Long-Term Data From LIBERTY 360° Show Positive Impact for Patients Receiving Endovascular Therapy

A roundtable discussion of the real-world LIBERTY 360° 12-month data and the study's significance in treating patients with peripheral artery disease and critical limb ischemia.

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The LIBERTY 360° study is a prospective, observational, multicenter trial to evaluate procedural and long-term clinical and economic outcomes of endovascular device interventions in patients with symptomatic lower extremity peripheral artery disease (PAD), including critical limb ischemia (CLI).[1] The design of this study is unique, with liberal inclusion criteria and few exclusions to encompass a broad range of patients and treatment modalities.

Any US Food and Drug Administration–approved device could be used for endovascular treatment of target lesions located within or extending into 10 cm above the medial epicondyle to the digital arteries. Endpoints included procedural and lesion success, major adverse events (MAEs), duplex ultrasound, quality of life (QOL), wound status, and economic analysis. Four core laboratories were utilized for independent analysis and additional clinical rigor.

A total of 1,204 patients with symptomatic PAD were enrolled at 51 sites and treated by 131 individual operators. Enrollment included 500 Rutherford class 2-3 subjects, 589 Rutherford 4-5 subjects, and 100 Rutherford 6 subjects. Of the enrolled subjects, 388 Rutherford 2-3, 402 Rutherford 4-5, and 41 Rutherford 6 subjects completed 1-year follow-up.

What is the primary takeaway from the 12-month results of the LIBERTY 360° trial, and how do these results build off the existing 6-month data?

Dr. Mustapha: The primary takeaway of this large, all-comers peripheral vascular intervention (PVI) study is that endovascular treatment is safe and effective in patients with symptomatic PAD. The LIBERTY 360° 12-month data continue to build off the excellent 6-month results, showing high freedom from major amputation in all patients with CLI, along with significant improvements in Rutherford class, QOL, and wound status. These data allow us to challenge treatment guidelines and continue to push the envelope when it comes to the treatment of patients with advanced disease whose only alternative is amputation.

Dr. Armstrong: The 12-month LIBERTY 360° results show that patients across the spectrum of PAD severity, from Rutherford 2-6, had excellent outcomes in terms of freedom from MAEs. There was also a low rate of continued events from 6 months to 12 months, which affirms the continued efficacy of endovascular interventions in this population. It's important to remember that most patients with these lesion types would never be included in most clinical

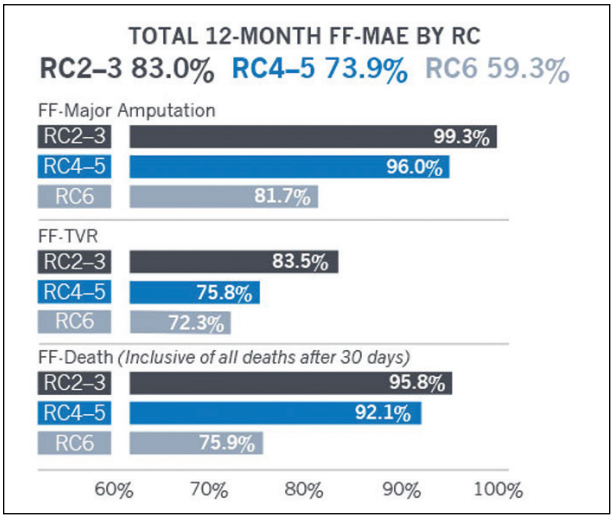

Figure 1. Total freedom from (FF) MAEs at 12 months by Rutherford classification (RC). Rutherford 2-3, n = 388; Rutherford 4-5, n = 402; Rutherford 6, n = 41.

trials, so these results are crucial for understanding real-world outcomes among patients with advanced PAD.

Dr. Pliagas: This study provides us with a real-world, 12-month data set that is empowered by the development and maturation of the data it presents. LIBERTY 360° showed continuous progress across the board, with improvement from the initial 30-day and 6-month data. We want to see our patients have sustainable results with improvement in their QOL throughout the follow-up period. This allows us to intervene on our patients with the confidence required for limb salvage even in the Rutherford 6 patients, whom otherwise would have few treatment options.

Dr. Yoho: This landmark study enables us to see real-world data that can be correlated with the patients we treat each day. High-risk patients with advanced disease are often excluded from studies, leading to difficulty translating trial results to real-world clinical practice. The data from this study should lead to changes in the practice paradigm in the United States. Most importantly, the study confirms my belief that PVI can be successful in patients with the worst disease and highest risk of limb loss. The primary amputation approach needs to be reevaluated. The 12-month data show continued success in all endpoints, including freedom from MAEs, amputation, and death, as well as QOL and improvement of Rutherford classes.

What struck you as interesting, surprising, or affirming in the 12-month results?

Dr. Pliagas: It was gratifying to see Rutherford 4-6 patients do well during the first 12 months. These patients continued their 30-day and 6-month improvements with showing excellent freedom from MAEs results, including amputation and concomitant improved trends in wound status.

Dr. Yoho: There were several intriguing aspects illuminated in the LIBERTY 360° trial. Most significantly, 78% of the Rutherford 6 patients were discharged to home with a target lesion success rate of 77%. The 30-day data had shown a very high freedom from MAEs in all Rutherford classes, including 91% in Rutherford 6 patients. This success continued out to 12 months with a 74% freedom from MAEs in Rutherford 4-5 patients, and a 59% freedom from MAEs in Rutherford 6 patients (Figure 1). These data affirm the results I have seen with my patients. More importantly, these results run counter to the ingrained perception practitioners have in treating these sick patients, suggesting PVI is safe and can be very successful at saving patients' limbs.

Dr. Armstrong: I was impressed that the overall rates of MAEs remained low from 6 to 12 months, especially for limb-related events. It appears that with advanced endovascular techniques, most of the amputation risk is in the first 6 months after revascularization. Subsequently, the continued patient risk is attributable more to the overall risk of mortality and cardiovascular events. These findings affirm that successful revascularization has great benefit to the patient over a short time, but also emphasize that we need to closely monitor these patients for wound healing. Saving the limb allows physicians to then focus on the overall atherosclerotic risk profile of patients with PAD.

How do you interpret the subanalysis data involving the orbital atherectomy device specifically?

Dr. Yoho: A subanalysis of the data reveal durable clinical outcomes when evaluating 12-month MAEs in patients who underwent orbital atherectomy as part of the treatment strategy. For example, in Rutherford 6 patients treated with orbital atherectomy, the 12-month freedom from composite MAEs was 71% and freedom from major amputation was an impressive 91% (Figure 2).

Looking back at the overall LIBERTY 360 data, this is significant because approximately 60% of the lesions treated were calcified and of those that were calcified, severity of calcification increased with Rutherford class. Of the calcified lesions, more than 85% of Rutherford 6 lesions had moderate or severe calcification.

Dr. Armstrong: The subanalysis of patients treated with orbital atherectomy demonstrated excellent freedom from MAEs across all Rutherford classes. Impressively, the freedom from major amputation at 12 months was 96% among Rutherford 4-5 patients and 91% among Rutherford 6

patients. The amputation rate for Rutherford 6 patients is among the lowest I have seen and suggests that orbital atherectomy may have application for the treatment of patients with wounds and calcified vessels who are at the highest risk for major amputation. The rates of target vessel revascularization (TVR) were also low, suggesting excellent patency and high rates of wound healing* in this subgroup.

Dr. Mustapha: The freedom from amputation data of the 493 patients in LIBERTY 360° treated with orbital atherectomy were phenomenal. There were no amputations in the Rutherford 2-3 patients, and 96% and 91% freedom from amputation in the Rutherford 4-5 and Rutherford 6 patient population, respectively. As such, we clearly see that using orbital atherectomy is an essential piece of the CLI toolkit. The CSI Orbital Atherectomy System was the most used atherectomy device in this patient population, especially Rutherford 6, because of its low profile and ability to access the most distal vasculature, combined with a mechanism of action specifically designed for hard, calcified plaque.

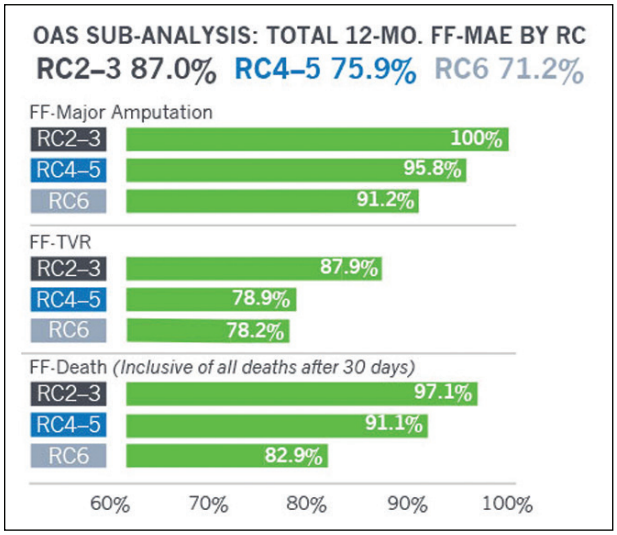

Figure 2. High freedom from MAEs at 12 months in patients treated with the orbital atherectomy system (OAS) across all Rutherford classes (RC). Kaplan-Meier method used to estimate event-free rates. Rutherford 2-3, n = 211; Rutherford 4-5, n = 226; Rutherford 6, n = 56.

What do you take away from the CLI data (Rutherford class 4-6 patients) in LIBERTY 360°? Have these data changed or reinforced your definition of a successful outcome in CLI patients?

Dr. Mustapha: We have never seen a data set that included so many CLI patients, especially those with Rutherford 6, so there is not a good barometer to compare the success of these patients in the LIBERTY 360° trial. LIBERTY 360° demonstrated extremely positive findings in CLI patients, including low rates of angiographic complications and positive procedural success rates, which translated to 96% and 78% discharge-to-home rates in Rutherford 4-5 and Rutherford 6 patients, respectively. We were concerned about low CLI patient follow-up at 12 months, but LIBERTY 360° demonstrated extremely favorable freedom from amputation and all-cause death rates out to 12 months, forcing us to reevaluate the time frame we use to observe these patients. In fact, MAE rates were driven by TVR; however, this seems less important when combined with reduction in number of wounds and low amputation rates.

Dr. Yoho: The beauty of the LIBERTY 360° study is that it consists of real-world data. High-risk patients with advanced disease are typically excluded from studies, which can often lead to difficulty in translating results into clinical practice and practice guidelines. This trial has reinforced my belief that too many patient limbs are lost, and with more education, we can improve overall outcomes. In Rutherford 4-5 patients, the desired outcome was achieved 96% of the time, and in Rutherford 6 patients, the desired outcome was achieved 97% of the time. Surprisingly, there was no significant increase in procedural length or contrast usage with the more complex cases. Furthermore, there was a decrease in contrast usage and no severe angiographic complications in 89% of Rutherford 6 patients. Most of these were performed with a combination treatment involving atherectomy.

These patients are among the sickest, and still there was a high success rate. This indicates that these procedures are manageable and in the right hands can be very successful and should change the current treatment paradigm.

Dr. Pliagas: The ability to increase perfusion to the lower extremities is paramount in any lower extremity revascularization procedure. LIBERTY 360° demonstrated that intervention in Rutherford 4-6 patients did improve runoff vessels. I see this because of successful intervention in CLI patients. This is something I look for at the end of every case by comparing the initial angiogram with the completion angiogram. It is encouraging to see the additional runoff vessels in the patients with extreme CLI. This was confirmed by the 70% to 78% procedural success rate and the nearly 80% lesion success rate in each intervention carried out.

In practice, we see wound healing progression with adjunctive therapy over the ensuing months. The 72% freedom from TVR in the first 12 months is in line with results seen in day-to-day clinical practice. The continued improvement and stabilization results, and the ability to reintervene as needed, are all valid 6-month and 12-month analytical endpoints in such a disease process with inherent progression.

Dr. Armstrong: Among Rutherford 6 patients, it appears that there is continued reduction in number of

wounds from 6 to 12 months; for these patients, a full year may be required to decrease the number of wounds. A better understanding of the predictors of wound healing, as they relate to target vessel patency, will help optimize the subsequent care of these patients and the need for any reintervention.

What is your interpretation of the significance of the more patient-centric data points such as change in Rutherford class and QOL?

Dr. Yoho: As practitioners, we often focus on the success of the lesion and the case, and we lose sight of one of the most important metrics for our patients: happiness and QOL. QOL scores are often underestimated, and including them provides a powerful insight into the charts and numbers we always see with studies. It provides us with details on how these procedures and outcomes are affecting the patient. A device can yield great percentages and data, but if it does not improve our patients' QOL and change the trajectory of their disease state, then it is essentially not producing the most important result. We should evaluate similar QOL metrics and attempt to incorporate them more frequently in our academic studies.

Dr. Mustapha: At 12 months, we are all impressed with a continual improvement in Rutherford class and in QOL. On average, Rutherford 4-5 and Rutherford 6 patients improved to claudicant status by 12 months. Rutherford 2-3 patients saw an immediate effect at 30 days, which was sustained through 12 months (Figure 3), demonstrating the durability of treatment in these claudicant patients. For QOL, we saw that patients from all Rutherford classes continued to improve at 12 months. This speaks to the clinical significance from the patient's perspective in terms of what revascularization can do for decreasing symptoms of PAD, while improving important physical and emotional aspects of their lives. LIBERTY 360° is unique in that most prospective multicenter studies lack QOL data.

Dr. Pliagas: Patient well-being is codependent on procedural success rates and emotional and physical improvements as evaluated by the patient. Emotional satisfaction, physical activity, and the ability to independently care for one's self, as measured by the VascuQoL and EQ-5D, all showed marked improvement during the 12-month period. This was also accompanied with a concomitant reduction in pain by the patient. At the beginning of the treatment algorithm, all Rutherford classes were distinctly separated in their domains; however, by 12 months, the Rutherford classes converged toward a similar QOL measure, which is an extremely important milestone and achievement, especially for Rutherford 4-6 patients. Additionally, do not overlook the fact that Rutherford 2-3 patients also showed improvement and stabilization in all domains during the same 12-month period.

What are you most excited about, and what do we hope to learn regarding the future data releases and subanalyses for LIBERTY 360°?

Dr. Mustapha: Some of the most exciting aspects of LIBERTY 360° are the limb salvage and wound status subanalyses. Of the 100 Rutherford 6 patients enrolled in LIBERTY 360°, 17% had a previous major amputation of the target limb, which demonstrates the advanced disease state captured in this trial and the potential opportunity for earlier intervention. This is remarkable when you see such a high freedom from target limb amputation at 12 months (82%). I am most excited to see how this may change the current guidelines. We already see an important update to the recently published 2016 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines on the management of patients with CLI that states: "An evaluation for revascularization options should be performed by an interdisciplinary care team before amputation in the patient with CLI (class I)." Progress is most certainly being made, and it is encouraging to see real-world clinical data from studies like LIBERTY 360° to further support the recent changes in the 2016 AHA/ACC guidelines.[2]

Dr. Pliagas: During the LIBERTY 360° trial setup, we as interventionalists observed that we can make a difference in these patients with CLI. As noted earlier, all Rutherford class patients trended toward a similar QOL score at 12 months. I will be very interested to see whether LIBERTY 360° can continue to show improvement, or at least tabulate, how we alter the natural history of atherosclerotic occlusive disease in the lower extremities. We know that there are a lot of variables affecting lower extremity perfusion and maintenance of outflow patency, but with subset analysis, we may be able to isolate some factors that can be modified to improve long-term patency and limb salvage.

Future analysis will be able to address distinct tibial anatomic lesions and distributions that may allow insight into how best to approach these and whether tibial arteries respond differently to treatment. I am convinced there is much more work to do to address lower extremity perfusion and patency and any potential distinct tibial differences. The question we must ask moving forward is whether tibial arteries all behave the same way. We may be surprised that there are differences we were not aware of.

Dr. Yoho: The data on the use of orbital atherectomy and drug-coated balloons were intriguing. Although it is not a large data set (n = 21), it provides insight for future

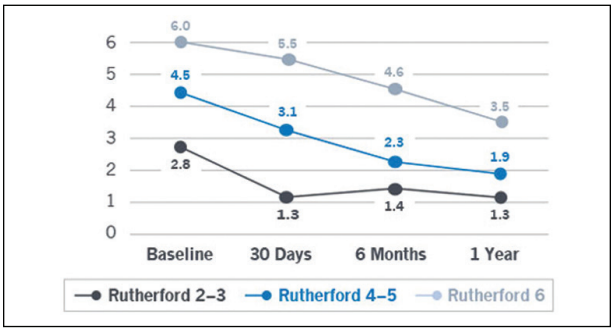

Figure 3. All Rutherford classes showed improvement from baseline to 12 months. Rutherford 4-5 and Rutherford 6 showed continued improvement from 30 days to 12 months, while Rutherford 2-3 maintained 30-day improvement at 12 months.

studies. The 12-month data confirm the presence of calcification in most lesions treated. Plaque modification of these lesions with orbital atherectomy before use of a drug-coated balloon appear to have yielded strong outcomes, with a 95% 12-month freedom from MAEs. This combination therapy warrants further evaluation as we look at expanding the application of drug-coated balloons in the peripheral vascular space.

Dr. Armstrong: The LIBERTY 360° data also has a wealth of information examining treatment patterns, including procedural and lesion success rates with tibial access, and information on predictors of wound healing*. Each of these subanalyses will provide important data regarding optimizing the outcomes of patients with severe claudication or CLI.

How will you personally utilize these findings?

Dr. Armstrong: These findings demonstrate that the full spectrum of patients with severe claudication or CLI benefit from endovascular intervention. Sharing this information with referring physicians and others who care for patients with CLI provides further evidence supporting early referral for endovascular intervention. The LIBERTY 360° data validate my current practice of the use of advanced endovascular techniques to maximize blood flow to the target wound among patients with CLI. These results will also inform the design of new CLI studies by providing important performance measures and estimates of outcomes for real-world trials of patients with CLI.

Dr. Yoho: I am a proponent of continued education and learning. If we want to change the status quo, it is up to us to continue to try and change the inertia that exists in medicine. It is very difficult to change long-standing habits of practitioners, but with powerful studies such as LIBERTY 360°, we can slowly improve the standards of practice. Too many patients lose their limbs without having something as basic as a vascular evaluation. Real-world results are influential and difficult to ignore. The more we can educate patients and physicians on the best treatment options available, the better chance we have.

Dr. Pliagas: The LIBERTY 360° trial was distinctly set up to gather new data variables not previously collected. Sharing these data with all our colleagues, patients, and their families will allow us to develop aggressive treatment strategies to meet the challenges presented by CLI patients. Looking ahead, LIBERTY 360° and other forward-thinking trials will allow us to meticulously examine the variables and treatment strategies to best address the complex entity known as CLI.

Dr. Mustapha: The LIBERTY 360° trial changes everything for CLI patients and reinforces my commitment to be aggressive in treating severe and complex patients. I will share these findings with everyone who sees PAD and CLI patients, especially those on the front lines such as podiatrists and those in the emergency department, where many of these patients first enter the health care system. We must increase clinicians' awareness about what is possible with minimally invasive endovascular procedures in these at-risk patients and ensure physicians are referring patients to doctors with a commitment to limb salvage. The data are clear: endovascular revascularization is the new hope for amputation-free survival for the Rutherford 6 patient, and communication will be key to ensuring that becomes the new standard of care. ■

*Improvement in number of wounds.

1. 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.
2. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation. 2017;135:e726–779.

***Indication and Safety Information**: The CSI Orbital Atherectomy System is a percutaneous orbital atherectomy system indicated for use as therapy in patients with occlusive atherosclerotic disease in peripheral arteries and stenotic material from artificial arteriovenous dialysis fistulae. Contraindications for the system include use in coronary arteries, bypass grafts, stents, or where thrombus or dissections are present. Although the incidence of adverse events is rare, potential events that can occur with atherectomy include: pain, hypotension, CVA/TIA, death, dissection, perforation, distal embolization, thrombus formation, hematuria, abrupt or acute vessel closure, or arterial spasm. Caution: Rx Only.*

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