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Three-Year Outcomes of Orbital Atherectomy for the Endovascular Treatment of Infrainguinal Claudication or Chronic Limb-Threatening Ischemia

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Abstract

Purpose: To investigate the outcomes of orbital atherectomy (OA) for the treatment of patients with peripheral artery disease (PAD) manifesting as claudication or chronic limb-threatening ischemia (CLTI). **Materials and Methods:** The database from the LIBERTY study (*ClinicalTrials.gov* identifier NCT01855412) was interrogated to identify 503 PAD patients treated with any commercially available endovascular devices and adjunctive OA for 617 femoropopliteal and/or infrapopliteal lesions. Cox regression analyses were employed to examine the association between baseline Rutherford category (RC) stratified as RC 2-3 (n=214), RC 4-5 (n=233), or RC 6 (n=56) and all-cause mortality, target vessel revascularization (TVR), major amputation, major adverse event (MAE), and major amputation/death at up to 3 years of follow-up. The mean lesion lengths were 78.7±73.7, 131.4±119.0, and 95.2±83.9 mm, respectively, for the 3 groups. **Results:** After OA, balloon angioplasty was used in >98% of cases, with bailout stenting necessary in 2.0%, 2.8%, and 0% of the RC groups, respectively. A small proportion (10.8%) of patients developed angiographic complications, without differences based on presentation. During the 3-year follow-up, claudicants were at lower risk for MAE, death, and major amputation/death than patients with CLTI. The 3-year Kaplan-Meier survival estimates were 84.6% for the RC 2-3 group, 76.2% for the RC 4-5 group, and 63.7% for the RC 6 group. The 3-year freedom from major amputation was estimated as 100%, 95.3%, and 88.6%, respectively. Among CLTI patients only, the RC at baseline was correlated with the combined outcome of major amputation/death, whereas RC classification did not affect TVR, MAE, major amputation, or death rates. **Conclusion:** Peripheral artery angioplasty with adjunctive OA in patients with CLTI or claudication is safe and associated with low major amputation rates after 3 years of follow-up. These results demonstrate the utility of OA for patients across the spectrum of PAD.

Keywords

amputation, balloon angioplasty, critical limb ischemia, endovascular treatment/therapy, femoropopliteal segment, infrapopliteal arteries, mortality, orbital atherectomy, peripheral artery disease, stent

Introduction

Peripheral artery disease (PAD) affects more than 8 million people in the United States[1,2] and has increased in prevalence by almost 24% from 2000 to 2010.[2,3] PAD is associated with morbidity and mortality rates similar to or higher than coronary artery disease.[4–6] Approximately 20% of patients older than 50 years are afflicted, and it is even more common in diabetics, smokers, and patients with chronic kidney disease (CKD).[6–9] The degree of PAD severity can be categorized according to the Rutherford category (RC)[10] as mild to severe intermittent claudication (RC 1-3) and chronic limb-threatening ischemia (CLTI) with/without tissue loss (RC 4-6). About 10% of patients with PAD suffer from CLTI.[11,12]

CLTI is a multilevel disease that has been associated with up to 45% 1-year mortality[13–15] and high amputation rates,[16,17] significantly increasing overall health care costs.[18–20] The American College of Cardiology/American Heart Association guidelines[21] have recommended that revascularization is a reasonable treatment option for patients with RC >2 symptoms

when optimal medical therapy and/or exercise fail to improve symptoms. However, data regarding best revascularization strategies for CLTI are sparse.[22–24]

Extensive arterial calcification remains a major challenge for peripheral interventions owing to the increased risk of periprocedural complications (eg, flow-limiting dissections[25,26]), higher restenosis rates,[26–32] and slow flow or spasm, especially when treating infrapopliteal lesions.[33] Endovascular treatment of calcified plaques has also been associated with distal embolization, particularly when treating CLTI patients with mildly calcified, fibrotic, soft-plaque lesions.[34] Thus, vessel calcification is directly correlated to the overall implications of PAD.[35,36] As such, numerous treatment methods have been developed for plaque modification before angioplasty[31,37–41] in order to minimize periprocedural complications, enhance vessel patency, and minimize the need for provisional stenting.[42]

Orbital atherectomy (OA) is an effective device for vessel preparation before balloon angioplasty (BA) and was designed for the treatment of infrainguinal arteries with severe calcification.[31,41,43–48] The current study investigated the short- and long-term outcomes of OA for the treatment of severe claudication and CLTI using a subgroup of patients from the LIBERTY study.[49] In addition to describing overall procedural safety and 3-year outcomes, the results were also stratified by Rutherford category.

Materials and Methods

Study Design and Patient Enrollment

LIBERTY 360 was a prospective, observational, multicenter study investigating the clinical and economic outcomes of patients with symptomatic PAD who underwent lower extremity endovascular interventions with any approved or cleared device between 2013 and 2016. A steering committee, including principal investigators, representatives from the study core laboratories, and the sponsor (Cardiovascular Systems, Inc, St Paul, MN, USA), developed the study's protocol; the sponsor was also responsible for effective oversight of the research process. The institutional review board of each site approved the protocol. The trial was registered on the National Institutes of Health website (*ClinicalTrials.gov*; identifier NCT01855412).

The detailed inclusion and exclusion criteria of the LIBERTY 360 study were previously reported.[50] Angiographic data were adjudicated by SynvaCor/Prairie Educational and Research Cooperative (PERC; Springfield, IL, USA). When data from the core laboratory evaluation were not available, site-reported data were used for the analysis. The current study included only patients treated with adjunctive OA (Diamondback/Stealth; Cardiovascular Systems, Inc) and comparisons were stratified by RC. Patients treated with more than one atherectomy device were excluded from the analysis, and as such only cases treated solely with OA were included. Lesions above and below the knee were revascularized, while the target area at the infrapopliteal segment was any lesion in a native vessel located within or extending to 10 cm above the medial epicondyle to the digital arteries.

A total of 503 patients from the LIBERTY trial met the criteria and were included in this analysis. Patient demographics and lesion characteristics stratified by RC are illustrated in Tables 1 and 2, respectively. There were 214 patients with claudication (RC 2-3) and 289 patients with CLTI (233 with RC 4-5 and 56 with RC 6) who underwent endovascular treatment for 617 lesions (251 RC 2-3, 289 RC 4-5, and 77 RC 6). Over half of the lesions (54.1%) were located solely at the infrapopliteal segment, a third of the lesions (32.6%) were in the femoropopliteal arteries, while 13.3% of the treated lesions involved diffuse segments above and below the knee.

Study Outcomes

Primary outcomes were lesion success and the incidence of major adverse events (MAEs). Lesion success was assessed by the angiographic core laboratory as $<50\%$ residual stenosis without significant angiographic complications [ie, flow-limiting dissection (types C-F), perforation, distal embolization, abrupt closure]. MAEs were defined as death within 30 days of the primary procedure, unplanned major amputation of the target limb, or clinically-driven target vessel revascularization (CD-TVR) as assessed by the angiographic core laboratory when angiographic images were available.

Secondary endpoints were TVR, death, major amputation, death or major amputation combined, and wound healing up to 3 years of follow-up. A wound was defined as healed at the follow-up visit if the area was reduced to zero, including cases where amputation occurred and the surgical

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Table 1. Baseline Characteristics of the Participants.[a]

Characteristics	RC 2-3: Claudicants[b] (n=214)	RC 4-5: CLTI (n=233)	RC 6: CLTI (n=56)	p
Age, y	70.4±9.6	71.3±10.9	67.9±14.2	0.106
Men	149/214 (69.6)	138/233 (59.2)	40/56 (71.4)	0.154
Race				
American Indian or Alaska Native	1/214 (0.5)	1/233 (0.4)	0/56	>0.99
Asian	1/214 (0.5)	1/233 (0.4)	1/56 (1.8)	0.467
Black or African American	26/214 (12.1)	26/233 (11.2)	13/56 (23.2)	0.068
Native Hawaiian or Other Pacific Islander	0/214	1/233 (0.4)	0/56	>0.99
White	181/214 (84.6)	198/233 (85.0)	42/56 (75.0)	0.178
Other	5/214 (2.3)	6/233 (2.6)	0/56	0.753
BMI, kg/m^2	28.8±5.5	29.1±6.7	29.3±7.1	0.785
eGFR, mg/dL/1.73 m^2	69.0±28.6	58.3±26.4	57.2±34.4	<0.001
Smoking history				0.128
Current	44/214 (20.6)	41/233 (17.6)	10/56 (17.9)	0.731
Former	111/214 (51.9)	100/233 (42.9)	26/56 (46.4)	0.166
Diabetes	109/214 (50.9)	157/233 (67.4)	44/56 (78.6)	<0.001
Hyperlipidemia	195/214 (91.1)	207/233 (88.8)	38/56 (67.9)	<0.001
Hypertension	201/214 (93.9)	218/233 (93.6)	52/56 (92.9)	0.931
Renal disease	55/214 (25.7)	99/233 (42.5)	23/56 (41.1)	<0.001
Hemodialysis	9/55 (16.4)	20/99 (20.2)	10/23 (43.5)	0.033
Coronary artery disease	132/214 (61.7)	157/233 (67.4)	28/56 (50.0)	0.047
Myocardial infarction	46/214 (21.5)	66/233 (28.3)	9/56 (16.1)	0.085
Stroke/TIA	39/214 (18.2)	36/233 (15.5)	4/56 (7.1)	0.112
Runoff vessels[c]	179	215	47	0.141
Pretreatment				
3	33/179 (18.4)	32/215 (14.9)	8/47 (17.0)	0.654
2	69/179 (38.5)	82/215 (38.1)	18/47 (38.3)	>0.99
1	67/179 (37.4)	83/215 (38.6)	12/47 (25.5)	0.232
0	10/179 (5.6)	18/215 (8.4)	9/47 (19.1)	0.018
Posttreatment				0.96
3	32/147 (21.8)	38/181 (21.0)	7/36 (19.4)	0.982
2	61/147 (41.5)	80/181 (44.2)	14/36 (38.9)	0.785
1	51/147 (34.7)	61/181 (33.7)	15/36 (41.7)	0.653
0	3/147 (2.0)	2/181 (1.1)	0/36	0.795
Previous EVT of target limb	58/214 (27.1)	71/233 (30.5)	14/56 (25.0)	0.172
Previous bypass surgery of target limb	9/214 (4.2)	9/233 (3.9)	4/56 (7.1)	0.397
Prior stent placed in target limb	31/214 (14.5)	28/233 (12.0)	7/56 (12.5)	0.889

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; EVT, endovascular therapy; ICU, intensive care unit; RC, Rutherford category; TIA, transient ischemic attack.

[a]Continuous data are presented as the mean ± standard deviation (sample size if different from the group number); categorical data are given as the number/sample (percentage). Sample sizes may differ from the group number owing to missing data.

[b]Two patients (with a total of 3 wounds) were classified as RC 2-3 by the treating physician and therefore were analyzed with that group.

[c]As determined by the core laboratory.

site completely healed. The type of wound (eg, ischemic, neurogenic) was not captured; involvement of a wound care specialist was reported only when the wound was located on the target limb. No adjustments were made for missing data. The ankle-brachial index (ABI), toe-brachial index (TBI), and RC were also assessed during follow-up; however, as the 3-year evaluation was a phone visit, these measures could be assessed only up to 2 years.

Statistical Analysis

Descriptive statistics were used for baseline and lesion characteristics. All summary data are based on non-missing assessments. Categorical variables are presented as the number per sample (percentage) and were compared with Monte Carlo approximation of the Fisher exact test. Continuous data are presented as mean ± standard deviation and were compared using the analysis of variance or paired *t* test. Discrete data were compared with the Kruskal-Wallis test; paired data were evaluated using the Wilcoxon signed rank test. Significant angiographic complications for procedural and lesion success outcomes were imputed using site data when the core laboratory was unable to perform angiographic assessment.

Cox regression models (RC 2-3 vs RC 4-5 vs RC 6) were synthesized for MAE, death, major amputation, and major amputation or death combined in up to 36 months of follow-up. Results are presented as the hazard ratio (HR) with a 95%

Table 2. Baseline Lesion Characteristics.[a]

Characteristics	RC 2-3: Claudicants (214 patients, 251 lesions)	RC 4-5: CLTI (233 patients, 289 lesions)	RC 6: CLTI (56 patients, 77 lesions)	p
Lesion location ATK or BTK				<0.001
ATK only	111/251 (44.2)	71/289 (24.6)	19/77 (24.7)	<0.001
ATK and BTK	32/251 (12.7)	44/289 (15.2)	6/77 (7.8)	0.225
BTK only	108/251 (43.0)	174/289 (60.2)	52/77 (67.5)	<0.001
Lesion location				<0.001
SFA only	30/251 (12.0)	5/289 (1.7)	2/77 (2.6)	<0.001
SFA to popliteal	35/251 (13.9)	31/289 (10.7)	8/77 (10.4)	0.489
Popliteal only	46/251 (18.3)	35/289 (12.1)	9/77 (11.7)	0.106
SFA to BTK	0/0	12/289 (4.2)	1/77 (1.3)	0.001
Popliteal to BTK	32/251 (12.7)	32/289 (11.1)	5/77 (6.5)	0.315
Lesion length, mm	78.7±73.7 (n=240)	131.4±119.0 (n=273)	95.2±83.9 (n=73)	<0.001
<40	94/240 (39.2)	67/273 (24.5)	25/73 (34.2)	0.002
40–99	85/240 (35.4)	80/273 (29.3)	15/73 (20.5)	0.047
≥100	61/240 (25.4)	126/273 (46.2)	33/73 (45.2)	<0.001
Distal RVD, mm	3.7±1.2 (n=243)	3.2±1.2 (n=277)	2.9±0.9 (n=74)	<0.001
MLD, mm	0.8±0.8 (n=245)	0.7±0.9 (n=279)	0.6±0.6 (n=76)	0.019
Stenosis, %	77.9±19.4 (n=245)	80.7±20.3 (n=280)	81.6±17.9 (n=76)	0.187
Chronic total occlusion	55/245 (22.4)	100/280 (35.7)	26/76 (34.2)	0.004
TASC type				<0.001
A	169/246 (68.7)	141/278 (50.7)	39/73 (53.4)	<0.001
B	38/246 (15.4)	41/278 (14.7)	21/73 (28.8)	0.02
C	26/246 (10.6)	61/278 (21.9)	8/73 (11.0)	0.001
D	13/246 (5.3)	35/278 (12.6)	5/73 (6.8)	0.012
Predominantly calcified plaque	168/232 (72.4)	176/261 (67.4)	46/72 (63.9)	0.286
PARC stenosis				0.043
Mild	23/245 (9.4)	21/280 (7.5)	4/76 (5.3)	0.506
Moderate	56/245 (22.9)	56/280 (20.0)	18/76 (23.7)	0.634
Severe	111/245 (45.3)	103/280 (36.8)	28/76 (36.8)	0.117
Occluded	55/245 (22.4)	100/280 (35.7)	26/76 (34.2)	0.002
PARC concentric calcification				0.069
Focal	17/220 (7.7)	19/244 (7.8)	2/67 (3.0)	0.4
Mild	47/220 (21.4)	28/244 (11.5)	6/67 (9.0)	0.005
Moderate	35/220 (15.9)	42/244 (17.2)	15/67 (22.4)	0.45
Severe	57/220 (25.9)	70/244 (28.7)	18/67 (26.9)	0.79
Inflow vessel disease (>50% stenosis)	83/214 (38.8)	70/233 (30.0)	37/56 (66.1)	<0.001

Abbreviations: ATK, above the knee; BTK, below the knee; MLD, minimum lumen diameter; PARC, Peripheral Academic Research Consortium; RC, Rutherford category; RVD, reference vessel diameter; SFA, superficial femoral artery; TASC, TransAtlantic Inter-Society Consensus.
[a]Continuous data are presented as the mean ± standard deviation (sample size if different from the group number); categorical data are given as the number/sample (percentage). Sample sizes may differ from the group number owing to missing data.

confidence interval (CI). Kaplan-Meier survival curves were plotted for primary and secondary outcomes. A $p<0.05$ was considered statistically significant for all tests. Statistical analyses were conducted by NAMSA (Northwood, OH, USA).

Results

Comparison of Patient and Lesion Characteristics

Patients with CLTI (RC 4-6) had significantly lower estimated glomerular filtration rates at baseline compared with claudicants. The RC 2-3 group included more patients with smoking history than the RC 4-5 group (p=0.009). Moreover, patients with CLTI (RC 4-5: 67.4% and RC 6: 78.6%) were more likely to be diabetic compared to patients with claudication (RC 2-3: 50.9%).

At baseline, RC 4-5 [22/233 (9.4%)] and RC 6 [8/56 (14.3%)] patients more often had noncompressible vessels than RC 2-3 patients [10/214 (4.7%)], so ABI was measurable in fewer RC 4-5 (p=0.004) and RC 6 cases (p=0.002) compared with RC 2-3. Therefore, at baseline the average ABI of the target limb was similar among all 3 groups (RC 2-3: 0.84±0.26; RC 4-5: 0.86±0.29; RC 6: 0.86±0.32), whereas the average TBI at baseline was significantly worse (RC 2-3 vs RC 6: p=0.005; RC 4-5 vs RC 6: p=0.037) in

patients with more severe disease (RC 2-3: 0.54±0.22; RC 4-5: 0.52±0.26; RC 6: 0.41±0.19).

Overall, patients with CLTI had longer average target lesion lengths, smaller mean reference vessel diameters, and more stenosed lesions, with a mean minimum lumen diameter at the target lesion of 0.6±0.6 mm for the RC 6 vs 0.8±0.8 mm for the RC 2-3 vs 0.7±0.9 mm for the RC 4-5 groups. In addition, chronic total occlusions were more often observed among patients with CLTI, without any difference between the RC 4-5 and RC 6 groups. Inflow vessel disease (>50% stenosis) was also more prevalent among RC 6 cases. Predominately calcified lesions were observed in 390 of 565 lesions (69.0%), without any difference between the groups (p=0.286).

Procedure Characteristics

Most endovascular procedures were performed through a contralateral retrograde access and utilized an antegrade crossing approach (Table 3). All patients treated with OA were included; details regarding the crown size of the atherectomy devices are presented in Supplementary Table 1 (available in the online version of the article). After OA, balloon angioplasty was used in >98% of cases, with bail-out stenting necessary in 2.0%, 2.8%, and 0% of the RC 2-3, RC 4-5, and RC 6 groups, respectively.

Core laboratory–adjudicated data regarding stent or balloon utilization were available for 245 RC 2-3, 283 RC 4-5, and 73 RC 6 cases. Conventional balloons were used in the majority of cases in all groups (Table 3). Stents, predominately bare metal models, were used in 27 RC 2-3 cases (10.6%), 27 RC 4-5 (9.2%), and 13 RC 6 cases (17.8%). Drug-eluting technology [drug-coated balloons (DCB) or drug-eluting stents (DES)] was used infrequently but were equally utilized between the 3 groups. The mean procedure durations were longer for patients with CLTI, while the overall fluoroscopy times were not different between the 3 groups.

Periprocedural Complications

Overall, angiographic complications (ie, dissection, perforation, distal embolization, abrupt closure) occurred in 65 of 609 lesions (10.7%), without any differences between the 3 groups (Table 4). Target lesion success was 83.8% (201/240) in the RC 2-3 group vs 80.8% (219/271) in the RC 4-5 or 78.9% (56/71) in the RC 6 group (p=0.551). The hospitalization and admission to the intensive care unit (ICU) rates were higher among patients with CLTI and RC 6 at baseline, with a mean 99.0±151.0 hours of hospitalization (p<0.001).

No in-hospital MAE, death, major amputation, or TVR occurred for the RC 2-3 and RC 4-5 groups. Among patients with RC 6 at baseline, 3 experienced in-hospital MAEs: 2 died and one underwent major amputation during hospitalization. Claudicants were at lower risk for 30-day MAE compared to patients with CLTI (RC 2-3 vs RC 4-5: HR 0.24, 95% CI 0.05 to 1.11, p=0.068; RC 2-3 vs RC 6: HR 0.10, 95% CI 0.02 to 0.53, p=0.006); however, MAE rates between RC 4-5 and RC 6 groups did not differ significantly (HR 0.42, 95% CI 0.14 to 1.25, p=0.119). No differences were observed between the groups in terms of 30-day death, major amputation, TVR, or combined major amputation/death risk rates. Odds ratios for periprocedural complications and short-term outcomes are illustrated in Supplementary Table 2.

Outcomes in Follow-up

At 30 days, the mean ABI of each group was improved compared to the corresponding preprocedural values (mean change from baseline: RC 2-3: 0.16±0.25; RC 4-5: 0.12±0.32; and RC 6: 0.12±0.29); however, no difference was observed between groups (RC 2-3: 0.99±0.24 vs RC 4-5: 0.97±0.30 vs RC 6: 0.94±0.21; p=0.565). Nonetheless, at 6 months, the ABI values remained similar between the groups (RC 2-3: 0.93±0.25; RC 4-5: 0.94±0.31; RC 6: 0.83±0.28). However, at 12 months, the mean ABI of the RC 6 group (0.77±0.32) was significantly worse than the values of the RC 2-3 (0.97±0.29; p=0.005) and RC 4-5 groups (0.95±0.30; p=0.017). The average ABI remained similar among the RC 2-3 (0.97±0.25) and RC 4-5 (0.91±0.25) groups during 2 years of follow-up (p=0.078).

At 3 years' follow-up, claudicants were at significantly lower risk for any MAE compared to CLTI patients (RC 2-3 vs RC 4-5: HR 0.61, 95% CI 0.42 to 0.89, p=0.010; RC 2-3 vs RC 6: HR 0.49, 95% CI 0.29 to 0.84, p=0.009). Nonetheless, the RC at baseline was not associated with MAE risk among patients with CLTI at 3-year follow-up (RC 4-5 vs RC 6: HR 0.82, 95% CI 0.49 to 1.36, p=0.441). The 3-year Kaplan-Meier estimates of freedom from MAE (Figure 1A) were 74.1% (95% CI 67.6% to 80.6%), 64.3% (95% CI 57.1% to 71.4%), and 56.3% (95% CI 40.0% to 72.5%) for the RC 2-3, RC 4-5, and RC 6 groups, respectively. Moreover, patients among the RC 2-3 group had a lower risk for all-cause death during 3 years of follow-up (RC 2-3 vs RC 4-5: HR 0.59, 95% CI 0.37 to 0.96, p=0.033; RC 2-3 vs RC 6: HR 0.35, 95% CI 0.19 to 0.64, p<0.001).

An analysis of CLTI patients demonstrated that there was no significant difference between RC 4-5 and RC 6 patients in terms of late mortality, but patients with RC 6 had a strong trend toward higher risk for all-cause death (RC 4-5 vs RC 6: HR 0.59, 95% CI 0.33 to 1.05, p=0.071). The 3-year Kaplan-Meier survival estimates (Figure 1B) were 84.6% (95% CI 79.3% to 89.9%) for the RC 2-3 group, 76.2% (95% CI 69.9% to 82.6%) for the RC 4-5, and 63.7% (95% CI 48.9% to 78.6%) for the RC 6 group. Furthermore, no statistically significant difference was detected in terms of major amputation risk at 3 years in RC 4-5 vs RC 6 (HR 0.46, 95% CI 0.16 to 1.34, p=0.154).

Table 3. Procedure Characteristics and Device Use.[a]

Characteristics	RC 2-3: Claudicants (214 patients, 251 lesions)	RC 4-5: CLTI (233 patients, 289 lesions)	RC 6: CLTI (56 patients, 77 lesions)	p
Access site				0.005
Femoral	254/267 (95.1)	278/307 (90.6)	76/81 (93.8)	0.106
Popliteal	1/267 (0.4)	0/307	1/81 (1.2)	0.113
Tibial	11/267 (4.1)	29/307 (9.4)	2/81 (2.5)	0.012
Pedal	5/267 (1.9)	15/307 (4.9)	3/81 (3.7)	0.153
Approach				0.014
Ipsilateral	71/267 (26.6)	96/307 (31.3)	17/81 (21.0)	0.155
Contralateral	192/267 (71.9)	194/307 (63.2)	62/81 (76.5)	0.02
Dual access	4/267 (1.5)	17/307 (5.5)	2/81 (2.5)	0.026
Access site position relative to lesion				0.007
Antegrade	248/267 (92.9)	257/307 (83.7)	75/81 (92.6)	0.001
Retrograde	15/267 (5.6)	33/307 (10.7)	4/81 (4.9)	0.049
Dual access	4/267 (1.5)	17/307 (5.5)	2/81 (2.5)	0.025
Inflow treatment in target limb	44/151 (29.1)	24/136 (17.6)	10/38 (26.3)	0.065
Target lesions per subject[b]	1.2±0.4 (n=214)	1.2±0.5 (n=233)	1.4±0.7 (n=56)	0.04
Devices used per subject	2.8±1.3 (n=214)	3.2±1.9 (n=233)	3.1±1.8 (n=56)	0.151
Balloons used in target lesions	242/245 (98.8)	277/283 (97.9)	73/73 (100)	0.509
BA	203/245 (82.9)	241/283 (85.2)	43/73 (58.9)	<0.001
DCB	22/245 (9.0)	12/283 (4.2)	5/73 (6.8)	0.074
Cutting	15/245 (6.1)	18/283 (6.4)	16/73 (21.9)	<0.001
Focal force	33/245 (13.5)	41/283 (14.5)	18/73 (24.7)	0.069
Scoring	2/245 (0.8)	1/283 (0.4)	1/73 (1.4)	0.352
Maximum nominal balloon diameter, mm	4.2±1.3 (n=242)	3.8±1.2 (n=277)	3.7±1.2 (n=73)	<0.001
Maximum balloon length, mm	105.7±68.7 (n=242)	140.3±74.2 (n=277)	115.1±64.4 (n=73)	<0.001
Bailout stenting	5/245 (2.0)	8/283 (2.8)	0/73	0.454
Lesions treated with atherectomy	245/245 (100)	283/283 (100)	73/73 (100)	-
Lesions treated with stent	26/245 (10.6)	26/283 (9.2)	13/73 (17.8)	0.124
DES	10/245 (4.1)	8/283 (2.8)	5/73 (6.8)	0.238
BMS	17/245 (6.9)	17/283 (6.0)	8/73 (11.0)	0.324
Covered	0/245	2/283 (0.7)	0/73	0.613
Maximum stent diameter, mm	6.1±1.0 (n=27)	5.1±1.3 (n=26)	5.2±0.8 (n=13)	0.003
Maximum stent length, mm	97.7±39.3 (n=27)	85.7±42.2 (n=26)	87.5±36.1 (n=13)	0.52
Postprocedure MLD, mm	2.8±1.2 (n=241)	2.3±1.2 (n=269)	2.2±1.1 (n=72)	<0.001
Acute MLD gain, mm	2.0±1.1 (n=238)	1.6±1.0 (n=268)	1.6±0.9 (n=72)	<0.001
Postprocedure stenosis, %	29.9±16.1 (n=241)	33.6±20.1 (n=269)	29.8±18.8 (n=72)	0.054
Procedure time, min	66.7±39.3 (n=213)	76.5±39.8 (n=232)	70.8±44.6 (n=56)	0.037
Fluoroscopy time, min	22.3±17.0 (n=213)	25.9±17.3 (n=231)	22.1±19.7 (n=56)	0.072
Contrast volume, mL	157.1±75.9 (n=214)	161.7±95.1 (n=230)	123.6±79.4 (n=56)	0.011
Antiplatelet therapy at discharge	205/214 (95.8)	220/233 (94.4)	44/56 (78.6)	<0.001
Aspirin	173/214 (80.8)	189/233 (81.1)	38/56 (67.9)	0.093
Clopidogrel	156/214 (72.9)	183/233 (78.5)	31/56 (55.4)	0.003
Prasugrel	4/214 (1.9)	12/233 (5.2)	1/56 (1.8)	0.137
Other	16/214 (7.5)	10/233 (4.3)	0/56	0.051
Dual	139/214 (65.0)	166/233 (71.2)	26/56 (46.4)	0.002
Anticoagulants at discharge	18/214 (8.4)	26/233 (11.2)	4/56 (7.1)	0.523
Warfarin	9/214 (4.2)	14/233 (6.0)	3/56 (5.4)	0.681
Other	9/214 (4.2)	12/233 (5.2)	1/56 (1.8)	0.634
Antihyperlipidemic drugs at discharge	176/214 (82.2)	196/233 (84.1)	39/56 (69.6)	0.054
Antihypertensive drugs at discharge	197/214 (92.1)	213/233 (91.4)	50/56 (89.3)	0.779
Hospitalization	61/214 (28.5)	108/233 (46.4)	31/56 (55.4)	<0.001
ICU admission	13/61 (21.3)	9/108 (8.3)	7/31 (22.6)	0.025
Length of hospital stay, h	13.3±14.1 (n=213)	33.9±72.8 (n=233)	99.0±151.0 (n=55)	<0.001

Abbreviations: BA, plain balloon angioplasty; BMS, bare metal stents; DCB, drug-coated balloon; DES, drug-eluting stents; MLD, minimum lumen diameter; RC, Rutherford category.

[a]Continuous data are presented as the mean ± standard deviation (sample size if different from the group number); categorical data are given as the number/sample (percentage). Sample sizes may differ from the group number owing to missing data.

[b]As determined by the core laboratory.

Table 4. Complications and In-Hospital Outcomes.[a]

Characteristics	RC 2-3: Claudicants (214 patients, 251 lesions)	RC 4-5: CLTI (233 patients, 289 lesions)	RC 6: CLTI (56 patients, 77 lesions)	p
Procedure success[b] per patient	170/205 (82.9)	169/213 (79.3)	38/50 (76.0)	0.434
Lesion success[b]	201/240 (83.8)	219/271 (80.8)	56/71 (78.9)	0.551
Severe angiographic complications (per lesion)	23/248 (9.3)	32/287 (11.1)	10/74 (13.5)	0.669
Severe dissection (types C-F)	4/251 (1.6)	7/289 (2.4)	2/77 (2.6)	0.741
Perforation	3/251 (1.2)	6/289 (2.1)	1/77 (1.3)	0.707
Distal embolization	16/247 (6.5)	16/287 (5.6)	6/74 (8.1)	0.487
Abrupt closure	1/251 (0.4)	7/289 (2.4)	1/77 (1.3)	0.115
MAE	0/211	0/227	3/55 (5.5)	0.001
Death	0/211	0/227	2/55 (3.6)	0.015
Major amputation	0/211	0/227	1/55 (1.8)	0.109
TVR	0/211	0/227	0/55	

Abbreviations: MAE, major adverse events; RC, Rutherford category; TVR, target vessel revascularization.
[a]Data are given as the number/sample (percentage). Sample sizes may differ from the group number owing to missing data.
[b]Success defined as <50% residual stenosis, without significant angiographic complications.

No patient in the RC 2-3 group underwent major amputation during 3 years of follow-up. The 3-year freedom from amputation estimates (Figure 1C) were 100%, 95.3% (95% CI 92.5% to 98.2%), and 88.6% (95% CI 79.1% to 98.1%) for the RC 2-3, RC 4-5, and RC 6 groups, respectively. However, the risk for the combined outcome of major amputation/death was significantly higher among the RC 6 group compared with RC 2-3 (HR 0.26, 95% CI 0.14 to 0.46, p<0.001) and RC 4-5 groups (HR 0.55, 95% CI 0.33 to 0.92, p=0.024). Patients with RC 4-5 at baseline were also at higher risk for major amputation or death at the end of follow-up compared to claudicants (RC 2-3 vs RC 4-5: HR 0.48, 95% CI 0.31 to 0.77, p=0.002).

The 3-year Kaplan-Meier estimates of freedom from major amputation/death were 84.6% (95% CI 79.3% to 89.9%) for the RC 2-3 group, 72.3% (95% CI 65.8% to 78.9%) for the RC 4-5 group, and 56.5% (95% CI 41.5% to 71.6%) for the RC 6 group. TVR was less frequently required among patients with RC 2-3 compared to patients with RC 4-5 (HR 0.67, 95% CI 0.45 to 0.99, p=0.044). Interestingly, no difference in the risk for TVR was observed between the RC 6 and other groups during 3 years of follow-up (Figure 1D).

Wound Healing

At 6 months, 5 of 174 RC 2-3 (2.9%), 35 of 172 RC 4-5 (20.3%), and 10 of 32 RC 6 (31.3%) patients were seeing a wound care specialist. At 6 months, wounds identified at baseline on the target limb had completely healed in two-thirds of RC 2-3 (66.7%), 51 of 71 RC 4-5 (65.4%), and 18 of 31 RC 6 (58.1%).

At 12 months, 3 of 165 RC 2-3 patients (1.8%), 32 of 152 RC 4-5 patients (21.1%), and 5 of 22 RC 6 patients (22.7%) were seeing a wound care specialist. At this time, wounds identified at baseline on the target limb had completely healed in 1 of 1 (100%), 17 of 27 (63.0%), and 9 of 12 (75.0%), respectively.

At 24 months, 2 of 136 RC 2-3 patients (1.5%), 12 of 112 RC 4-5 patients (10.7%), and 1 of 19 RC 6 patients (5.3%) were seeing a wound care specialist. At 24 months, wounds identified at baseline on the target limb had completely healed in 9 of 10 RC 4-5 (90%) and 2 of 2 RC 6 (100%).

Discussion

The evidence from this study supports peripheral BA with adjunctive OA in patients with CLTI or intermittent claudication as demonstrated by the low rates of periprocedural complications, the high procedural success rates, and the low major amputation rates after 3 years of follow-up. BA compared with bypass surgery has demonstrated similar limb salvage rates with shorter hospital stay and fewer periprocedural complications, even when treating patients with advanced PAD.[51,52] Therefore, endovascular intervention has been increasingly utilized for the treatment of severe claudication or CLTI.[53] Expeditious and appropriate evaluation has led to an increase in revascularization rates and subsequent reduction in amputation rates.[54,55]

Although BA with or without bare metal stenting for femoropopliteal disease has had an acceptable safety profile, the rates of restenosis are still considerable in CLTI patients.[56–58] Modification of calcified plaque and vessel preparation prior to endovascular intervention may decrease the risk of periprocedural complications, improve success rates, and achieve sustained patency over time.[25,41,48,59] The use of OA has been associated with improved angioplasty results, with low bailout stenting rates,[31,60] and has provided

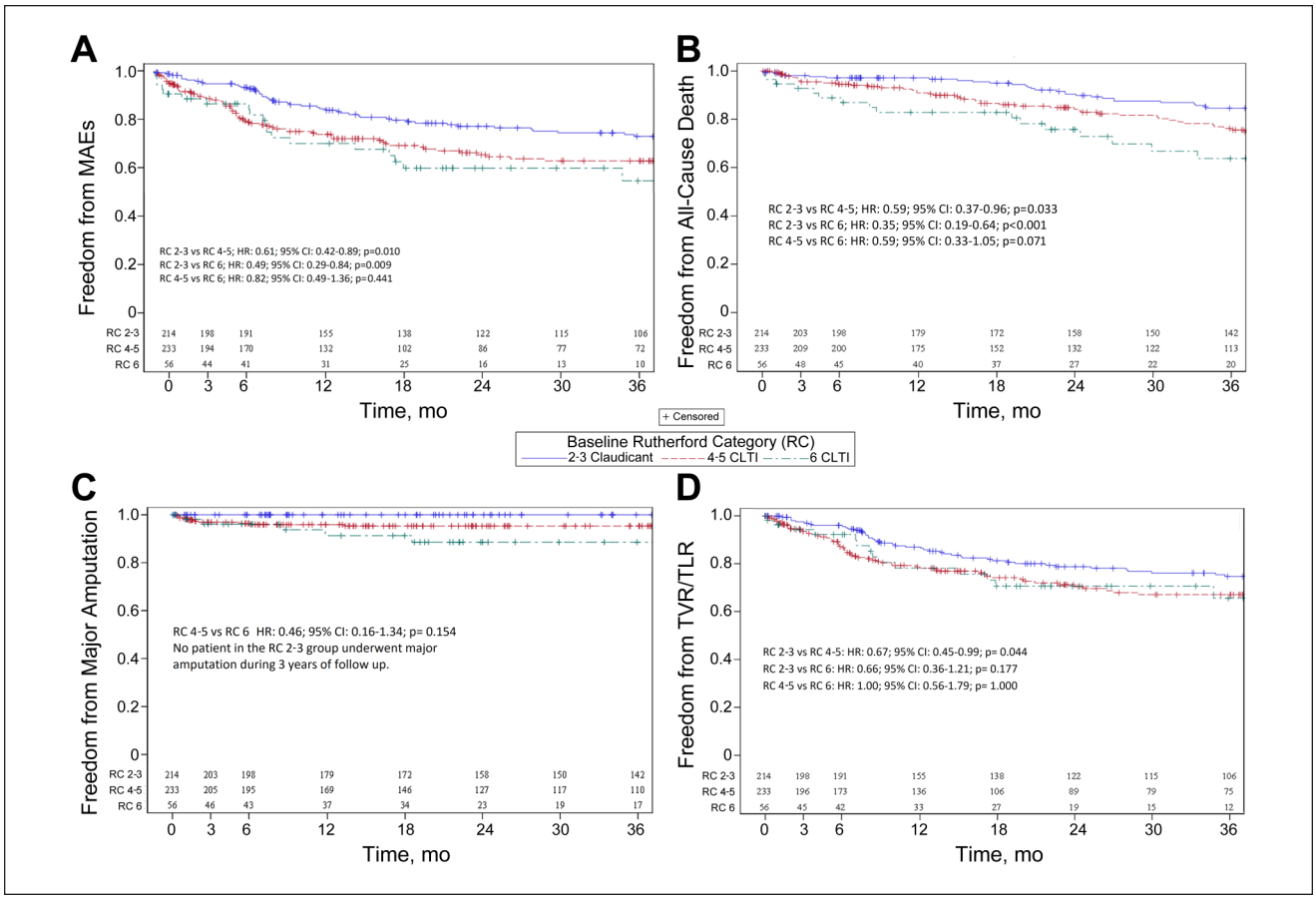

Figure 1. Kaplan-Meier estimates of freedom from (A) major adverse events (MAEs), (B) all-cause death, (C) major amputation, and (D) target vessel/limb revascularization (TVR/TLR). CLTI, chronic limb-threatening ischemia.

similar clinical outcomes (ie, dissection, slow-flow, vessel spasm, distal embolization) in patients with higher RC status at baseline and complex lesions vs patients with milder disease.[33,34,60,61] This system employs a 360° rotational device with a diamond-coated crown that orbits eccentrically within the vessel.[43] This circumferential calcium removal by OA has been hypothesized to improve vessel compliance, facilitating angioplasty and as such leading to favorable periprocedural outcomes (ie, lower rates of complications, better vessel expansion).[46,47]

The Orbital Atherectomy System for the Treatment of Peripheral Vascular Stenosis (OASIS) study, the first-in-human study investigating the outcomes of OA in infrapopliteal lesions, showed 90% procedural success and 97.4% freedom from TLR at 6 months of follow-up.[45] A prospective analysis of 3135 patients from the CONFIRM registry demonstrated that OA followed by BA performed at lower pressures was safe and was associated with a low 3.8% to 5.8% provisional stent rate.[62] In our real-world study, with most lesions being isolated calcified infrapopliteal lesions, the periprocedural complication rate was low in all 3 groups despite the unfavorable baseline and lesion characteristics of the 2 CLTI groups; bailout stenting was required in only 2.2% of all lesions. Thus, this study suggested that OA is a safe and effective modality in all RC populations, significantly decreasing the plaque burden of any type of atherosclerotic lesion in patients with any degree of PAD severity. Similarly, the Comparison of Orbital Atherectomy Plus Balloon Angioplasty vs Balloon Angioplasty Alone in Patients with Critical Limb Ischemia (CALCIUM 360°) trial, comparing the outcomes of BA + OA vs BA alone, showed fewer periprocedural complications in the combination group than the BA only arm, indicating that OA not only improves the result of an endovascular intervention but also minimizes the risk for any complications.[31]

Up to 10% of patients with PAD have CLTI, and 5% to 10% of patients with intermittent claudication or mild asymptomatic PAD will eventually progress to CLTI after 5 years.[11,12] Thus, delay of intervention may lead to PAD progression and the development of diffuse, difficult to treat lesions (ie, CLTI) and overall poor prognosis.[63] This study showed 100% 3-year freedom from amputation when utilizing BA with adjunctive OA for RC 2-3 patients, indicating that early treatment of claudication with BA + OA might

benefit this population by obtaining desirable angioplasty results; however, future prospective studies are needed to evaluate these findings.

CLTI has been associated with 20% 1-year all-cause mortality and 20% 1-year limb loss,[24] while several studies have reported up to a 50% incidence of major amputation or death within the first year of diagnosis.[16,17] In this study utilizing OA prior to BA, the 1-year major amputation rates (RC 2-3: 0%; RC 4-5: 4.1%; RC 6: 8.7%) were significantly improved relative to historical data, indicating that OA is safe and effective regardless of PAD severity.

Furthermore, the CALCIUM 360° randomized trial demonstrated that the combination of OA and BA was superior to BA alone when treating patients with CLTI.[31] The combined arm of the study demonstrated 93.3% 1-year freedom from TLR/TVR, 100% 1-year survival, and 93.3% 1-year freedom from MAE.[31] In contrast, in our study all 3 groups demonstrated lower freedom from MAE and from TVR/TLR at 1 year. The small sample size of the CALCIUM 360° study and the differences in baseline characteristics between the populations might have contributed to this discrepancy. However, in our study, combined therapy with BA + OA among CLTI patients still had acceptable survival rates (RC 4-5 76.2% and RC 6 63.7%) and very low amputation rates (4.7% and 11.4%, respectively) after 3 years. The similar risk for death or major amputation at 3 years between the 2 CLTI groups suggested that BA + OA can be effective, with acceptable hemodynamic improvement, even in difficult to treat RC 6 subjects, significantly minimizing the need for amputation in this high-risk subgroup. Additionally, the numbers of healed wounds on the target limb within the first 2 years after the primary procedure were encouraging, indicating that a good angioplasty result with adjuvant OA might contribute to better wound healing. Further research should investigate whether optimal vessel preparation with OA might lead to similar outcomes between RC 4-5 and RC 6 patients, validating our results.

Limitations

The LIBERTY study was a multicenter, core laboratory–adjudicated study that included patients who are typically excluded from large clinical trials. However, our results should be interpreted in the context of several limitations. First, the LIBERTY study was an observational nonrandomized study of endovascular therapies.[49] Second, site and patient participation bias may have occurred because not all patients treated for PAD were enrolled. Furthermore, the operator's choice regarding the most optimal therapeutic approach (eg, stenting vs BA, antithrombotic therapy, statin therapy) and the treatment or not of postangioplasty dissections might have affected the outcomes. Thereby, future studies with adequate follow-up should determine the role of statin use and optimized medical therapy (eg, antiplatelet coverage) in preventing limb ischemic events and cardiovascular mortality.

Third, it should be noted that the combined outcome of major amputation/death was significantly different between RC 4-5 and RC 6 patients, with RC 4-5 patients being at lower risk for this endpoint during follow-up, although separate analyses for death and major amputation did not show any difference between RC 4-5 and RC 6. Thus, our study might be underpowered in order to demonstrate differences in the outcomes of BA treatment between RC 6 vs RC 4-5 groups.

Moreover, at the time of patient enrollment, drug-eluting technology was not widely applied; therefore, the different rates of DCB angioplasty among the groups should be taken into account when interpreting the results of this study. Additionally, significant inflow and outflow disease (>50% stenosis) was treated at the discretion of the operator, which might have affected the outcomes. Last, it should be noted that although the lesion location exhibited high heterogeneity, with below-the-knee lesions being more prevalent among CLTI patients, sensitivity analyses for lesions limited to the infrapopliteal or femoropopliteal segment could not be synthesized.

Conclusion

The use of OA, adjunctive to BA, has been associated with improved angioplasty results, with low bailout stenting rates, and has provided similar periprocedural complications (ie, dissection, perforation, distal embolization) regardless of PAD severity. Claudication was associated with lower risk of adverse events during a 3-year follow-up among patients undergoing endovascular revascularization with adjuvant OA. Among CLTI patients, the RC at presentation was correlated only with the combined outcome of major amputation or death; no differences were identified between RC 4-5 vs RC 6 in terms of late all-cause death, MAE, TVR, or major amputation. Further studies should validate our results and investigate whether early combined BA + OA of patients with claudication is associated with improved overall prognosis. Additional studies should identify if there is any difference among patients with higher RC classifications at baseline and complex lesions vs patients with milder disease.

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Supplementary Material

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