

# Six-Month Data From Landmark Clinical Trial Demonstrates Sustained Benefit of Endovascular Intervention in Patients With Lower Extremity Peripheral Artery Disease

A roundtable interview discussing the significance of the LIBERTY 360° 6-month results.



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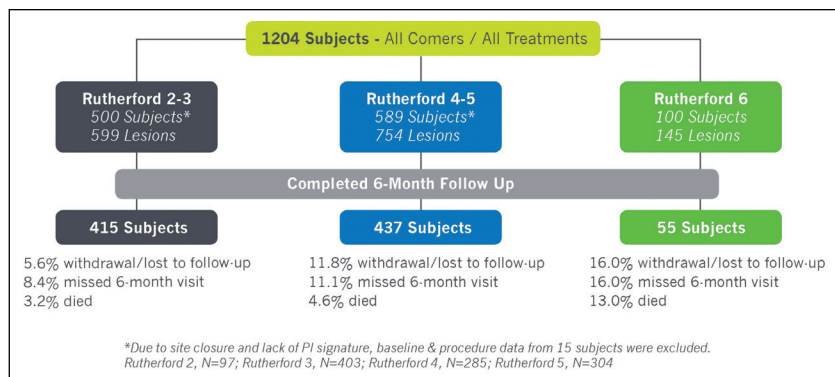
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The LIBERTY 360° study is a prospective, observational, multicenter trial sponsored by Cardiovascular Systems, Inc. to evaluate procedural and long-term clinical and economic outcomes of endovascular device interventions in patients with symptomatic lower extremity peripheral artery disease (PAD), including critical limb ischemia (CLI).<sup>1</sup> The design of this study is truly unique, with liberal inclusion criteria and few exclusion criteria, so that the study encompasses a broad range of patients and treatment modalities. Additionally, any US Food and Drug Administration (FDA)-approved device could be utilized for endovascular treatment of the target lesion(s). LIBERTY includes quantitative and qualitative data collection, with patient follow-up at 30 days, 6, 12, 18, and 24 months, and then annually up to 5 years. Clinical

evaluations include physical examination, wound assessment, ankle-brachial index (ABI), toe-brachial index, duplex ultrasound (DUS) testing, 6-minute walk test, and EQ-5D-5L and VasculQoL questionnaires. In addition, health care resource utilization and hospital billing data from all index and subsequent PAD-related evaluations, office visits, treatment procedures, and hospitalizations will be collected to provide a thorough acute and long-term economic analysis. LIBERTY study enrollment was completed in February 2016 with 1,204 subjects enrolled across 51 sites in the United States.

## STUDY OUTCOMES

Study outcomes include procedural and lesion success, major adverse events (MAEs), patency (DUS), quality of life (QoL), 6-minute walk test, and economic analysis.



**Figure 1. Enrollment and 6-month follow-up.** The LIBERTY 360° study included 51 sites and 131 operators, with 37 individual operators treating Rutherford 6 patients.

## STUDY RIGOR

Four core laboratories were used for independent analysis of procedural and lesion success (SynvaCor); rate of target vessel revascularization (TVR); DUS interpretations (VasCore); 6-minute walk test (CPC Clinical Research); and economic analysis (Mid America Heart Institute).

## ROUNDTABLE DISCUSSION

Four national key opinion leaders were asked to discuss the significance of the LIBERTY study design and findings from the 6-month data set, which was recently presented as a late-breaking clinical trial at the International Society of Endovascular Therapy (ISCT) conference in February 2017.

### What is unique or novel regarding the overall design of the LIBERTY study?

**Dr. Mustapha:** The LIBERTY study is unique in that it represents as close to a real-world experience as possible with various endovascular strategies across Rutherford classes 2 to 6. Many of the subjects enrolled in LIBERTY would not have met the enrollment criteria for other clinical trials, particularly those classified as Rutherford 6. The LIBERTY study also includes any FDA-approved technology to treat claudication and CLI to give us a more representative landscape of endovascular treatment than what has been previously studied.

**Dr. Razavi:** Many industry-sponsored studies focus on a narrow group of patients to satisfy stringent inclusion/exclusion criteria. They are not always applicable to our daily practice, and it is hard to know how many of these devices perform in our everyday patients. The strength of LIBERTY is that it collected core lab-adjudicated data on an all-comers basis, meaning various endovascular devices are included. Hence, this data is more relevant to daily practice.

**Dr. Pliagas:** I found it surprising but also reassuring that LIBERTY did not exclude any patient in the symptomatic Rutherford classes. We see and evaluate each and every

patient in the office, regardless of Rutherford classification. To me, this reinforces the fact that LIBERTY has real-world significance. LIBERTY is also unique in that it will track patient-centric outcomes using two different QoL questionnaires and a walking assessment (required for Rutherford 2-5 subjects only) at follow-up visits.

**Dr. Davis:** Being able to utilize any FDA-approved technology for this broad patient set provides the medical community a unique lens through a more contemporary land-

scape and treatment algorithm than previous studies that have been published in the peripheral space. The addition of an economic core lab to analyze procedural costs will also bring tremendous value to the medical community.

### What is the primary takeaway from the 6-month results and how do these results build off the existing 30-day data?

**Dr. Razavi:** We need to emphasize and share the 6-month LIBERTY data, including the very low rate of major adverse events in CLI patients in this study. This is of particular importance in Rutherford 6 patients. Existing literature, mostly based on surgical series, seem to indicate that as many as 40% of Rutherford 4-6 patients end up with an amputation within 6 months.<sup>2</sup> Although only 100 Rutherford 6 patients were enrolled, this is one of the first Rutherford 6 data sets that exists that captures procedural and long-term outcomes. Also, the 87.1% freedom from major amputation of the target limb at 6 months is very encouraging.

**Dr. Mustapha:** Marked improvement in Rutherford classification was seen at 6 months. The Rutherford 4-5 and Rutherford 6 groups demonstrated continued improvement from 30 days to 6 months, while Rutherford 2-3 patients maintained improvement at 6 months. Patients also completed two QoL questionnaires at 6 months, and results demonstrated improved quality of life from baseline across all Rutherford classes.

**Dr. Davis:** Rutherford 6 patients continued to demonstrate a low incidence of major adverse events out to 6 months. This tracks well with the originally reported low rates of significant angiographic complications in this patient cohort. Interestingly, the “severe” complications that did occur with this group required zero bailout stent utilization.

**Dr. Pliagas:** The 6-month data reveals that the endovascular intervention shows beneficial and sustainable

results; however, as surveillance continues, it will also help us understand when and where we may need to re-intervene.

### What struck you as interesting or surprising in the 6-month results?

**Dr. Mustapha:** The results of this novel all-comers PAD study continue to suggest that watchful waiting in Rutherford 2-3 patients and primary amputation in Rutherford 6 patients may not be necessary—peripheral vascular interventions (PVI) can be successful in those patient populations as well. In addition, these data demonstrate that on average, PVI can restore Rutherford 4-5 patients with CLI status to moderate claudicant status. Therefore, LIBERTY provides further evidence to support PVI treatment in Rutherford 4-5 patients, with continued improvement of Rutherford classification and sustained quality-of-life results out to 6 months.

**Dr. Pliagas:** It was excellent to see that even at 6 months, the freedom from major amputation was 96.8% in Rutherford 4-5 patients. This reinforces the fact that our dedication to endovascular revascularization and the time and effort we put forth to revascularize these ischemic limbs plays a meaningful role in changing our patients' lives for the better.

**Dr. Davis:** It was interesting to see patients with Rutherford 6 disease continue to do very well 6 months after their procedure. This study demonstrated excellent procedural results in this difficult patient set, including low rates of significant angiographic complications and a remarkable 78% of Rutherford 6 patients discharged to home rate. Combined with a positive trend in major adverse events at 6 months, the LIBERTY

data push the envelope that we must treat these patients in need.

**Dr. Razavi:** A lower prevalence of hyperlipidemia in Rutherford 6 patients was a surprise to me. Perhaps these patients receive more aggressive medical management as compared to claudicants, which, unfortunately, is often seen as a benign condition.

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

**Dr. Davis:** At 6 months, it's impressive to see that all Rutherford class patients maintained the improvement in QoL scores from baseline to 30 days. 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.

**Dr. Pliagas:** Analysis of Rutherford 2-6 patients indicates that their QoL scores improved across the board in all domains, again reinforcing the benefits of endovascular intervention. We can honestly say that we are making a difference in these patients' lives.

**Dr. Razavi:** Many prospective multicenter studies in real world patients lack QoL data. These data are not only important to us and our patients but also to payers. However, anatomic and physiologic endpoints such as patency and ankle-brachial index are important metrics for comparative analyses and assessment of technologies and devices producing incremental improvements. Hence, it is crucial that studies report both types of data moving forward.

**Dr. Mustapha:** The significance of change in the Rutherford class is the value associated with it. For the patients who saw improvement from Rutherford 4-6 to Rutherford 3 or less, the primary value that comes to mind is the reduction in mortality, which tends to correlate with long-standing advanced Rutherford classification. Also, the reduction in Rutherford class means an improvement in the clinical status of the patient. It appears that the improved QoL across the board is directly proportional to the improved clinical status and reduced Rutherford class.

### What impact will these data have on the current treatment guidelines, especially in regards to treatment of patients with claudication and CLI?

**Dr. Mustapha:** Two important updates were recently published with

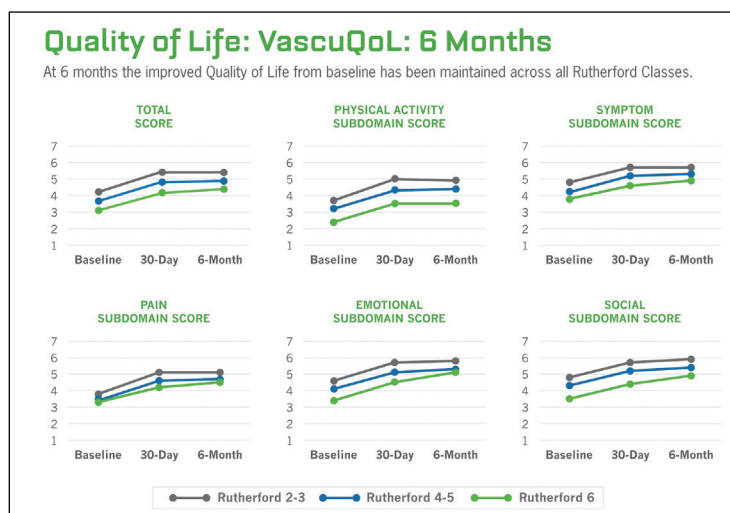
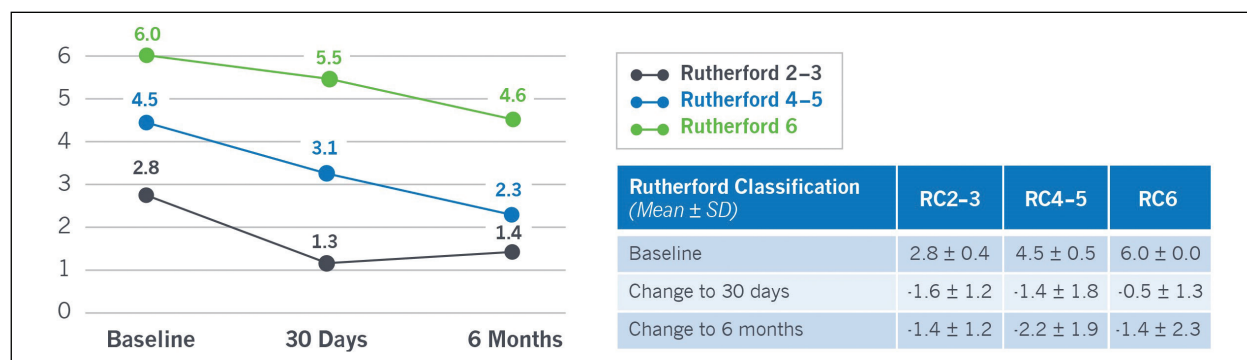


Figure 2. All Rutherford classes demonstrated improvement in VascuQoL scores at 30 days and either continued to improve or maintained improvement through 6 months.



**Figure 3.** Patients in all Rutherford classes showed improvement in Rutherford class from baseline to 30 days. Rutherford 4-5 and Rutherford 6 patients showed continued improvement from 30 days to 6 months, while Rutherford 2-3 patients maintained improvement at 6 months.

the 2016 AHA/ACC guidelines on the management of patients with lower extremity PAD.<sup>3</sup> The updated guidelines state, “Revascularization is a reasonable treatment option for patients with lifestyle-limiting claudication and an inadequate response to medical management and exercise” (class IIa).

Additionally, “an evaluation for revascularization options should be performed by an interdisciplinary care team before amputation in the patient with CLI” (class I). We practice in a world with limited guidance on the benefit of endovascular treatment over surgical bypass in these difficult patients. This is probably best exemplified by the ongoing BEST-CLI trial designed to address that very question. Progress is most certainly being made and it is encouraging to see real-world clinical data from studies like LIBERTY to support the 2016 AHA/ACC guidelines.

**Dr. Pliagas:** The data continue to reinforce the notion that a high level of commitment to treating CLI patients adds benefit to this population and may result in limb salvage and overall improvement in their daily lives. Specifically, the LIBERTY data have shown us that skilled operators can safely intervene on all symptomatic PAD patients with low rates of significant angiographic complications and high rates of procedural success. Hopefully this will prompt other vascular societies to take the LIBERTY data into consideration and help them develop new strategies and algorithms for treatment of PAD and CLI.

**Dr. Razavi:** Professional society guidelines are usually behind practice, especially in fields such as endovascular treatment, where rapid change is a rule rather than the exception. The impact of this type of robust real-world observational study is more on our daily practice than on guidelines. Having said that, however, quality data are always influential in changing guidelines.

**Dr. Davis:** Endovascular intervention of claudicant patients can be done with low risk and sustained benefits. We continue to hear fear of “making matters worse” and

“shutting down already patent runoff vessels” as a reason for not treating claudicant patients, opting instead for medical management and monitoring. LIBERTY demonstrated that endovascular treatment led to worsened runoff status in only 5.9% of Rutherford 2-3 patients. At 6 months, the freedom from MAE rate was 92.6% in Rutherford 2-3 patients and these patients had a mean improvement of  $1.4 \pm 1.2$  in Rutherford class from baseline.

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

**Dr. Razavi:** I was pleased to see the sustained improvement of patients from 30 days to 6 months, especially in regards to the CLI patients with multiple comorbidities. I am particularly interested in seeing if these favorable 6-month outcomes continue to show durability through 12 months and beyond. The long-term economic analysis will also be interesting and will shed much-needed light on the cost-effectiveness of different treatment strategies.

**Dr. Davis:** I think one of the most exciting aspects of LIBERTY are the limb salvage and wound status sub-analyses. Seventeen percent (17%) of the Rutherford 6 patients enrolled in LIBERTY had a previous major amputation of the non-target limb, demonstrating the advanced disease state captured in this trial and the potential opportunity for earlier intervention. We already see freedom from major amputation in 99.8% of Rutherford 2-3 patients, 96.8% of Rutherford 4-5 patients, and 87.1% of Rutherford 6 patients at 6 months, so it will be interesting to see if this limb salvage is sustained and if we see a corresponding improvement in wound status.

**Dr. Pliagas:** I truly liked that the LIBERTY study not only included all symptomatic PAD patients, but also included various sites of care such as large teaching hospitals, small community hospitals, VA centers, and outpa-



	RUTHERFORD CLASS		
	2-3	4-5	6
Freedom from (FF) MAE (6-Month)	92.6%	81.2%	73.7%
FF Major Amputation	99.8%	96.8%	87.1%
FF Target Vessel Revascularization (TVR)	93.0%	83.1%	85.1%
FF Death	97.1%	95.3%	85.1%

**Table 1. High freedom from MAEs at 6 months across all Rutherford classes.** Kaplan-Meier method used to estimate event-free rates. MAE defined as death ( $\leq 30$  days after the procedure), major amputation of the target limb, and TVR.

tient clinics. With 15 of the 51 LIBERTY sites being office-based labs, I am excited for additional analysis regarding the type of patients and procedures, as well as the safety of endovascular procedures, at this particular site of care.

**Dr. Mustapha:** For the first time, we were able to look at a trial involving Rutherford 6 patients with scientific optimism. It is hard not to be hopeful, and here is some insight as to why. Rutherford class 6 and some rare cases of complex Rutherford 5 patients have been forever labeled as “no option” patients. Today I can say with confidence that the “no option” label can be removed. This is primarily based on the data we have seen thus far from LIBERTY, especially from the Rutherford 6 arm. The fact that 78% of Rutherford 6 patients were discharged home post-revascularization reinforces new hope for patients with advanced CLI. LIBERTY shows us that at 6 months, the rates of death, major amputation, and TVR/target lesion revascularization in Rutherford 6 patients were numerically similar to Rutherford 4-5 patients, yet there would be no debate on the benefit of treating a Rutherford 4 or 5 patient. We should therefore think hard and look deep into every Rutherford 6 patient before scheduling a life-changing amputation. The data are clear. Endovascular revascularization is the new hope for amputation-free survival for the Rutherford 6 patient.

### How will you personally utilize these findings (ie, will you share these with diagnosing physicians in your area? Will this change your treatment strategy? Will this inform the design of new trials moving forward, etc)?

**Dr. Piagas:** The data collected by LIBERTY allow us to share with our colleagues our passion and commitment to limb salvage and the treatment of CLI. It reinforces the fundamental idea proposed all along by CLI experts that no one should undergo an amputation without a selective angiogram and intervention. Finally, we see the guidelines starting to follow suit and stipulate the need

for endovascular assessment prior to an amputation. With the advent of new technology, LIBERTY data can serve as a baseline standard of current endovascular treatment options when evaluating future technologies.

**Dr. Davis:** I will communicate this with the local diagnosing physician community, including podiatrists at various upcoming meetings, to share the benefits of treating an understudied and underdiagnosed patient population. We need to ensure that

the diagnosing community is aware that we have come a long way in treating CLI patients, and that a limb salvage focus and partnership can lead to fewer amputations. We know that the disease is prevalent and the patients are out there, but we need to educate those upstream diagnosing physicians as to the benefit of endovascular treatment in order to more broadly affect this at-risk population.

**Dr. Mustapha:** The LIBERTY trial changes everything for CLI patients. It will absolutely change my practice to become more aggressive in treating severe and complex patients. I will definitely share this finding with all specialties to increase awareness about the benefit of treating Rutherford 5-6 patients who do receive benefit from revascularization. Transmetatarsal amputation is not associated with mortality, but major amputation is. It is the responsibility of everyone who is aware of the positive findings of the LIBERTY trial to raise awareness so patients receive what might end up being a life-saving procedure.

**Dr. Razavi:** All of the above. While LIBERTY may not be randomized data powered to show a significant advantage of one treatment over another, it adds substantial insight into a much needed data gap in real-world, advanced PAD and CLI patients. This is a significant milestone in the medical community, because it provides both procedural and long-term economic, qualitative, and clinical outcomes for a wide variety of PAD patients. These aspects will continue to guide our decision making and help inform the study design of future endovascular device trials. ■

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. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC working group. TransAtlantic inter-society consensus (TASC). *J Vasc Surg*. 2000;31:S1–S296.

3. 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. *J Am Coll Cardiol*. 2016 Nov 8. pii: S0735-1097(16)36902-9. doi: 10.1016/j.jacc.2016.11.007. [Epub ahead of print]

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