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Promising New 30-Day Data for Lower Extremity Endovascular Treatment

Discussion and roundtable interview of the LIBERTY 360° study of 1,204 Rutherford class 2 to 6 patients, including 100 Rutherford class 6 patients.

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The LIBERTY 360° study is a prospective, observational, multicenter trial that evaluates 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 truly unique, with liberal inclusion criteria and few exclusions to encompass a broad range of patients and treatment modalities. Additionally, any US Food and Drug Administration–approved device could be utilized for endovascular target lesion treatment. LIBERTY 360° includes a variety of quantitative and qualitative analyses, with patient follow-up occurring at 30 days, 6, 12, 18, and 24 months, and then yearly up to 5 years. Clinical evaluations include physical examination, wound assessment, ankle-brachial index, toe-brachial index, duplex ultrasound

(DUS) testing, 6-minute walk test, and EQ-5D-5L and VascuQoL 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 thorough acute and long-term economic analysis.

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.

STUDY RIGOR

Four core laboratories have been included for independent analysis: procedural and lesion success (SynvaCor,

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Springfield, IL); rate of target vessel revascularization (TVR); DUS interpretations (VasCore, Boston, MA); 6-minute walk test (CPC Clinical Research, Aurora, CO); and economic analysis (Mid America Heart Institute, Kansas City, MO).

STUDY CONCLUSIONS

Four national Principal Investigators for the LIBERTY 360° study were asked to discuss the significant findings and future of the study.

What is important to consider in the overall design of LIBERTY 360°?

Dr. Gray: The trial design of LIBERTY 360° is novel and unique in several ways. It is not a device approval trial but is run at the same level of controlled lesion and outcome assessment. In an effort to reduce confounding variables, most trials will try to achieve a homogenous subject population by means of inclusion/exclusion criteria. However, in LIBERTY 360° there are very few exclusion criteria, specifically because the intent was to have as unrestricted a population as possible. Lastly, no specific device use was mandated by protocol. The result is that we will not only see multiple device approaches to a diverse set of lesions and patients, but also a snapshot of the practice of endovascular therapy in the United States circa 2015 along with the economic implications of that practice.

Dr. Ansel: To the credit of the sponsor, there was great supervision. LIBERTY 360° is attempting to look at real-world endovascular treatments. The population is inclusive across all clinically important Rutherford classifications, from claudication to CLI (even class 6 patients). There are four core labs with independent adjudication. As is evident, there were many operators that were very comfortable utilizing orbital atherectomy as part of their treatment paradigm.

Are there any significant findings within each Rutherford class studied?

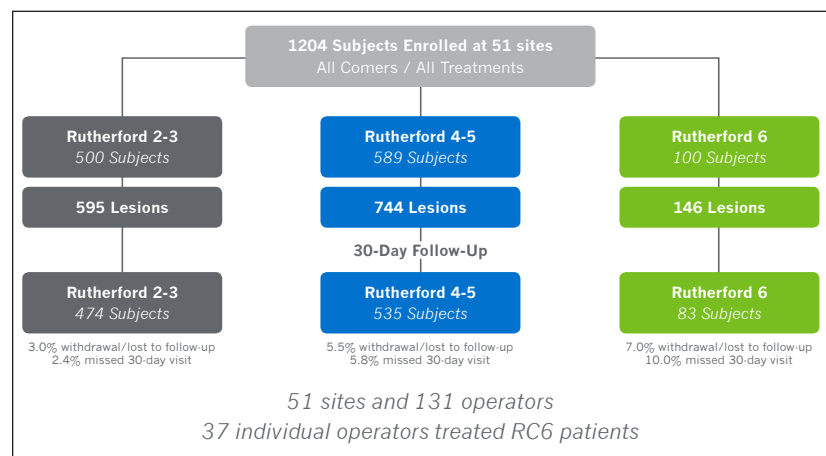
Dr. Adams: Rutherford class 2 to 3 patients were more likely to have previous drug therapy and/or endovascular treatment compared to Rutherford class 4 to 6 patients; this may be secondary to Rutherford class 6 patients presenting late for medical care. Additionally, a significantly higher percentage of Rutherford class 6 patients had previous amputation of the target limb (17%) compared to patients with Rutherford class 2 to 3 and class 4 to 5 disease. Lastly, longer lesions and more chronic total occlusions were seen as Rutherford classification increased.

Dr. Mustapha: Although it's too early to make final statements on the findings, the signals look great, especially for advanced Rutherford class patients. At 30 days, the rate of freedom from MAEs was 99% in Rutherford class 2 to 3, 95.7% in Rutherford class 4 to 5, and 90.7% in Rutherford class 6. Only 4.2% of the LIBERTY 360° Rutherford class 6 patients had a major amputation at 30 days.

Dr. Ansel: Interestingly, there was a high degree of technical success across all Rutherford classes. I think that the high prevalence of diabetes, renal impairment (including dialysis), and calcification in Rutherford classes 4 to 6 reconfirms the risk of clinically significant PAD in these patient populations.

What are key characteristics/demographics of the patient population?

Dr. Gray: By design, the trial enrolled a prespecified number of patients by Rutherford classification (class 2–3, approximately 500 patients; class 4–5, approximately 600 patients; class 6, approximately 100 patients); this patient population is clinically defined. More than half of the lesions had calcification as determined by the angiographic core lab, and because approximately 65% to 75% of the lesions were treated with atherectomy, lesion complexity was likely significant.



Patient classification breakdown. RC6, Rutherford class 6.

Dr. Mustapha: Hypertension stood out as a hallmark of PAD across all Rutherford classes. Coronary artery disease, smoking, and hyperlipidemia are highly prevalent risk factors in the PAD population regardless of Rutherford classification. Also, there was a high prevalence of calcification regardless of Rutherford class.

Dr. Ansel: Overall, the majority of patients, even in this large trial, were white. There are many possible explanations, including racial disparity in care or a real/perceived potential problematic follow-up. There was also a higher prevalence of Rutherford class 6 patients that could demonstrate differ-

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ent prevalence of diabetes and renal failure or limitations to access of care.

Dr. Adams: What stood out to me was that Rutherford classes 4 to 5 and class 6 were more likely to be diabetic and/or have renal insufficiency than Rutherford classes 2 to 3. This may be indicative to this population having more outflow disease than inflow disease. On the contrary, Rutherford classes 2 to 3 were more likely to be smokers and hyperlipidemic compared to Rutherford classes 4 to 6. This may be a signal of this population having more inflow disease rather than outflow disease.

In your opinion, what is the primary take away from the 30-day results?

Dr. Adams: The early findings suggest that “watchful waiting” in Rutherford classes 2 to 3 and “primary amputation” in Rutherford class 6 may not be necessary. Peripheral vascular intervention (PVI) can be successful in these patient populations.

Dr. Mustapha: I agree with Dr. Adams, that is the primary take away from this early data set. For example, endovascular treatment for Rutherford class 6 was associated with high rates of successful revascularization and low rates of complications in one of the first outcome data sets reported on Rutherford class 6 patients by lesion. In this group, there was < 50% residual stenosis in 83.7% of the lesions treated and no angiographic complications in 89% of lesions.

Dr. Gray: Early safety and procedural effectiveness related to the endovascular option for the broad array of patients with both claudication and CLI should give patients and operators alike reassurance that this is a reasonable option for revascularization and symptom relief. The longer-term data will help further define the durability of the effectiveness of revascularization and will be very interesting as it relates to both the failure and success modes related to the various lesions and patient characteristics.

Dr. Ansel: The 30-day results provide insight into the treated populations and procedural technical results. They don't provide much in the way of efficacy or outcome data. There was high technical success and procedural safety across the study. In my opinion, the high prevalence (approximately 60%) of concomitant coronary disease across all Rutherford classes continues to point out the need for continuous focus on risk factor modification (especially smoking) and assessment for coronary disease. In a world where > 60% of the patients had a history of current or past smoking, we need to double back on assistance on this, and the payers and providers need to reassess the

decreased focus and payment for this service as of late. Again, there was a high prevalence of diabetes and renal impairment, especially in the CLI population, and there should be an emphasis for evaluation of PAD as part of their routine care.

We also see a significant history of amputation in both the ipsilateral and contralateral extremities, thus pointing out the continued challenge to maintain the limbs in patients with CLI.

	RUTHERFORD CLASS		
	R2-3	R4-5	R6
Freedom from MAE (30-Day)	99.0%	95.7%	90.7%
Major Amputation	100%	98.8%	95.8%
Target Vessel Revascularization (TVR)	99.4%	96.9%	97.9%
Death	99.6%	99.7%	95.9%

Freedom from major adverse events (MAEs) at 30 days including major amputation, target vessel revascularization (TVR), and death.

What struck you as interesting or surprising in the 30-day results?

Dr. Adams: More than 95% of the Rutherford class 6 patients were free from death and unplanned major amputation at 30 days, and QoL assessments demonstrated improvement from baseline to 30 days across all Rutherford classes.

Dr. Mustapha: The number of runoff vessels increased after PVI, with significant improvement seen in Rutherford class 4 to 5 and Rutherford class 6 compared to Rutherford class 2 to 3, showing the utility of PVI for even the most difficult patients. The 30-day data showed improvement in both the sicker patients (Rutherford class 4–6) and less sick patients (Rutherford class 2–3) with early treatment versus a wait-and-see approach, which shows worse outcomes in the literature.

Dr. Ansel: I was surprised that 15% to 20% of the lesions did not meet success definitions, even in the claudicant population. Personally, I think we will need to evaluate this finding in more detail as we develop future technologies. However, contrary to this, there was higher success in Rutherford class 6 patients than I would have expected.

At the lesion level, there were 7% to 11% severe angiographic complications across Rutherford classes. We will need to dive into these data again as we develop newer technologies.

Although the investigators and sponsor attempted to recruit sites that did not focus on atherectomy, we were not as successful as we would have liked. There were few stents (including drug-eluting stents) or drug-coated balloons utilized.

What's next for LIBERTY 360°?

Dr. Gray: In addition to the clinical data set that is forthcoming for the longer-term outcomes, the economic data will help to shape the cost–benefit of these interventions.

Dr. Mustapha: Every month that passes adds value to the LIBERTY 360° data analysis. In particular, the more advanced Rutherford classifications, such as Rutherford class 4 to 6, tend to show conclusive signals at earlier time-lines, such as 3 and 6 months. A multidisciplinary approach to Rutherford class 5 to 6 patients is absolutely crucial, and we all must be aware that these patients need additional care beyond revascularization, such as wound care, medical therapy, etc. When it comes to 12 months and beyond, the focus will be the same for Rutherford class 4 to 6 patients, and we will start describing in more detail the findings of the Rutherford class 2 to 3 subjects, such as patency rates via DUS.

Dr. Ansel: The 12-month and longer-term results will be centered around clinical success and outcomes versus the early technical success. There will be much more enlightening data regarding patency and reintervention rates.

What do we hope to learn from this study?

Dr. Adams: I believe we need to start analyzing these data to develop algorithms of care for each Rutherford class. This will take into account outcomes, QoL improvement, device selection, and the economic analysis.

Dr. Mustapha: Rarely do we learn something from a study at as early as 30 days, but in this study, we were nicely surprised with a very positive and hopeful finding. Procedural complications rarely (0.8%–2%) resulted in post-procedural hospitalization in all Rutherford classes, and 78% of Rutherford class 6 patients were discharged home. This alone is sufficient to describe a new hope for Rutherford class 6 patients who historically did not have this option of treatment and a discharge to home within a median time of 27 hours after revascularization.

Numerous infrapopliteal treatment modalities remain controversial; percutaneous transluminal angioplasty (PTA) remains the standard of care. A contemporary meta-analysis was performed (2005–2015) to assess current PTA outcomes.² The 1-year outcomes from this contemporary meta-analysis compared to the Romiti et al meta-analysis³ showed that infrapopliteal PTA outcomes have not changed over the last decade despite advanced knowledge and techniques (technical success, 91% vs 89%; primary patency, 63% vs 58%; major amputation, 15% vs 14%; all-cause mortality, 15% vs 13%).

Clearly, we are in dire need of new ways to treat CLI patients. Over the course of 20 years, PTA did not show what we just learned in 30 days from the LIBERTY 360° study.

What impact will these data have on current treatment guidelines?

Dr. Mustapha: Whenever it comes to guidelines, one must look at the broad spectrum of data and key opinion leader input, along with the multiple societies involved with PAD treatment. On the other hand, personally I can't deny that the guidelines for Rutherford class 6 patients should be reevaluated and a new recommendation made in regard to the treatment course. The LIBERTY 360° 30-day outcome data taught us that Rutherford class 6 patients were successfully treated and discharged home. This is a big change from the current mindset of the general approach and, of course, the guidelines as well.⁴ Many will say that it may be too early to draw conclusions from 30-day data. I agree, but at least there is hope—soon to be followed with long-term data from which we can then draw proper conclusions to aid guideline committees in the creation of new PAD treatment recommendations.

Dr. Gray: It's too early to say, but typically guidelines are based on multiple trial outcomes, so it is not clear that this single study will have major impact.

Dr. Adams: Once we have 12-month data, guidelines may change because we will have data on all Rutherford classes, especially Rutherford classes 2 to 3 and Rutherford class 6, rather than just expert consensus.

Who else needs to hear about these data?

Dr. Gray: Patients, referring physicians, engineers working on medical devices, pharmaceutical companies, and payers will all have their own valuable take on these data, especially as they become more fleshed out over time.

Dr. Mustapha: Every physician and mid-level provider (from every specialty) should hear about these data, which I think translates to the cornerstone of PAD/CLI treatment via a multidisciplinary team.

Dr. Adams: The whole team, starting with the front line—primary care physicians, endocrinologists, and nephrologists to the physicians who improve blood flow either endovascularly or surgically (ie, cardiologists, radiologists, surgeons), to those who perform wound care (ie, podiatrists, medicine physicians, surgeons). But most of all, the patient should be informed, especially patients with Rutherford class 6 disease who are often subject to amputation.

Want more information on LIBERTY 360°? Visit: www.liberty360study.com. ■

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