Three-Year Outcomes From the LIBERTY 360 Study of Endovascular Interventions for Peripheral Artery Disease Stratified by Rutherford Category

Stefanos Giannopoulos, MD, Jihad Mustapha, MD, William A. Gray, MD, Gary Ansel, MD, George Adams, MD, Eric A. Secemsky, MD, and Ehrin J. Armstrong, MD, MSc

Abstract

Purpose: To report the 3-year results of the LIBERTY 360 study, which investigated outcomes of endovascular treatment of symptomatic peripheral artery disease (PAD). Materials and Methods: The LIBERTY trial (ClinicalTrials.gov identifier NCT01855412) was a prospective, observational, core laboratory–assessed, multicenter study of endovascular interventions enrolling >1200 participants treated at 51 sites. Data from 1189 patients were stratified according to Rutherford category (RC) and analyzed [RC 2-3 (n=500), RC 4-5 (n=589), and RC 6 (n=100)]. The primary outcomes were major amputation of the target limb and all-cause death; secondary outcomes were target vessel revascularization (TVR) or target lesion revascularization (TLR); major adverse events (MAEs; death within 30 days, TVR or TLR, and major amputation); death or major amputation combined; and change in self-reported quality of life (QoL) measures (VascuQol-25). The Kaplan-Meier (KM) method was employed to estimate the outcomes; estimates are presented with the 95% confidence intervals (CI). Predictors of 3-year MAE, death, TVR, and major amputation were analyzed using Cox proportional hazard regression modeling. Results: The 36-month KM survival rates were 86.0% in RC 2-3, 79.8% in RC 4-5, and 62.0% in RC 6 groups. The KM estimates of freedom from major amputation at 36 months were 98.5% in RC 2-3, 94.0% in RC 4-5, and 79.9% in RC 6. The 36-month KM estimates for freedom from TVR/TLR were 71.1% in RC 2-3, 64.2% in RC 4-5 and 61.9% in RC 6 groups. Patients with claudication at baseline were at lower risk for MAEs compared with RC 4-5 and RC 6 patients during the 36-month follow-up. Vascular QoL improved from baseline and persisted up to 36 months in all patients. Conclusion: Endovascular therapy is a viable treatment option for patients with symptomatic PAD, with sustained improved quality of life in both claudicants and patients with chronic limb-threatening ischemia. These results provide important point estimates for midterm outcomes after modern endovascular interventions for PAD.

Keywords
amputation, claudication, chronic limb-threatening ischemia, critical limb ischemia, endovascular therapy, mortality, peripheral artery disease, revascularization, Rutherford category

Introduction

It has been estimated that >200 million people worldwide suffer from peripheral artery disease (PAD), while its prevalence is expected to increase over the next 2 decades. The severity of PAD can be categorized according to the Rutherford category (RC) as mild to severe intermittent claudication (RC 1-3) or chronic limb-threatening ischemia (CLTI) without (RC 4) or with (RC 5-6) tissue loss. CLTI, which constitutes the most severe form of PAD, is a diffuse vascular disease that affects up to 10% of PAD patients. CLTI is associated with up to 45% 1-year mortality and high rates of major amputation, which significantly increases the utilization of healthcare resources. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that revascularization should be performed for the treatment of lifestyle-limiting claudication (RC 2-3) or CLTI (RC 4-6)
when optimized medical therapy and/or exercise fail to adequately relieve the symptoms, although this applies to heterogeneous groups of patients with moderate to severe disease. However, data regarding the best revascularization strategies for CLTI are sparse.

The LIBERTY 360 study was designed to provide evidence related to optimal revascularization strategies and the associated outcomes, especially for patients with CLTI. LIBERTY 360 is one of the largest, real-world, core laboratory–adjudicated studies to include patients with varying degrees of PAD severity. The 12-month results of this study have been previously published and supported endovascular therapy as a viable treatment option for RC 2-3, RC 4-5, and even RC 6 patients. Based on the need for additional post-markert analyses and studies with longer follow-up, this article presents the 3-year results of endovascular treatment of the participants enrolled in the LIBERTY 360 study.

Materials and Methods

Study Design and Patient Enrollment

LIBERTY 360 was a prospective, observational, multicenter clinical study to evaluate acute and long-term clinical and economic outcomes of endovascular interventions using any Food and Drug Administration (FDA)–approved or cleared endovascular device in symptomatic patients with distal outflow PAD. Procedures were performed 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 protocol, while the sponsor was responsible for oversight of the research process. The institutional review boards of the 51 participating sites (Supplementary Table 1; available in the online version of the article) approved the study protocol. All patients provided written informed consent, and this trial was conducted in accordance with the Declaration of Helsinki. The trial was registered on the National Institutes of Health website (ClinicalTrials.gov identifier NCT01855412).

The current study included patients with varying degrees of PAD severity treated with endovascular techniques at the discretion of the operator. 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 into 10 cm above the medial epicondyle to the digital arteries. Eligible participants were additionally required to have at least 1 lesion in the target vessel successfully crossed and endovascularly treated with an FDA-approved or cleared endovascular device. Patients requiring conversion to an open procedure, surgical revascularization, or with a life span <1 year were excluded from the study, as were patients with in-stent restenotic lesions in the target vessel. Detailed information about the inclusion and exclusion criteria of the LIBERTY 360 study were previously reported and can also be found at clinicaltrials.gov/ct2/show/NCT01855412.

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.

Among the 1204 participants enrolled in the Liberty 360 study, data from 1189 patients were analyzed and stratified according to RC 2-3 (n=500), RC 4-5 (n=589), and RC 6 (n=100). Fifteen participants were excluded owing to incomplete records. Patient and lesion characteristics stratified by RC are presented in Tables 1 and 2, respectively, and graphically illustrated in Figure 1. Over half of the patients (57.6%, 685/1189) completed the 2- and 3-year follow-up. Details regarding participant accountability are presented in Supplementary Table 2. Overall, 1528 lesions were treated (605 in the RC 2-3 group, 755 in the RC 4-5 group, and 148 in the RC 6 group). Over half of the lesions (51.4%) were located solely in the infrapopliteal segment and a third (35.3%) were in the femoropopliteal segment, while the remainder of the lesions (13.2%) involved diffuse segments above and below the knee.

As shown in Table 2, patients with CLTI had a longer average target lesion length, smaller mean reference vessel diameter, and more stenosed lesions, with a smaller mean minimum lumen diameter at the target lesion (0.6 mm for the RC 4-5 and RC 6 groups vs 0.7 mm for the RC 2-3 group). Predominately calcified lesions were observed in 58.5% (830/1418) of the lesions, without any difference among the groups.

Study Outcomes and Statistical Analysis

The primary outcomes were major amputation of the target limb and all-cause death. Secondary outcomes were target vessel revascularization (TVR) or target lesion revascularization...
### Table 1. Baseline Characteristics of the Participants.\(^d\)

| Characteristics                                                                 | RC 2-3: Claudicants\(^b\) (n=500) | RC 4-5: CLTI (n=589) | RC 6: CLTI (n=100) | p     |
|---------------------------------------------------------------------------------|----------------------------------|----------------------|---------------------|-------|
| **Age, y**                                                                      | 69.7±10.0 (n=500)                | 70.3±10.9 (n=589)    | 68.0±13.0 (n=99)    | 0.139 |
| **Race**                                                                        |                                  |                      |                     |       |
| American Indian or Alaska Native                                                | 1 (0.2)                          | 4 (0.7)              | 0 (0.0)             | 0.601 |
| Asian                                                                           | 5 (1.0)                          | 1 (0.2)              | 1 (0.1)             | 0.119 |
| Black or African American                                                       | 68 (13.6)                        | 89 (15.1)            | 21 (21.0)           | 0.170 |
| Native Hawaiian or other Pacific Islander                                       | 1 (0.2)                          | 1 (0.2)              | 0 (0.0)             | 1.000 |
| White                                                                           | 411 (82.2)                       | 483 (82.0)           | 78 (78.0)           | 0.574 |
| Other                                                                           | 14 (2.8)                         | 11 (1.9)             | 0 (0.0)             | 0.192 |
| **Body mass index, kg/m\(^2\)**                                                 | 28.8±5.3 (n=500)                 | 29.1±6.2 (n=589)     | 29.1±7.6 (n=100)    | 0.569 |
| **eGFR, mg/dL/1.73 m\(^2\)**                                                   | 68.5±28.0 (n=500)                | 59.7±27.6 (n=589)    | 56.7±37.1 (n=99)    | <0.001|
| **Smoking history**                                                             |                                  |                      |                     |       |
| Current smoker                                                                  | 110 (22.0)                       | 100 (17.0)           | 16 (16.0)           | 0.084 |
| Former smoker                                                                   | 260 (52.0)                       | 278 (47.2)           | 45 (45.0)           | 0.204 |
| **Diabetes**                                                                    |                                  |                      |                     |       |
| Hyperlipidemia                                                                  | 454 (90.8)                       | 510 (86.6)           | 69 (69.0)           | <0.001|
| Hypertension                                                                    | 468 (93.6)                       | 549 (93.2)           | 93 (93.0)           | 0.939 |
| Renal disease                                                                   | 137 (27.4)                       | 232 (39.4)           | 43 (43.0)           | <0.001|
| Hemodialysis                                                                    | 17 (12.4)                        | 48 (20.7)            | 22 (51.2)           | <0.001|
| Coronary artery disease                                                         | 288 (59.6)                       | 375 (63.7)           | 54 (54.0)           | 0.119 |
| Myocardial infarction                                                           | 115 (23.0)                       | 155 (26.3)           | 15 (15.0)           | 0.037 |
| Stroke/TIA                                                                     | 77 (15.4)                        | 92 (15.6)            | 9 (9.0)             | 0.213 |
| **Runoff vessels\(^c\)**                                                       |                                  |                      |                     |       |
| Pretreatment                                                                    | 410 (82.2)                       | 532 (90.0)           | 83 (83.0)           | 0.005 |
| Posttreatment                                                                   | 341 (68.2)                       | 463 (85.0)           | 71 (71.0)           | 0.752 |
| **Previous EVT of target limb**                                                 |                                  |                      |                     |       |
| No                                                                              | 358 (71.6)                       | 394 (66.9)           | 75 (75.0)           | 0.085 |
| Yes                                                                             | 140 (28.0)                       | 194 (33.1)           | 25 (25.0)           | 0.004 |
| Unknown                                                                        | 2 (0.4)                          | 1 (0.2)              | 0 (0.0)             |       |
| **Previous bypass surgery of target limb**                                      | 479 (95.8)                       | 566 (96.1)           | 94 (94.0)           | 0.465 |
| No                                                                              | 19 (3.8)                         | 22 (3.7)             | 6 (6.0)             |       |
| Yes                                                                             | 2 (0.4)                          | 1 (0.2)              | 0 (0.0)             |       |
| **Prior stent placed in target limb**                                           | 413 (82.6)                       | 504 (85.6)           | 86 (86.0)           | 0.622 |
| No                                                                              | 85 (17.0)                        | 84 (14.3)            | 14 (14.0)           |       |
| Yes                                                                             | 2 (0.4)                          | 1 (0.2)              | 0 (0.0)             |       |
| **Antithrombotic therapy at discharge**                                         | 484 (96.8)                       | 554 (94.1)           | 83 (83.0)           | <0.001|
| Aspirin                                                                        | 405 (81.0)                       | 478 (81.2)           | 71 (71.0)           | 0.066 |
| Clopidogrel                                                                    | 384 (76.8)                       | 456 (77.4)           | 53 (53.0)           | <0.001|
| Dual antiplatelet therapy                                                      | 336 (67.2)                       | 425 (72.2)           | 45 (45.0)           | <0.001|
| Anticoagulants                                                                 | 44 (8.8)                         | 70 (11.9)            | 8 (8.0)             | 0.207 |
| Warfarin                                                                       | 25 (5.0)                         | 45 (7.6)             | 6 (6.0)             | 0.211 |
| Other anticoagulants                                                           | 19 (3.8)                         | 25 (4.2)             | 3 (3.0)             | 0.870 |
| **Antihyperlipidemic therapy**                                                  | 409 (81.8)                       | 466 (79.1)           | 70 (70.0)           | 0.032 |
| **Antihypertensive therapy**                                                   | 461 (92.2)                       | 529 (89.8)           | 88 (88.0)           | 0.237 |
| **Hospitalization**                                                            | 153 (30.6)                       | 304 (51.6)           | 61 (61.0)           | <0.001|
| **ICU admissions**                                                             | 28 (18.3)                        | 24 (7.9)             | 16 (26.2)           | <0.001|
| **Time from admission to discharge, h**                                         | 14.2±16.1 (n=496)                | 32.0±73.4 (n=588)    | 106.3±169.8 (n=99)  | <0.001|

Abbreviations: CLTI, chronic limb-threatening ischemia; eGFR, estimated glomerular filtration rate; EVT, endovascular therapy; ICU, intensive care unit; TIA, transient ischemic attack.

\(^d\)Continuous data are presented as the mean ± standard deviation (sample size if different from group number); categorical data are given as the number (percentage).

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

\(^c\)As determined by the core laboratory.
(TLR); major adverse events (MAEs) defined as death within 30 days of the primary procedure, TVR or TLR, and major amputation; death or major amputation combined; and change in self-reported quality of life measures from the Vascular Quality of Life Questionnaire (VascuQol-25).

Categorical variables are presented as the number (percentage) and were compared with Monte Carlo approximation of the Fisher exact test. Numerical data are presented as mean ± standard deviation or median [interquartile range (IQR) Q1, Q3] and were compared using analysis of variance or a paired t test. Discrete data were compared with the Kruskal-Wallis test or the Wilcoxon signed rank test when they were paired. Significant angiographic complications for procedural and lesion success outcomes were imputed using site data when the core laboratory

Table 2. Baseline Lesion Characteristics.a

| Characteristics                                      | RC 2-3: Claudicantsb (n=605) | RC 4-5: CLTI (n=775) | RC 6: CLTI (n=148) | p     |
|------------------------------------------------------|------------------------------|----------------------|-------------------|-------|
| ATK or BTK lesions                                   | n=605                        | n=775                | n=148             | <0.001|
| ATK only                                             | 293 (48.4)                   | 207 (26.7)           | 40 (27.0)         | <0.001|
| ATK and BTK                                          | 80 (13.2)                    | 103 (13.3)           | 18 (12.2)         | 0.959 |
| BTK only                                             | 232 (38.3)                   | 464 (59.9)           | 89 (60.1)         | <0.001|
| Unknown                                              | 0 (0.0)                      | 1 (0.1)              | 1 (0.7)           | 0.184 |
| Lesion location                                      | n=605                        | n=775                | n=148             | <0.001|
| SFA only                                             | 78 (12.9)                    | 23 (3.0)             | 6 (4.1)           | <0.001|
| SFA to popliteal                                     | 99 (16.4)                    | 86 (11.1)            | 13 (8.8)          | 0.005 |
| SFA to BTK                                           | 18 (3.0)                     | 26 (3.4)             | 3 (2.0)           | 0.757 |
| Popliteal only                                       | 116 (19.2)                   | 98 (12.6)            | 21 (14.2)         | 0.004 |
| Popliteal to BTK                                     | 62 (10.2)                    | 77 (9.9)             | 15 (10.1)         | 0.965 |
| BTK only                                             | 232 (38.3)                   | 464 (59.9)           | 89 (60.1)         | <0.001|
| Unknown                                              | 0 (0.0)                      | 1 (0.1)              | 1 (0.7)           | 0.192 |
| Target lesion length, mm                            | n=562                        | n=727                | n=137             | <0.001|
| <40                                                  | 206 (36.7)                   | 190 (26.1)           | 45 (32.8)         | <0.001|
| 40–99                                                | 185 (32.9)                   | 190 (26.1)           | 31 (22.6)         | 0.007 |
| ≥100                                                 | 171 (30.4)                   | 347 (47.7)           | 61 (44.5)         | <0.001|
| Distal RVD, mm                                       | 3.8 ± 1.2 (n=578)            | 3.2 ± 1.2 (n=745)    | 3.0 ± 1.1 (n=140) | <0.001|
| Preprocedure MLD, mm                                 | 0.7 ± 0.8 (n=589)            | 0.6 ± 0.8 (n=750)    | 0.6 ± 0.8 (n=144) | 0.002 |
| Preprocedure stenosis, %                             | 80.7 ± 19.2 (n=590)          | 83.3 ± 19.7 (n=753)  | 80.5 ± 20.1 (n=145)| 0.027 |
| Chronic total occlusion                              | 195/590 (33.1)               | 331/753 (44.0)       | 57/145 (39.3)     | <0.001|
| TASC type                                            | n=581                        | n=744                | n=142             | <0.001|
| A                                                     | 366 (63.0)                   | 348 (46.8)           | 68 (47.9)         | <0.001|
| B                                                     | 105 (18.1)                   | 129 (17.3)           | 34 (23.9)         | 0.185 |
| C                                                     | 65 (11.2)                    | 141 (19.0)           | 20 (14.1)         | <0.001|
| D                                                     | 45 (7.7)                     | 126 (16.9)           | 20 (14.1)         | <0.001|
| Predominantly calcified plaque                       | 334/560 (59.6)               | 411/717 (57.3)       | 85/141 (60.3)     | 0.646 |
| PARC stenosis                                         | n=590                        | n=753                | n=145             | 0.004 |
| Mild                                                 | 46 (7.8)                     | 49 (6.5)             | 11 (7.6)          | 0.630 |
| Moderate                                             | 128 (21.7)                   | 135 (17.9)           | 36 (24.8)         | 0.069 |
| Severe                                               | 221 (37.5)                   | 238 (31.6)           | 41 (28.3)         | 0.027 |
| Occluded                                             | 195 (33.1)                   | 331 (44.0)           | 57 (39.3)         | <0.001|
| PARC concentric calcification                        | n=530                        | n=672                | n=130             | 0.016 |
| None                                                 | 226 (42.6)                   | 306 (45.5)           | 56 (43.1)         | 0.591 |
| Focal                                                | 37 (7.0)                     | 51 (7.6)             | 5 (3.8)           | 0.315 |
| Mild                                                 | 71 (13.4)                    | 54 (8.0)             | 6 (4.6)           | 0.001 |
| Moderate                                             | 78 (14.7)                    | 102 (15.2)           | 26 (20.0)         | 0.329 |
| Severe                                               | 118 (22.3)                   | 159 (23.7)           | 37 (28.5)         | 0.318 |

Abbreviations: ATK, above the knee; BTK, below the knee; CLTI, chronic limb-threatening ischemia; 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.

aContinuous data are presented as the mean ± standard deviation (sample size if different from group number); categorical data are given as the number (percentage).

bTwo patients (with a total of 3 wounds) were classified as RC 2-3 by the treating physician and were therefore analyzed with that group.
was unable to perform angiographic assessment. No additional imputation methods were used to manage missing data, as such the denominators may change based on available data.

The Kaplan-Meier method was employed to estimate the probability of the primary and secondary outcomes over time for patients in each group; estimates are presented with the 95% confidence intervals (CI). Predictors of 3-year MAE, death, TVR, and major amputation were analyzed using Cox proportional hazard regression modeling. Traditional predictors of adverse outcomes and relevant patient baseline characteristics were selected as covariates. The results are presented as the hazard ratio (HR) and 95% CI. Multivariate models were synthesized with the significant covariates (ie, \( p < 0.1 \)) using a stepwise selection process (entry criterion \( p = 0.15 \); stay criterion \( p = 0.05 \)).

Procedural outcomes were compared using logistic regression analysis. A \( p < 0.05 \) was considered statistically significant for all tests. Statistical analyses were conducted by NAMSA (Northwood, OH, USA).

**Results**

As described in Table 3, balloon angioplasty with or without atherectomy ± stenting was the preferred treatment method. The procedure was successful for the majority of subjects among all RC groups, while the incidence of severe angiographic complications was low, without any significant differences among the groups. Detailed procedural and postprocedural characteristics, as well as short-term outcomes were previously published.17 The odds ratios for associations of per-lesion and per-patient success and angiographic complications in RC 2-3 vs RC 4-5, RC 2-3 vs RC 6, and RC 4-5 vs RC 6 are presented in Supplementary Table 3.

**Outcomes in Follow-up**

As shown in Supplementary Table 4, the mean RC improved from baseline through 24 months in all groups. The median ankle-brachial index values at 24-month follow-up were 0.95 (IQR 0.77, 1.08) in RC 2-3 (n=284), 0.96 (IQR 0.82, 1.08) in RC 4-5 (n=246), and 0.97 (IQR 0.71, 1.17) in RC 6 (n=20).

The Kaplan-Meier estimates of freedom from MAEs at 24 and 36 months were 74.6% (95% CI 70.5% to 78.7%) and 70.3% (95% CI 65.9% to 74.7%), respectively, in RC 2-3; 65.3% (95% CI 61.0% to 69.6%) and 62.0% (95% CI 57.5% to 66.5%) in RC 4-5; and 51.0% (95% CI 39.5% to 62.5%) and 47.4% (95% CI 34.7% to 60.0%) in RC 6, with statistically significant differences among all groups.

The estimates of freedom from major amputation (Figure 2A) at 24 and 36 months were 99.1% (95% CI 98.2% to 100.0%) and 98.5% (95% CI 97.3% to 99.7%), respectively, in RC 2-3; 94.6% (95% CI 92.6% to 96.6%) and 94.0% (95% CI 91.8% to 96.1%) in RC 4-5; and 79.9% (95% CI 70.8% to 88.3%) and 79.9% (95% CI 70.8% to 88.9%) in RC 6. Patients with CLTI (ie, RC 4-6) at presentation had significantly worse amputation survival rates compared with the RC 2-3 group. Moreover, patients with RC 6 at baseline had worse freedom from amputation rates than the RC 4-5 group.

The 24- and 36-month Kaplan-Meier estimates of freedom from all-cause death (Figure 2B) were 91.4% (95% CI 88.8% to 94.0%) and 86.0% (95% CI 82.7% to 89.3%), respectively, in RC 2-3; 85.9% (95% CI 82.9% to 89.0%) and 79.8% (95% CI 76.2% to 83.5%) in RC 4-5; and 71.6% (95% CI 61.9% to 81.4%) and 62.0% (95% CI 50.5% to 73.6%) in RC 6 groups, with significant differences among all groups.
### Table 3. Procedure Characteristics and Target Lesion Device Use.

| Characteristics                              | RC 2-3: Claudicants (500 patients, 605 lesions) | RC 4-5: CLTI (589 patients, 775 lesions) | RC 6: CLTI (100 patients, 148 lesions) | p   |
|----------------------------------------------|-----------------------------------------------|----------------------------------------|----------------------------------------|-----|
| Target lesion access site                    | n=654                                         | n=852                                  | n=158                                  | <0.001 |
| Femoral                                      | 618 (94.5)                                    | 796 (93.4)                             | 149 (94.3)                             | 0.701 |
| Popliteal                                    | 5 (0.8)                                       | 4 (0.5)                                | 1 (0.6)                                | 0.640 |
| Tibial                                       | 33 (5.0)                                      | 63 (7.4)                               | 5 (3.2)                                | 0.051 |
| Pedal                                        | 8 (1.2)                                       | 50 (5.9)                               | 8 (5.1)                                | <0.001 |
| Brachial                                     | 2 (0.3)                                       | 1 (0.1)                                | 0 (0.0)                                | 0.693 |
| Approach                                     | n=654                                         | n=852                                  | n=158                                  | <0.001 |
| Ipsilateral                                  | 149 (22.8)                                    | 225 (26.4)                             | 31 (19.6)                              | 0.097 |
| Contralateral                                | 492 (75.2)                                    | 560 (65.7)                             | 120 (75.9)                             | <0.001 |
| Dual access                                  | 13 (2.0)                                      | 67 (7.9)                               | 7 (4.4)                                | <0.001 |
| Access site position relative to lesion      | n=654                                         | n=852                                  | n=158                                  | <0.001 |
| Antegrade                                    | 603 (92.2)                                    | 727 (85.3)                             | 143 (90.5)                             | <0.001 |
| Retrograde                                   | 38 (5.8)                                      | 58 (6.8)                               | 8 (5.1)                                | 0.631 |
| Dual access                                  | 13 (2.0)                                      | 67 (7.9)                               | 7 (4.4)                                | <0.001 |
| Target lesions treated per subject           | 1.2±0.5 (n=497)                               | 1.3±0.6 (n=588)                        | 1.5±0.7 (n=99)                         | <0.001 |
| Devices used per subject                     | 3.3±1.8 (n=500)                               | 3.4±2.1 (n=589)                        | 3.4±2.2 (n=100)                        | 0.983 |
| Device information available from site        | 597/605 (98.7)                                | 766/775 (98.8)                         | 142/148 (95.9)                         | 0.014 |
| Balloons used in target lesions              | 578/597 (96.8)                                | 740/766 (96.6)                         | 141/142 (99.3)                         | 0.222 |
| Conventional                                 | 494/597 (82.7)                                | 635/766 (82.9)                         | 96/142 (67.6)                          | <0.001 |
| DCB                                          | 74/597 (12.4)                                 | 54/766 (7.0)                           | 11/142 (7.7)                           | 0.003 |
| Cutting                                      | 42/597 (7.0)                                  | 58/766 (7.6)                           | 26/142 (18.3)                          | <0.001 |
| Focal force                                   | 73/597 (12.2)                                 | 97/766 (12.7)                          | 31/142 (21.8)                          | 0.013 |
| Scoring                                      | 3 (0.5)                                       | 7 (0.9)                                | 4 (2.8)                                | 0.048 |
| Maximum nominal balloon diameter, mm         | 4.4±1.4 (n=578)                               | 3.8±1.4 (n=740)                        | 3.8±1.3 (n=141)                        | <0.001 |
| Maximum balloon length, mm                   | 109.0±68.3 (n=578)                            | 141.2±107.5 (n=740)                   | 122.7±67.0 (n=141)                     | <0.001 |
| Lesions treated with atherectomy             | 437/597 (73.2)                                | 495/766 (64.6)                         | 107/142 (75.4)                         | 0.001 |
| Diamondback/Stealth device                   | 274/597 (45.9)                                | 347/766 (45.3)                         | 88/142 (62.0)                          | 0.001 |
| Bailout stenting                             | 27/597 (4.5)                                  | 34/766 (4.4)                           | 0/142 (0.0)                            | 0.011 |
| Lesions treated with stent                   | 120/597 (20.1)                                | 111/766 (14.5)                         | 25/142 (17.6)                          | 0.023 |
| DES                                          | 34/597 (5.7)                                  | 37/766 (4.8)                           | 12/142 (8.5)                           | 0.204 |
| BMS                                          | 88/597 (14.7)                                 | 72/766 (9.4)                           | 16/142 (11.3)                          | 0.010 |
| Covered                                      | 5/597 (0.8)                                   | 6/766 (0.8)                            | 0/142 (0.0)                            | 0.812 |
| Maximum stent diameter, mm                   | 5.8±1.1 (n=122)                               | 5.2±1.4 (n=111)                        | 4.9±1.1 (n=25)                         | <0.001 |
| Maximum stent length, mm                     | 95.5±45.0 (n=122)                             | 82.4±48.1 (n=111)                     | 86.6±39.2 (n=25)                       | 0.091 |
| Postprocedure MLD, mm                        | 2.9±1.2 (n=575)                               | 2.3±1.2 (n=723)                        | 2.2±1.2 (n=142)                        | <0.001 |
| Acute MLD gain, mm                           | 2.1±1.2 (n=571)                               | 1.7±1.1 (n=715)                        | 1.5±0.9 (n=140)                        | <0.001 |
| Postprocedure stenosis, %                    | 29.5±15.9 (n=577)                             | 33.9±20.8 (n=724)                     | 35.0±23.5 (n=142)                      | <0.001 |
| Procedure time, min                          | 72.2±43.5 (n=499)                             | 82.8±45.5 (n=588)                     | 79.4±44.9 (n=100)                      | <0.001 |
| Fluoroscopy time, min                        | 23.9±18.7 (n=497)                             | 26.9±17.6 (n=585)                     | 25.5±21.1 (n=99)                       | 0.030 |
| Contrast volume, mL                          | 167.7±88.5 (n=499)                            | 169.4±91.6 (n=586)                    | 146.3±95.0 (n=100)                     | 0.059 |
| Hospitalization                              | 153/500 (30.6)                                | 304/589 (51.6)                        | 61/100 (61.0)                          | <0.001 |
| ICU admissions                                | 28/153 (18.3)                                 | 24/304 (7.9)                          | 16/61 (26.2)                           | <0.001 |
| Time from admission to discharge, h          | 14.2±16.1 (n=496)                             | 32.0±73.4 (n=588)                     | 106.3±169.8 (n=99)                     | <0.001 |

Abbreviations: BMS, bare metal stents; CLTI, chronic limb-threatening ischemia; DCB, drug-coated balloon; DES, drug-eluting stents; ICU, intensive care unit; MLD, minimum lumen diameter; RC, Rutherford category.

aContinuous data are presented as the mean ± standard deviation (sample size if different from group number); categorical data are given as the number/sample (percentage).

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

cAs determined by the core laboratory.

The 24- and 36-month Kaplan-Meier estimates for freedom from TLR/TVR were 75.1% (95% CI 71.0% to 79.1%) and 71.1% (95% CI 66.7% to 75.4%), respectively, in RC 2-3; 67.7% (95% CI 63.5% to 72.0%) and 64.2% (95% CI 59.7% to 68.6%) in RC 4-5; and 65.7% (95% CI 54.5% to 76.9%) and 61.9% (95% CI 49.0% to 74.7%) in the RC 6.
groups. Interestingly, at 36 months of follow-up, there was a suggestion of lower freedom from TVR/TLR rates among RC 6 patients vs the RC 2-3 group (p=0.050), whereas the TVR/TLR rates were similar between the RC 4-5 and RC 6 groups (p=0.776).

Patients with claudication at presentation were at lower risk for MAEs at 36 months (RC 2-3 vs RC 4-5: HR 0.68, 95% CI 0.55 to 0.86, p<0.001; RC 2-3 vs RC 6: HR 0.40, 95% CI 0.28 to 0.57, p<0.001), all-cause death (RC 2-3 vs RC 4-5: HR 0.65, 95% CI 0.47 to 0.90, p=0.010; RC 2-3 vs RC 6: HR 0.28, 95% CI 0.18 to 0.44, p<0.001), major amputation (RC 2-3 vs RC 4-5: HR 0.22, 95% CI 0.09 to 0.52, p<0.001; RC 2-3 vs RC 6: HR 0.05, 95% CI 0.02 to 0.14, p<0.001), and major amputation/death (RC 2-3 vs RC 4-5: HR 0.54, 95% CI 0.40 to 0.73, p<0.001; RC 2-3 vs RC 6: HR 0.20, 95% CI 0.13 to 0.30, p<0.001). The RC 2-3 group was also less likely to require TVR at 24 months compared to the RC 4-5 group (HR 0.70, 95% CI 0.55 to 0.89, p=0.004) and the RC 6 group (HR 0.64, 95% CI 0.41 to 0.98, p=0.042). At 36-month follow-up, the risk for TVR was lower for the RC 2-3 vs RC 4-5 groups (HR 0.72, 95% CI 0.57 to 0.91, p=0.006). No statistical difference was observed between RC 2-3 vs RC 6 (HR 0.66, 95% CI 0.43 to 1.00, p=0.052), although a strong trend for higher risk of TVR was observed among RC 6 patients.

**Predictors of 3-Year MAEs**

As listed in Table 4, a multivariable analysis identified statistically significant predictors of 3-year MAE, specifically, age (HR 0.99, 95% CI 0.98 to 1.00, p=0.009), number of wounds on the target limb at baseline (HR 1.17, 95% CI 1.08 to 1.28, p<0.001), total treated lesion length (HR 1.01, 95% CI 1.00 to 1.02, p=0.03), history of previous lower limb endovascular interventions (HR 1.53, 95% CI 1.20 to 1.95, p=0.001), previous major (above ankle) amputation on the nontarget limb (HR 1.66, 95% CI 1.01 to 2.73, p=0.048), number of target limb procedures in the past 3 years (HR 1.08, 95% CI 1.03 to 1.13, p=0.003), and the presence of chronic total occlusion at baseline (HR 1.88, 95% CI 1.45 to 2.45, p<0.001).

Age (HR 1.03, 95% CI 1.01 to 1.05, p<0.001), the number of wounds on the target limb at baseline (HR 1.27, 95% CI 1.13 to 1.43, p<0.001), history of previous major amputation on the nontarget limb (HR 1.84, 95% CI 1.01 to 3.34, p=0.045), history of renal disease (HR 2.11, 95% CI 1.54 to 2.89, p<0.001), Rutherford category at baseline (HR not estimable, p=0.016), and history of stroke/transient ischemic attack (HR 1.83, 95% CI 1.24 to 2.71, p=0.002) were associated with increased mortality risk at 3-year follow-up.

In addition, there was higher risk for major amputation during 3 years of follow-up in patients with more wounds on the target limb at baseline (HR 1.27, 95% CI 1.03 to 1.58, p=0.027), a history of myocardial infarction (HR 2.52, 95% CI 1.27 to 4.99, p=0.008), distal lesions treated (HR not estimable; p=0.033), previous major amputation on the non-target limb (HR 2.70, 95% CI 1.08 to 6.74, p=0.033), a history of renal disease (HR 2.19, 95% CI 1.14 to 4.19, p=0.018), and worse RC at baseline (HR not estimable; p<0.001).

TVR was more likely to be necessary for patients with more wounds on the target limb at baseline (HR 1.15, 95% CI 1.05 to 1.26, p=0.003), a history of previous lower limb endovascular treatments (HR 1.49, 95% CI 1.16 to 1.92, p=0.002), and chronic total occlusions (HR 2.00, 95% CI 1.80 to 2.92, p<0.001) at 3 years of follow-up. The number of previous (up to 3 years before the index procedure) target limb procedures was also correlated with increased risk for TVR during follow-up (HR 1.08, 95% CI 1.03 to 1.14, p=0.003).

**Quality of Life**

Vascular-related quality of life improved from baseline, and the change in total score was maintained at 12 months (RC 2-3: 1.0±1.3; RC 4-5: 1.2±1.4; RC 6: 1.5±1.2), 24 months...
(RC 2-3: 1.0 ± 1.2; RC 4-5: 1.1 ± 1.4; RC 6: 1.3 ± 1.5), and 36 months (RC 2-3: 1.0 ± 1.3; RC 4-5: 1.1 ± 1.5; RC 6: 1.1 ± 1.4). Two- and 3-year VascuQoL total scores were 5.3 ± 1.3 and 5.3 ± 1.4, respectively, in RC 2-3, 5.0 ± 1.4 and 5.0 ± 1.4 in RC 4-5, and 4.7 ± 1.5 and 4.7 ± 1.6 in RC 6 groups.

**Wound Healing**

At 6 months of follow-up, 10 of 409 RC 2-3 patients (2.4%), 103 of 431 RC 4-5 patients (23.9%), and 21 of 49 RC 6 patients (42.9%) were seeing a wound care specialist. At 12 months of follow-up, 8 of 379 RC 2-3 patients (2.1%), 76 of 390 RC 4-5 patients (19.5%), and 9 of 35 RC 6 patients (25.7%) were seeing a wound care specialist. At 12 months, 4 of 6 wounds (66.7%) identified at baseline on the target limb had completely healed, while 161 of 215 wounds (74.9%) in RC 4-5 patients and 34 of 51 wounds (66.7%) in RC 6 patients were healed.
At 24 months, 6 of 314 RC 2-3 patients (1.9%), 36 of 301 RC 4-5 patients (12.0%), and 2 of 27 RC 6 patients (7.4%) were seeing a wound care specialist. By 2 years, 4 of 5 wounds (80.0%) identified at baseline in RC 2-3 patients, 181 of 185 wounds (97.8%) in RC 4-5 patients, and 41 of 44 wounds (93.2%) in RC 6 patients had completely healed.

Discussion
This analysis of the LIBERTY 360 trial investigated the 3-year outcomes of investigator-selected endovascular procedures performed in patients with symptomatic PAD. The 12-month results of the LIBERTY study supported a role for endovascular interventions to treat all symptomatic patients with claudication or CLTI. The current analysis confirmed this observation and demonstrated sustained improvement in quality of life measures and significant amputation prevention during 36 months of follow-up. Although there were significant discrepancies in clinical and lesion characteristics among the groups at baseline, the 36-month survival rates were promising for all 3 groups (RC 2-3, 86.0%; RC 4-5, 79.8%; RC 6, 62.0%). However, as expected, the sicker patients at baseline had more adverse events (ie, major amputation) during follow-up, so the RC 6 group exhibited the lowest survival rates. Thus, further research is warranted in order to determine the optimal treatment approach for CLTI patients, with the actual goal of improving the quality of life and overall survival in this high-risk population.

The ACC/AHA guidelines recommended that revascularization should be performed for the treatment of lifestyle-limiting PAD if symptoms are unresponsive to optimized medical therapy and/or exercise. Endovascular therapy has emerged as a safe and effective treatment for symptomatic PAD, leading to significant improvement in quality of life and reducing procedural complication rates compared to bypass surgery. Our study, which included real-world patients, confirmed previous reports by demonstrating favorable 36-month amputation rates and sustained improved VascuQoL total score for all groups; however, patients with progressive disease had higher amputation rates compared to claudicants. Among patients with lifestyle-limiting claudication, revascularization (ie, surgical or endovascular) and exercise are superior to medical management alone in terms of quality of life. Our study showed that patients with RC 2-3 symptoms undergoing endovascular therapy had a 98.5% 36-month freedom from major amputation and a VascuQoL total score of 5.3 ± 1.4, suggesting that it would be reasonable to intervene early in claudicants, when they have failed medical and/or exercise therapy, in order to improve their quality of life.

CLTI, the most advanced stage of PAD, has a prevalence of 1.3% and a reported incidence of 0.4%. CLTI is a highly morbid condition that reduces the patient quality of life and costs more than $4 billion per year in the United States. The goals of CLTI treatment include revascularization to prevent major amputation or limit the level of amputation and optimal medical care (ie, antiplatelet therapy) to reduce incident cardiovascular events. Hereby, the Global Vascular Guidelines recommended that no patient with CLTI should be denied revascularization if that patient is a suitable candidate for limb salvage. In addition to revascularization, the Global Vascular Guidelines also underlined the need for adequate management of all modifiable atherosclerotic risk factors with best medical therapy (eg, antithrombotic, lipid-lowering, antihypertensive, and glycemic control agents), and counseling (ie, multidisciplinary teams and centers) on smoking cessation, diet, exercise, and preventive foot care.

The TransAtlantic Inter-Society Consensus II recommendations suggest bypass surgery for the treatment of extensive atherosclerotic disease and CLTI. However, a previous meta-analysis found that there is no high-level evidence demonstrating the superiority of open surgery compared to endovascular therapy for the treatment of challenging lower limb atherosclerotic lesions. Nonetheless, although it is yet unclear whether surgery or endovascular repair is the more optimal approach for this high-risk population, balloon angioplasty has been increasingly utilized as the first choice for CLTI because, compared with bypass surgery, it has demonstrated similar limb salvage rates but shorter hospital stay and fewer periprocedural complications.

Our study demonstrated that patients with RC 4-5 and RC 6 symptoms at baseline exhibited sustained improved quality of life scores through 36 months of follow-up. Furthermore, it reported encouraging 36-month rates for freedom from major amputation [RC 4-5 (94%) and RC 6 (79.9%)] as well as death [RC 4-5 (20.2%) and RC 6 (38%)]. Thus since almost one quarter of CLTI patients will suffer cardiovascular death and almost one half will suffer major amputation, our study provided evidence that endovascular treatment is reasonable even for difficult to treat patients (ie, RC 4-6) and that major unplanned amputation is not always necessary for RC 6 patients. However, it should be underlined that patients with RC 5-6 are expected to have increased TLR rates during follow-up due to the natural course of the disease, and as such TLR in this group could be a confounding factor for the higher than normal freedom from amputation rates observed in our study.

It should be underlined that the 36-month combined MAE rates remain high, even for patients with milder disease (ie, RC 2-3), while more than a third of patients with CLTI required a repeat revascularization procedure. Thus, this study indicated that further research evaluating new endovascular devices and combined treatment approaches (eg, angioplasty with adjunctive atherectomy ± stenting) should be conducted in an effort to reduce overall adverse events during follow-up and improve prognosis. Furthermore, the 62%
36-month survival rate and the 47.4% 36-month MAE rate observed in the RC 6 group indicate the need for standardized approaches to CLTI to further improve the prognosis of this subgroup of patients with PAD.

Several novel devices that were not available or were not commonly used at the time of patient enrollment for the LIBERTY study include drug-eluting stents (DES) and drug-coated balloons (DCBs). Treatment of femoropopliteal disease with either DES or DCBs has produced superior angiographic and clinical efficacy vs balloon angioplasty with or without bare metal stenting. Moreover, drug-eluting technology has been associated with significantly reduced restenosis and limited need for TLR with several trials investigating DCBs vs other endovascular technologies showing a clear benefit of DCB vs balloon dilation alone. Although it still remains unclear what impact paclitaxel could have on long-term outcomes of endovascular therapy, a recent FDA update recommended the use of paclitaxel-coated devices in populations at high risk for restenosis and repeat femoropopliteal interventions with several trials investigating DCBs vs other endovascular technologies as their use might outweigh the risk of long-term mortality.

We believe that further research should be conducted to evaluate the safety and efficacy of new developing technologies and help optimize angioplasty in terms of short- and long-term outcomes. Furthermore, large peripheral endovascular therapy registries should be created for more accurate post-market surveillance. Propensity score outcome data from retrospective comparisons showed that atherectomy was statistically superior to balloon angioplasty, stenting, and bypass surgery in a cohort of 36,000 patients with CLTI over the course of 4 years. As we continue to evaluate different treatment modalities in prospective and retrospective analyses, the outcomes are pointing toward a favorable long-term benefit when CLTI patients are treated early rather than late, especially when the treatment includes atherectomy.

**Limitations**

The LIBERTY study was a multicenter, core laboratory– adjudicated study that included patients who were 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 registry of endovascular therapies and did not include patients treated with surgical approaches. Second, site and patient participation bias may have occurred in the setting of clinical trial oversight, with more detailed follow-up than in usual care. Third, it should be noted that our study may be underpowered to demonstrate differences in the outcomes of endovascular treatment with any FDA-approved or -cleared device among RC 6 vs RC 4-5 groups.

Fourth, although the lesion location exhibited high heterogeneity, with below knee lesions being more prevalent among CLTI patients, sensitivity analyses for lesions limited to the infrapopliteal or femoropopliteal segment could not be synthesized. In addition, drug-eluting technology, which is proven to be superior to plain balloon angioplasty, was not often utilized, as at the time of enrollment only a few drug-coated devices were available, and the experience with their use was small.

Fifth, as follow-up was available for only 58% of patients at 2 years and 51% at 3 years, selection bias might have been introduced, and the results should be interpreted with caution. Sixth, although RC 2 and 3 were combined for analysis purposes, these 2 groups are highly heterogeneous and include patients with moderate to severe claudication. As such, further research investigating the need for reintervention in RC 2-3 patients according to disease severity is warranted.

Seventh, additional studies with adequate follow-up and wound care surveillance are necessary to determine the wound healing rates among CLTI patients undergoing endovascular procedures. Eighth, the study inclusion criteria are not representative of the entire population of patients with claudication, as all patients in the study had PAD of the distal SFA, popliteal, and/or infrapopliteal vessels. This may explain the high prevalence of infrapopliteal interventions in the claudicant subgroup. Last, this study was industry sponsored and could have potential attendant bias. However, the results were adjudicated by a core laboratory.

**Conclusion**

This study, which utilized data and real-world patients with the most severe stages of PAD, study confirmed that endovascular therapy is a viable treatment option for patients with symptomatic PAD refractory to medical and/or exercise therapy. Additionally, this LIBERTY 360 analysis reported acceptable 3-year freedom from major amputation rates and sustained improved quality of life in all groups. However, patients with more severe disease were at higher risk for MAEs during follow-up. Future research with real-world data should further evaluate the safety and efficacy of endovascular therapy for patients with advanced PAD (ie, for more accurate postmarket surveillance) and investigate the use of innovative technologies and/or combined therapies (ie, balloon angioplasty with atherectomy) in this at-risk population. Moreover, large registries are warranted to further investigate modern outcomes and provide surveillance of newer devices.

**Acknowledgments**

The authors thank Ann Behrens, BS, and Brad J. Martinsen, PhD, of Cardiovascular Systems, Inc, for editing and critical review of this manuscript.

**Declaration of Conflicting Interests**

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this
article: Dr Mustapha is a consultant to Bard Peripheral Vascular, Boston Scientific, Cardiovascular Systems, Medtronic, Spectranetics, and Terumo. Dr Gray is a consultant to Philips, Medtronic, Boston Scientific, and Abbott Vascular/Surmodics. Dr Ansel is a consultant to Medtronic, BSC, Philips, Surmodics, Reflow Medical, Abbott Vascular, and Cook. Dr. Secemsky is a consultant to CSI, Medtronic, and Philips, and has received grants for his institution from AstraZeneca, BD Bard, Cook, CSI, and Medtronic. Dr Adams receives consultant fees from Bard Peripheral Vascular, vascular Interventional Systems, Medtronic, Medtronic. Dr. Secemsky is a consultant to Abbott Vascular, Boston Scientific, CSI, W. L. Gore & Associates, Medtronic, Philips, PQ Bypass, and Shockwave.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Cardiovascular Systems, Inc.

ORCID iDs
Stefanos Giannopoulos https://orcid.org/0000-0002-1942-911X
Jihad Mustapha https://orcid.org/0000-0002-6351-8080
Eric A. Secemsky https://orcid.org/0000-0003-3861-3163
Ehrin J. Armstrong https://orcid.org/0000-0002-1381-4754

Supplemental Material
The online materials are available at http://journals.sagepub.com/doi/suppl/10.1177/1526602820962972

References
1. Shu J, Santulli G. Update on peripheral artery disease: Epidemiology and evidence-based facts. Atherosclerosis. 2018;275:379–381.
2. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013;382:1329–1340.
3. Hirsch AT, Duval S. The global pandemic of peripheral artery disease. Lancet. 2013;382:1312–1314.
4. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26:517–538.
5. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45(suppl S):S5–S67.
6. Levin SR, Arinine N, Saracuse JJ. Lower extremity critical limb ischemia: a review of clinical features and management. Trends Cardiovasc Med. 2020;30:125–130.
7. Becker F, Robert Ebadi H, Ricco JB, et al. Chapter I. Definitions, epidemiology, clinical presentation and prognosis. Eur J Vasc Endovasc Surg. 2011;42(Suppl 2):S4–S12.
8. Conte SM, Vales PR. Peripheral arterial disease. Heart Lung Circ. 2018;27:427–432.
9. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med. 2001;344:1608–1621.
10. Baubeta Frith E, Andeersen M, Thuresson M, et al. Amputation rates, mortality, and pre-operative comorbidities in patients revascularised for intermittent claudication or critical limb ischaemia: a population based study. Eur J Vasc Endovasc Surg. 2017;54:480–486.
11. Mustapha JA, Katzen BT, Neville RF, et al. Determinants of long-term outcomes and costs in the management of critical limb ischemia: a population-based cohort study. J Am Heart Assoc. 2018;7:e009724.
12. Duff S, Maffios MS, Bhounsule P, et al. The burden of critical limb ischemia: a review of recent literature. Vasc Health Risk Manag. 2019;15:187–208.
13. Gerhard-Herman MD, Bornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;69:1465–1508.
14. Jones WS, Dolor RJ, Hasselblad V, et al. Comparative effectiveness of endovascular and surgical revascularization for patients with peripheral artery disease and critical limb ischemia: systematic review of revascularization in critical limb ischemia. Am Heart J. 2014;167:489–498.e7.
15. Jones WS, Schmit KM, Vemulapalli S, et al. AHRQ comparative effectiveness reviews. In: Treatment Strategies for Patients With Peripheral Artery Disease. Rockville, MD: Agency for Healthcare Research and Quality; 2013.
16. Swami N, Vemulapalli S, Patel MR, et al. Lower extremity amputation in peripheral artery disease: improving patient outcomes. Vasc Health Risk Manag. 2014;10:417–424.
17. Mustapha J, Gray W, Martinsen BJ, et al. One-year results of the LIBERTY 360 study: evaluation of acute and midterm clinical outcomes of peripheral endovascular device interventions. J Endovasc Ther. 2019;26:143–154.
18. Adams GL, Mustapha J, Gray W, et al. The LIBERTY study: Design of a prospective, observational, multicenter trial to evaluate the acute and long-term clinical and economic outcomes of real-world endovascular device interventions in treating peripheral artery disease. Am Heart J. 2016;174:14–21.
19. de Donato G, Bosiers M, Setacci F, et al. 24-Month data from the BRAVISSIMO: A large-scale prospective registry on iliac stenting for TASC A & B and TASC C & D lesions. Ann Vasc Surg. 2015;29:738–750.
20. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. J Vasc Surg. 2010;51(5 suppl):5S–17S.
21. Malgor RD, Alahdab F, Elraiyah TA, et al. A systematic review of treatment of intermittent claudication in the lower extremities. J Vasc Surg. 2015;61(3 suppl):54S–73S.
22. Jones WS, Krucoff MW, Morales P, et al. Registry Assessment of Peripheral Interventional Devices (RAPID): registry assessment of peripheral interventional devices core data elements. J Vasc Surg. 2018;67:637–644.e30.
23. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA. 2001;286:1317–1324.
24. TASC Steering Committee, Jaff MR, White CJ, et al. An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee
arteries: a supplement to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Endovasc Ther.* 2015;22:663–677.

25. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation.* 2006;113:e463–e564.

26. Sachse T, Pomposelli F, Hamdan A, et al. Trends in the national outcomes and costs for claudication and limb-threatening ischemia: angioplasty vs bypass graft. *J Vasc Surg.* 2011;54:1021–1031.e1.

27. Saraidaridis JT, Ergul E, Patel VI, et al. The Society for Vascular Surgery’s objective performance goals for lower extremity revascularization are not generalizable to many open surgical bypass patients encountered in contemporary surgical practice. *J Vasc Surg.* 2015;62:392–400.

28. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J Vasc Surg.* 2019;69(S6):3S–1258.e40.

29. Antoniou GA, Chalmers N, Georgiadis GS, et al. A meta-analysis of endovascular versus surgical reconstruction of femoropopliteal arterial disease. *J Vasc Surg.* 2013;57:242–253.

30. Goodney PP, Beck AW, Nagle J, et al. National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. *J Vasc Surg.* 2009;50:54–60.

31. Aboyans V, Ricco J-B, Bartelink M-LEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO); The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J.* 2018;39:763–816.

32. Antoniou GA, Georgiadis GS, Antoniou SA, et al. Bypass surgery for chronic lower limb ischaemia. *Cochrane Database Syst Rev.* 2017;4:CD002000.

33. Goksel OS, Karpuzoglu E, Issever H, et al. Midterm results with drug-coated balloons for SFA lesions in patients with CLTI: comparison with conventional bypass surgery. *Int Angiol.* 2018;37:365–369.

34. Krawisz AK, Secemsky EA. Paclitaxel-based devices for the treatment of PAD: balancing clinical efficacy with possible risk. *Curr Treat Options Cardiovasc Med.* 2019;21(10):57.

35. Tendera M, Aboyans V, Bartelink ML, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32(22):2851–2906.

36. Dake MD, Ansel GM, Jaff MR, et al. Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the Zilver PTX randomized and single-arm clinical studies. *J Am Coll Cardiol.* 2013;61:2417–2427.

37. Rosenfield K, Jaff MR, White CJ, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. *N Engl J Med.* 2015;373:145–153.

38. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med.* 2008;358:689–699.

39. Cassese S, Byrne RA, Ott I, et al. Paclitaxel-coated versus uncoated balloon angioplasty reduces target lesion revascularization in patients with femoropopliteal arterial disease: a meta-analysis of randomized trials. *Circ Cardiovasc Interv.* 2012;5:582–589.

40. Dake MD, Ansel GM, Jaff MR, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. *Circ Cardiovasc Interv.* 2011;4:495–504.

41. Giacoppo D, Cassese S, Harada Y, et al. Drug-coated balloon versus plain balloon angioplasty for the treatment of femoropopliteal artery disease: an updated systematic review and meta-analysis of randomized clinical trials. *JACC Cardiovasc Interv.* 2016;9:1731–1742.

42. Katsanos K, Spiliopoulos S, Karunanithy N, et al. Bayesian network meta-analysis of nitinol stents, covered stents, drug-eluting stents, and drug-coated balloons in the femoropopliteal artery. *J Vasc Surg.* 2014;59:1123–1133.e8.

43. Fusaro M, Cassese S, Ndrepepa G, et al. Paclitaxel-coated balloon or primary bare nitinol stent for revascularization of femoropopliteal artery: a meta-analysis of randomized trials versus uncoated balloon and an adjusted indirect comparison. *Int J Cardiol.* 2013;168:4002–4009.

44. Kayssi A, Al-Atassi T, Oureopoulos G, et al. Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for peripheral arterial disease of the lower limbs. *Cochrane Database Syst Rev.* 2016;(8):CD011319.

45. Anantha-Narayanan M, Shah SM, Jelani QU, et al. Drug-coated balloon versus plain old balloon angioplasty in femoropopliteal disease: an updated meta-analysis of randomized controlled trials. *Catheter Cardiovasc Interv.* 2019;94:139–148.

46. Liistro F, Porto I, Angioli P, et al. Drug-eluting balloon in femoropopliteal artery disease: an updated systematic review and meta-analysis of randomized trials. *Circulation.* 2013;128:615–621.

47. Fanelli F, Cannavale A, Corona M, et al. The “DEBELLUM”—lower limb multilevel treatment with drug eluting balloon—randomized trial: 1-year results. *J Cardiovasc Surg (Torino).* 2014;55:207–216.
48. The Food and Drug Administration Update: Treatment of peripheral arterial disease with paclitaxel-coated balloons and paclitaxel-eluting stents potentially associated with increased mortality. August 7, 2019. Accessed September 9, 2020. https://www.fda.gov/medical-devices/letters-health-care-providers/august-7-2019-update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel

49. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation*. 1999;100:1872–1878.

50. Bossi I, Klersy C, Black AJ, et al. In-stent restenosis: long-term outcome and predictors of subsequent target lesion revascularization after repeat balloon angioplasty. *J Am Coll Cardiol*. 2000;35:1569–1576.

51. Elmahdy MF, Buonamici P, Trapani M, et al. Long-term primary patency rate after nitinol self-expandable stents implantation in long, totally occluded femoropopliteal (TASC II C & D) lesions. *Heart Lung Circ*. 2017;26:604–611.

52. Brouillet J, Deloose K, Goueffic Y, et al. Primary stenting for TASC C and D femoropopliteal lesions: one-year results from a multicentric trial on 203 patients. *J Cardiovasc Surg (Torino)*. 2018;59:392–404.

53. Mustapha JA, Katzen BT, Neville RF, et al. Propensity score-adjusted comparison of long-term outcomes among revascularization strategies for critical limb ischemia. *Circ Cardiovasc Interv*. 2019;12:e008097.

54. Zia S, Juneja A, Shams S, et al. Contemporary outcomes of infrapopliteal atherectomy with angioplasty versus balloon angioplasty alone for critical limb ischemia. *J Vasc Surg*. 2020;71:2056–2064.