Playing Offense in Postthrombotic Syndrome: The C-TRACT Trial Opportunity

Why a randomized controlled trial is important to evaluate iliac vein stenting in PTS and how the C-TRACT trial can help resolve unanswered questions.

By Suresh Vedantham, MD

The C-TRACT trial is a multicenter, randomized controlled clinical trial evaluating the ability of endovascular iliac vein stent placement to reduce the severity of the postthrombotic syndrome (PTS) and improve quality of life in patients with previous deep vein thrombosis (DVT).[1] This study and its development have been funded by the National Heart Lung and Blood Institute (NHLBI), part of the National Institutes of Health (NIH), in a United States taxpayer commitment of > $12 million. The C-TRACT trial is being conducted at 30 clinical centers nationwide and is coordinated by researchers at Washington University in St. Louis, Missouri (clinical coordinating center); McMaster University in Hamilton, Ontario, Canada (data coordinating center); Massachusetts General Hospital in Boston, Massachusetts (vascular ultrasound core laboratory); and the Mid America Heart Institute in Kansas City, Missouri (health economic core laboratory). As of May 21, 2021, the study has enrolled 105 patients (targeted accrual is 374 patients).

BETTER LATE THAN NEVER

The history of endovascular intervention in chronic venous disease management dates back > 25 years, during which clinical practice development was largely driven by shared anecdotes, case series, and retrospective analyses that suggested that clinical improvement may often be observed in PTS patients who have their iliac veins reopened. In recent years, the use of iliac vein stents has seen a steep increase due to the advent and subsequent FDA approval of stents bioengineered for venous use, improved diagnosis of venous lesions by intravascular ultrasound (IVUS), and greater awareness of this form of treatment.[2]

Then, why conduct a randomized trial in 2021, so many years down the line? Don't we already understand this treatment modality? Certainly, we have made many worthwhile observations, but there remain a number of important unanswered questions.

First, does iliac vein stent placement produce benefits that are sufficiently large and durable to be worth the risks, costs, inconveniences, and uncertainties of permanent device implantation? There are good reasons to ask this loaded question. To date, there is no prospective evidence of efficacy for stent placement in PTS or any convincing characterization of the degree of benefit that is sustained beyond a single, small (n = 50) pilot randomized trial with a mixed group of patients followed for 6 months.[3] Previous studies indicate that perhaps one-third of stented PTS patients will require additional procedures to manage stent stenosis or occlusion during the first few years after placement.[4] Even when stents remain patent, some patients do not sustain the initial benefit achieved due to changes in other factors such as weight, cardiovascular status, superficial venous disease, and unknown variables. To responsibly recom-

mend stent therapy to patients, physicians need high-quality data to understand the nature of the associated benefits.

Second, the long-term safety of stents has not been systematically evaluated. Stent restenosis and occlusion are known complications, but the stability and mechanical integrity of new venous stents remain to be determined over a longer time horizon. Even in the first few years after FDA approval, two stents have already developed possible safety issues that have prompted global device recalls.[5,6]

Third, there is robust payer attention to the medical necessity of stent placement. A 2016 MEDCAC panel convened by the Centers for Medicare & Medicaid Services concluded that there was limited randomized trial data on which to base assertions of efficacy for chronic venous disease interventions. Private payers have also started to look more carefully at this practice, with updated policies introducing new barriers over the past few years. Absent high-quality data, insurers are likely to make decisions that have negative effects upon patients' access to quality care.

PLAYING OFFENSE

The above study rationale is valid but may seem inherently "defensive," especially to providers who are already sold on stent placement. Speaking as an experienced provider of medical, compressive, and endovascular PTS care, I respectfully disagree and would contend that the C-TRACT trial is actually the only ongoing initiative that can produce a large-scale quantum increase in well-justified stent placements.

As endovascular physicians, it is important to realize that our clinical referrals represent only the tip of the iceberg. From our experience with the ATTRACT trial, we know that a 500-bed hospital will see an average of 450 acute DVT cases per year, and that 10% to 20% of these patients will develop moderate-or-severe PTS over 2 years. But the majority of these patients have their DVT managed by their primary care physicians and hematologists; only a tiny fraction are ever referred to an endovascular provider. In addition, most localities only have a limited number of endovascular-capable specialists who manage the challenging PTS population, which further limits awareness among medical physicians. Although the cocktail of clinical experience, shared anecdote, exciting new devices, and single-arm studies may suffice to justify stent placement in the eyes of endovascular physicians, it has little chance of meaningfully expanding quality stent-based care because it is poorly suited to (1) define which patients benefit and (2) convince medical physicians (who are not inclined to subject their patients to risky interventions without evidence) to consider this option for their PTS patients. In fact, there is only one thing that can convince them: a rigorous multicenter, randomized controlled trial conducted with strong precautions against bias, showing compelling evidence of efficacy and safety. Until a trial of that nature is completed, stenting proponents will not be able to speak effectively to their medical colleagues and the majority of patients with moderate-to-severe PTS and reversible iliac vein lesions will live with disability, oblivious to the potential to be helped.

For many reasons, the C-TRACT trial is ideally suited to solve this problem. It was developed in close collaboration with and is led by highly credible leaders from the medical and endovascular DVT provider communities. In developing the protocol, study organizers queried and integrated the real-world clinical practice preferences of clinicians who manage PTS patients. It studies a highly relevant patient population—patients with moderate-to-severe PTS who have iliac vein occlusion or ≥ 50% stenosis and excludes patients who may be less likely to benefit (mild PTS or poor venous inflow). All patients in both arms receive close monitoring and optimal PTS care that includes medications, compression therapy, and (if needed) quality venous ulcer care. For patients randomized to stent placement, dilatation of stents to an adequate diameter is required, as are pre- and poststenting IVUS and postprocedure antithrombotic therapy. Although follow-up is for 2 years, the primary outcome of the study is the Venous Clinical Severity Score at 6 months, adjusted for baseline. Hence, C-TRACT stands a strong likelihood of being positive if completed as planned. If that proves to be the case, endovascular therapy proponents will have a highly attentive audience of medical physicians, creating a potential to greatly expand the number of patients who benefit.

The C-TRACT study protocol has been adapted to accommodate the real-world conditions posed by the coronavirus pandemic and currently requires just two to three in-person visits. Study patients benefit from close monitoring, free compression garments (donated by MediUSA), and independent safety oversight. Please type "C-TRACT" into your cellphone's app store, download the study's HIPAA-compliant Referral App, and efficiently refer your patients to the study (which takes about 15 seconds). Please visit https://bloodclotstudy.wustl.edu/c-tract/health-provider-referral/ for more information.

We are grateful to our study participants and to our partners who have publicly endorsed the study:

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the American Venous Forum, the American Vein and Lymphatic Society, the National Blood Clot Alliance, the North American Thrombosis Forum, the Society of Interventional Radiology Foundation, and the Society for Vascular Medicine. Please join this incredible community that is driving forward best care for PTS! ■

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