

# C-TRACT Trial: Coming Together to Tackle Chronic DVT

Why C-TRACT is needed, its study design, and how current endovascular practitioners can support it.

**BY SURESH VEDANTHAM, MD**

**O**n September 1, 2018, the National Institutes of Health's (NIH) National Heart, Lung, and Blood Institute (NHLBI) funded a pivotal clinical trial called C-TRACT (NCT03250247). C-TRACT is a multicenter, randomized controlled trial that will determine the ability of endovascular therapy (EVT) to reduce the severity of postthrombotic syndrome (PTS) in patients with moderate-to-severe PTS due to previous deep vein thrombosis (DVT). The funding of the trial, along with previous NHLBI support for the study's planning and start-up phases, represents an overall financial commitment from the United States taxpayer exceeding \$12 million.

## WHY IS THIS STUDY NEEDED?

The NHLBI's decision to fund C-TRACT is an acknowledgment of the impact of PTS upon patients' lives and the potential for EVT to alleviate this burden. Approximately half of patients with proximal DVT develop PTS, which causes daily leg pain, swelling, heaviness, and/or fatigue.<sup>1</sup> Patients with PTS may also develop skin changes and/or venous ulcers that are often slow to heal, have difficulty completing daily activities or working, and experience poorer quality of life (QOL). Unfortunately, no consistently effective evidence-based therapy exists to treat moderate-to-severe PTS.

For more than 20 years, image-guided, catheter-based treatments have been used in an attempt to reduce symptom severity in selected patients with PTS. A pooled analysis of available case series suggests that nearly two-thirds of patients may benefit from stent recanalization of chronic iliac vein obstruction,

with safety events occurring infrequently.<sup>2</sup> Subgroup data from the NHLBI-sponsored ATTRACT trial support the importance of an open iliac vein—patients who received thrombolytic therapy for acute ilio-femoral DVT experienced reduced PTS severity and improved QOL over 2 years compared with those who did not.<sup>3</sup> Moreover, endovascular clinical practice continues to improve; for example, intravascular ultrasound is increasingly used, which affords physicians improved capabilities in diagnosing iliac vein obstruction and optimizing stent placement.<sup>4</sup> Even more exciting, in 2019, two new venous-engineered stents received FDA approval and showed early results that hint at an even greater opportunity to advance patient care.

However, EVT has not been evaluated in well-designed clinical trials, so it is unclear if any benefits are large and durable enough to be worth the risks, costs, inconveniences, and uncertainties of permanent device implantation for most patients. A minority of stented PTS patients require additional procedures to manage stent stenosis or occlusion during the first few years after placement, and some patients do not sustain the initial benefit achieved. There is no high-quality data set to enhance our thinking on which patients will most benefit. This information gap is particularly awkward in the current era of precision medicine, in which expectations are high that interventions will be finely targeted to patients with characteristics that predict benefit.

Furthermore, there has been increasing recognition of a substantial occurrence of overstenting for disease that causes only mild clinical sequelae or based on

borderline imaging findings. The rapid increase in peripheral vascular stenting caught the eye of the media and governmental agencies a few years ago, resulting in the Centers for Medicare & Medicaid Services convening a Medicare Evidence Development & Coverage Advisory Committee panel in July 2016. Those who attended the panel saw that only randomized trial data were deemed credible by the panel, of which there were almost none for PTS interventions or EVT. With multiple companies now gaining the ability to promote their stents in the marketplace, near-term growth in the volume of stenting is certain to occur and will inevitably hit a threshold that prompts additional scrutiny and concern from governmental and private payers. In the absence of high-quality data, insurers will draw lines in whatever way seems best to them—often to the detriment of our patients' access to quality care. Shouldn't endovascular physicians be proactive in anticipating and addressing this challenge?

The developers of the C-TRACT trial would answer with a resounding YES! For 7 years, C-TRACT investigators have been preparing for a pivotal randomized controlled trial. C-TRACT is led by the same multidisciplinary steering committee that conducted the NHLBI-sponsored ATTRACT trial, with a few changes to add specialized expertise in different domains of PTS care. Like ATTRACT, the C-TRACT trial is centrally 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);

## THE C-TRACT TRIAL AT A GLANCE



### PATIENTS ENROLLED TO DATE:

**26** of **374** patient target



### NUMBER OF ENROLLING CENTERS:

**22** within the United States and actively working to add sites



### ELIGIBILITY CRITERIA:

#### ADULT PATIENTS WITH MODERATE-TO-SEVERE PTS

with iliac vein occlusion or  $\geq 50\%$  stenosis, with one or more of the following:

- VCSS  $\geq 8$
- Villalta score  $\geq 10$
- Presence of a venous ulcer



### EXCLUDED POPULATION:

**PATIENTS WITH POOR INFLOW TO THE COMMON FEMORAL VEIN**, previous ipsilateral venous stent placement, recent acute DVT, or severe PAD



### TREATMENT ARMS:

#### EVT VERSUS NO EVT

All patients receive close monitoring and optimal standard PTS care, including medications, compression therapy, and quality venous ulcer care

**1**

### PRIMARY ENDPOINT:

**6-MONTH VCSS** adjusted for baseline

**2**

### SECONDARY ENDPOINTS:

Assessed and compared through 24 months:

- PTS severity
- Ulcer healing
- QOL
- Safety
- Cost



### FOLLOW-UP:

**2 YEARS** with active management

Abbreviations: DVT, deep vein thrombosis; EVT, endovascular therapy; PAD, peripheral artery disease; PTS, postthrombotic syndrome; QOL, quality of life; VCSS, Venous Clinical Severity Score.

and the Mid America Heart Institute in Kansas City, Missouri (health economic core laboratory).

## TRIAL DESIGN

The C-TRACT trial was developed in close collaboration with the vascular provider community. During the NHLBI-supported planning phase, the study leadership conducted a detailed survey of practicing clinicians who manage patients with PTS to understand practice patterns and opinions on key issues. The survey results were discussed at an expert panel meeting in Chicago, Illinois, in April 2015 that was attended by 35 investigators across multiple PTS-related medical and scientific disciplines.<sup>5</sup> The discussions were explicitly structured to address trial design and its identifiable challenges and potential controversies.

The study eligibility criteria include adult patients with moderate-to-severe PTS who have iliac vein obstruction (ie, occlusion or  $\geq 50\%$  stenosis). To avoid enrolling patients with mild disease who might be less likely to benefit, inclusion is restricted to patients with a Venous Clinical Severity Score (VCSS)  $\geq 8$ , a Villalta score  $\geq 10$ , or a venous ulcer. Patients with poor inflow to the common femoral vein are excluded, as are patients who have had previous ipsilateral venous stent placement, recent acute DVT, or severe peripheral artery disease.

All patients in both arms will receive close monitoring and optimal standard PTS care that includes medications, compression therapy, and quality venous ulcer care, if needed. Patients are randomized to receive or not receive EVT. Patients in the EVT arm undergo iliac vein stent placement; per our investigational device exemption from the FDA, any legally marketed bare stent with a  $\geq 12$ -mm diameter made of Elgiloy or nitinol may be used per physician preference. Patients are followed for 2 years. At each follow-up visit, the previously mentioned elements of standard PTS care are reviewed and modified as needed so patients in both arms can benefit from an “active management” posture by a multispecialty expert team.

The investigators recognized the potential for crossover to undermine the study assessments. In the survey and at the expert panel meeting, physicians were asked how long they would be willing to withhold EVT from a nonimproving patient in the no-EVT arm. Ultimately, it was decided that to have the maximum chance of achieving an unpolluted comparison, the primary outcome of the study (the VCSS adjusted for baseline) would be assessed at 6-month follow-up. However, the secondary outcomes of PTS severity, ulcer healing, QOL, safety, and costs will be assessed and compared

through 24 months. Overall, we believe this study design provides the best chance of a true assessment of the safety and efficacy of EVT.

## THE ROLE OF THE ENDOVASCULAR DVT COMMUNITY

Investigator-initiated multicenter trials are enormously challenging to complete, and many such studies are ultimately forced to reduce their scientific objectives. NIH-sponsored studies lack the well-resourced “boots-on-the-ground” manpower that industry sponsors can use to promote clinical studies. Rather, NIH studies rely heavily on the provider community’s mission drive—a provider’s determination to deliver the necessary support and sacrifice over a sustained time period to enable the study to succeed. In its early months, these challenges are readily apparent for the C-TRACT trial; we have enrolled 26 of 374 target patients, but it has not been easy, and we have a long way to go. We are currently pursuing a protocol amendment to simplify patient entry into the study and update the protocol to new developments in venous care. This will help, but the jury is still out on whether this study will achieve its goals.

The reader can consider this article a fervent plea from the author, on behalf of the C-TRACT investigators, to strongly support our efforts during the upcoming years. Here’s what you can do:

- **Apply to become a study site.** If your clinical practice has a large population of PTS patients and includes physicians who can reliably open chronically occluded iliac veins and deliver quality antithrombotic, compressive, and venous ulcer care, apply to become a study site. We currently have 22 clinical centers enrolled in the United States and are moving quickly to add sites. To apply, download and complete the C-TRACT Study Site Questionnaire ([bloodclotstudy.wustl.edu/c-tract/becoming-a-c-tract-study-site](http://bloodclotstudy.wustl.edu/c-tract/becoming-a-c-tract-study-site)) and submit it to [CTRACT@wustl.edu](mailto:CTRACT@wustl.edu). If you are unsure if your site will be a good fit, we are happy to discuss with you or your collaborators to help you decide. Interested investigators can contact the author directly ([vedanthams@mir.wustl.edu](mailto:vedanthams@mir.wustl.edu)).
- **Connect PTS patients to our study teams.** Please refer your patients to the study and ask your colleagues to do the same. Because only a small fraction of referred patients will actually enter the study, you will not lose many patients from your clinical practice. Download and use the C-TRACT Referral app and ask your colleagues to do the same. This tool provides a HIPAA-compliant portal to enable quick referral of PTS patients who might qualify for the

study. Use the credibility of an NIH trial and the tools and resources we can provide to attract patients to your practice—the study will benefit and so will your practice. Please visit [bloodclotstudy.wustl.edu/c-tract/](http://bloodclotstudy.wustl.edu/c-tract/) health-provider-referral for more information.

- **Embrace the core rationale behind the study.** We need data to secure access to EVT for patients if it works as we hypothesize; we must know if and to what extent patients gain sustained benefit from EVT. We cannot minimize the potential consequences, known and unknown, of implanting permanent devices in our patients. We should be absolutely comfortable randomizing patients to EVT or no EVT. In fact, participation in C-TRACT enables patients to learn about their condition and receive state-of-the-art PTS care in a closely monitored setting and structure, with excellent communication from committed multispecialty study teams, while also contributing to new medical knowledge that will improve care for future patients.

## CONCLUSION

We are tremendously proud and grateful that the NHLBI has again chosen to invest significant dollars into a pivotal trial aimed at reducing PTS-related disability. We are thankful that the study has been endorsed by 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. This community support surely boosts the chances of success. To lead this study is an incredible privilege and responsibility—I'll be working hard to ensure its success, and I hope you will too! ■

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