.6, 98.8)	92.2 (89.5, 94.9)	89.6 (86.4, 92.8)
Freedom from TVR	97.0 (95.3, 98.7)	82.8 (78.8, 86.7)	72.1 (67.2, 77.0)
Amputation free survival	96.0 (94.1, 97.9)	84.7 (81.1, 88.4)	78.2 (73.9, 82.4)

Notes: *Death includes all-death, including those beyond 30 days. Values presented as estimated survival rate (lower, upper bound of 95% confidence interval).

Abbreviations: MAE, major adverse events; TVR, target vessel revascularization.

Table 3 Target Limb Wound Healing

	Baseline (N=404)	30 Days		6 Months		12 Months	
	Value	Value	Δ from Baseline	Value	Δ from Baseline	Value	Δ from Baseline
Number of wounds on target limb	1.5 ± 0.9 1.0 [1.0, 2.0] (N=404)	1.2 ± 1.0 1.0 [1.0, 2.0] (N=324)	−0.3 ± 0.8 0.0 [−1.0, 0.0]*	0.7 ± 0.8 0.0 [0.0, 1.0] (N=235)	−0.9 ± 1.1 −1.0 [−1.0, 0.0]*	0.4 ± 0.7 0.0 [0.0, 1.0] (N=207)	−1.2 ± 1.1 −1.0 [−2.0, −1.0]*

Notes: *Change in mean number of wounds from baseline significant via paired t-test ($p < 0.001$). Values presented as mean ± standard deviation/median [IQR].

the comorbidities and lesion characteristics of patients with rest pain (RC4) differed significantly from those with tissue loss (RC5-6).^{25,26} RC4 patients were significantly less likely than RC5-6 to have diabetes, end-stage renal disease, or chronic heart failure.^{25–27} Also, RC5-6 patients had longer lesions, more TASC C and D lesions, and fewer patent below-the-ankle arteries compared to RC4 patients.²⁶ In addition, CLI patients without wounds had better prognosis after intervention than those with wounds.²⁵ RC4 patients are also treated differently compared to RC5-6, as they more often undergo revascularization and less often undergo primary amputation. Retrospectively reviewing diagnosis and procedural data from the largest public health insurance in Germany, the authors found that only ~50% of RC5-6 patients had any revascularization compared to 71% of RC4 patients and 27.5% of them had in-hospital amputation compared to only 1.6% of RC4.²⁷ Reinecke and co-authors²⁷ found a high mortality rate in RC5-6 patients which was only comparable with that of some aggressive types of cancer, as they noted it appropriately.

For the reasons mentioned above and also per the reporting standards of the Society of Vascular Surgery for endovascular treatment of PAD,²⁸ as ‘rest pain and tissue loss patients should not be grouped together in reporting outcomes’, we present the outcomes for the LIBERTY RC5-6 patients only, and not for all CLI patients (RC4-6). This is the

first study to show the endovascular treatment outcomes in RC5-6 patients in the US. Notably, in the LIBERTY 360 RC5-6 patients, 65.1% of lesions were below-the-knee only, 46.4% were longer than 10 cm and approximately 60% were calcified. The preferred devices were balloon and/or atherectomy and orbital atherectomy was the most frequently used atherectomy device. Procedural complications rarely (1.7%) resulted in post-procedural hospitalization and 89.1% of RC5-6 patients were discharged to home. Agarwal et al,²³ using State Inpatient Databases from three US states from 2009 to 2013, studied trends and factors affecting readmission in CLI patients, 16.6% of whom had endovascular revascularization alone, and found that only 33.6% of primary CLI admissions were discharged home from the hospital. On the other hand, in a retrospective study of 219 CLI patients treated with atherectomy and balloon angioplasty in an outpatient center, all patients were discharged home the same day, including 51.6% RC5-6 patients.²⁹

Considering the advanced disease state in RC5-6 patients, there was a high rate of 12-month amputation free survival (AFS, 78.1%). The 1-year AFS was 83.1% in the above-mentioned outpatient study,²⁹ while in another retrospective study of 809 RC5-6 patients with diabetes, the 1-year AFS was 75% for the endovascular group compared with 69% in the bypass group.³⁰ Only 10.4% of the LIBERTY RC5-6 patients had a major amputation at 1 year – much lower than the 22% to 67%^{5,31–34} primary major amputation rates seen

in the literature for CLI patients that did not receive endovascular intervention (Figure 4).³⁵

The mortality rate in LIBERTY RC5-6 patients was 13.3% at 1 year, very comparable to the outpatient study where the death rate was 11.4% for the entire cohort²⁹ and much lower than the 30% 1-year mortality rate in a retrospective US study³⁶ of patients who underwent lower extremity amputation. This rate is very similar though to the mortality rate in a large German retrospective study,²⁷ where 34.2% of the RC6 patients died within the first 12 months after index hospitalization. Only 29.5% of these patients were treated with endovascular therapy and less than half of them had any revascularization procedure during index hospitalization.

It has been shown that endovascular revascularization improves wound healing in CLI patients³⁷ and direct blood flow to the wounds is a positive predictor of wound healing.³⁸ There was a significant improvement in the number of wounds on the target limb from baseline to 12 months in LIBERTY RC5-6 patients.

Quality of life (QoL), as measured by the total score and all subdomains of the VasuQoL, also improved significantly from baseline to 12 months. A recently published Japanese prospective study found the same; the health-related QoL was significantly improved compared to baseline in the CLI patients alive at 1 year after revascularization.³⁹ A handful of observational studies that compared the effects of primary

amputation and revascularization on QoL concluded that revascularization should be the preferred approach in patients with CLI. However, critics say that CLI patients have poor health prospects and life expectancy, irrespective of the treatment mode,⁴⁰ and a focus on QoL research is needed to prescribe the ideal treatment for patients suffering from CLI.⁴¹ This study adds more evidence to the scarce literature and LIBERTY data supporting a revascularization approach for CLI will likely be corroborated by the BEST-CLI trial⁴² that compares surgical bypass and endovascular therapy in CLI patients and also provide data about the impact of these treatments on the QoL of the study population.

Limitations

This was a post hoc analysis of LIBERTY 360 – an observational, non-randomized study of endovascular therapies and was not powered to assess clinical outcomes in RC5-6 CLI patients. As this study was sponsored by a company whose principal endovascular strategy is atherectomy, bias may be attributed to physician selection of orbital atherectomy in a high number of cases. Additionally, wound data collection was limited in the LIBERTY 360 study; exact wound area, wound volume, and the date of wound healing were not collected. Possible over or underreporting of outcomes is possible due to subject withdrawal prior to 12 months.

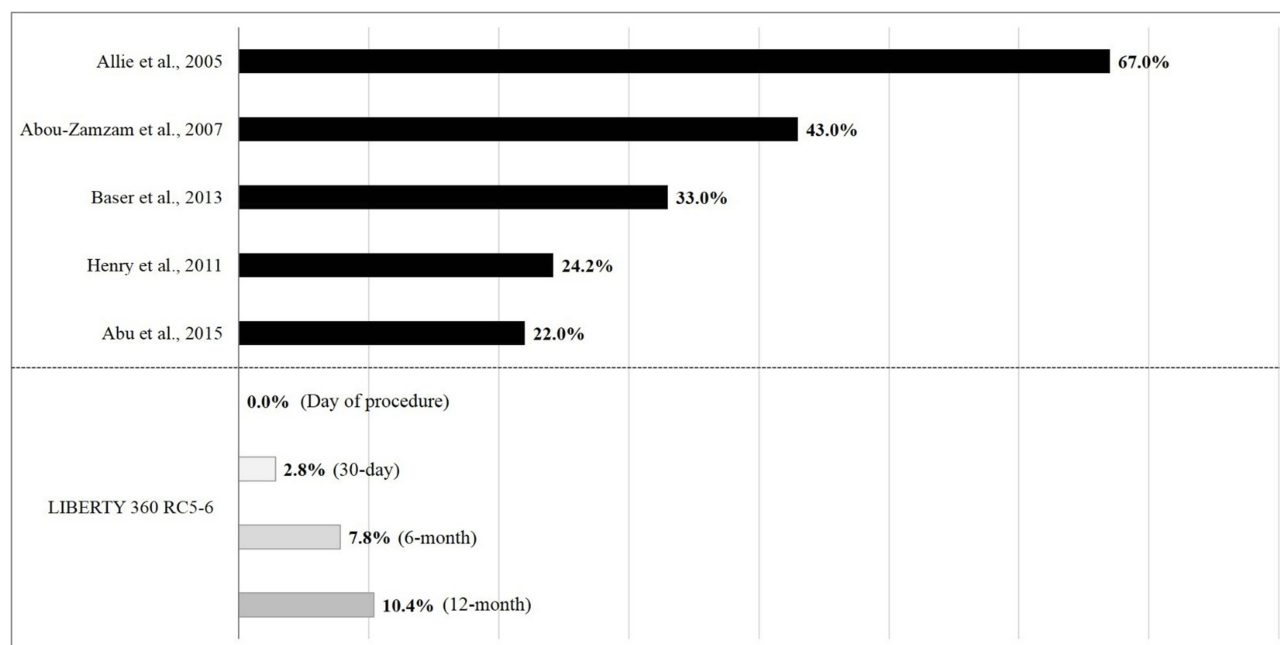


Figure 4 Critical limb ischemia (CLI) patients without revascularization (primary amputation treatment) vs LIBERTY 360 RC5-6 CLI patients (primary endovascular treatment). This summary graph shows the primary amputation rates presented in the literature and the major target limb amputation rates reported in LIBERTY, but it is not a head-to-head comparison since the analyses described vary in design.

Conclusions

LIBERTY investigated real-world PAD patients with independent oversight of outcomes. The findings in this novel “all-comers” PAD study reveal hope for RC5-6 CLI patients and suggest that “primary amputation” in RC5-6 may not be necessary – peripheral endovascular device intervention can be successful in this patient population.

Abbreviations

AFS, amputation free survival; ATK, above-the-knee; BMS, bare-metal stent; BTK, below-the-knee; CLI, critical limb ischemia; DCB, drug-coated balloon; DES, drug-eluting stent; MAE, major adverse events; OAS, orbital atherectomy system; PAD, peripheral artery disease; PARC, Peripheral Academic Research Consortium; PTA, percutaneous transluminal angioplasty; QoL, quality of life; RC, Rutherford Classification; TASC, Trans-Atlantic Inter-Society Consensus; TVR, target vessel revascularization.

Data Sharing Statement

Individual-deidentified participant data and study-related documents will not be made available.

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Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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