# A Clinical Trial of Venous Stent Placement for Post-thrombotic Syndrome: Current Status and Pandemic-related Changes

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## Abstract

Patients with post-thrombotic syndrome (PTS) and iliac vein obstruction have lower extremity symptoms, activity limitation and impairment of health-related quality of life. Preliminary studies suggest that iliac vein stent placement, which eliminates venous outflow obstruction, may reduce the clinical severity of PTS. However, stent placement is associated with patient risk, inconvenience and cost. Therefore, the Chronic Venous Thrombosis – Relief with Adjunctive Catheter-directed Therapy (C-TRACT) trial was launched to rigorously assess the risk–benefit ratio of stent placement for the treatment of moderate or severe PTS. In the trial, patients in both treatment groups receive a high quality of multi-modality PTS care that includes medical, compressive, and ulcer therapies. Due to the COVID-19 pandemic, the trial protocol and practices were modified to enhance the study feasibility while preserving its ability to answer its primary question. This review summarises the current status of the trial and the potential impact of the pandemic-related adaptations to future venous clinical practice and research.

## Keywords

Deep vein thrombosis, post-thrombotic syndrome, stent, randomised trial

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A substantial proportion of patients with proximal lower extremity deep vein thrombosis (DVT) develop post-thrombotic syndrome (PTS) within 2 years.[1] These patients often experience severe leg swelling, chronic pain, venous claudication and stasis dermatitis, with some progressing to skin ulceration. As a result, PTS is associated with substantial impairment of health-related quality of life (QOL), direct medical costs and indirect costs to society.[2,3]

Conservative means of managing PTS do not restore normal venous physiology. In contrast, endovascular stent placement directly addresses the venous outflow obstruction and ambulatory hypertension that underlie the most severe PTS manifestations. Although stents have been used to treat PTS by endovascular specialists for many years, no multicentre randomised controlled trial (RCT) has been completed to show that they reduce clinically important PTS in a durable, safe and cost-effective manner.[4] Due to the absence of such data, relatively few medical physicians routinely refer PTS patients for stent placement. In 2018, the Chronic Venous Thrombosis – Relief with Adjunctive Catheter-directed Therapy (C-TRACT) trial was launched to rigorously evaluate iliac vein stent placement in patients with moderate or severe PTS.[5] Although the results will not be available for a few years, this article summarises some ways in which this ongoing pivotal study can contribute to improving venous clinical practice and clinical trial implementation.

## Study Rationale

There currently exists only a single published pilot RCT evaluating stent placement for chronic venous disease.[6] In that double-blind, single-centre study performed in Brazil, 51 limbs with moderate–severe chronic venous disease and iliac vein obstruction were randomised to receive, or not receive, iliac vein stents. Patients in the non-stented arm underwent a sham procedure to maintain patient blinding, and patients in both arms received standard PTS therapy. Greater improvement in pain scores, Venous Clinical Severity Scale (VCSS) scores and QOL scores were seen over 6 months in the stented patients compared with the non-stented patients.[6,7] However, PTS patients comprised only half the study sample and the study did not use dedicated venous stents that may offer greater

resistance to axial compression. Given that it was a pilot study in a single centre, that trial was not designed to provide precise estimates of treatment effects and harms that can be broadly generalised to other clinical practices.

The absence of a pivotal multicentre RCT evaluating iliac stent placement has created a number of problems. One the one hand, whereas many thousands of patients with previous DVT live with moderate or severe PTS, only a tiny fraction are referred to endovascular specialists for consultation. Many of them experience tragic life consequences and long-term disability, and are entirely unaware that their condition may be amenable to treatment. With the advent of direct oral anticoagulants, improved venous diagnostic capabilities and new endovascular treatment tools on top of the existing array of venoactive drugs and compression devices, there appears to be substantial potential to help these individuals. On the other hand, it is equally clear that patient selection for endovascular therapy may be excessively lax in some centres, and the experience to date with venous stent therapy also hints at potential drawbacks.

Although dedicated venous stents appear to enable more precise deployment and may resist axial compression better than older devices that were designed for non-venous indications, stent patency in PTS populations has been at approximately only 80% at 1-year follow-up and 70% at 3-year follow-up.[8–10] In addition, maldeployment, migration and fracture of dedicated venous stents have been reported; and although the relative contributions of operator error and inexperience versus device limitations are unclear, these events have prompted two brands to be recalled from the marketplace.[11,12]

Overall, at this time, it is difficult to confidently forecast whether any individual patient will experience durable benefit from iliac vein stent placement and remain free of complications. This is of particular concern because many candidates for endovascular PTS therapy are relatively young, with long life expectancies. Given the absence of credible evidence of benefits, long-term complications and re-interventions after endovascular stent therapy can lead to patient dissatisfaction that negatively affects the patient–provider relationship and that poses risks for the provider as well. For these reasons, the successful completion of high-quality studies to rigorously quantify the risk–benefit ratio of venous stent placement is particularly urgent.

C-TRACT (NCT03250247) is a Phase III, multicentre, open-label, assessor-blinded, parallel two-arm RCT that is sponsored by the National Heart, Lung, and Blood Institute (NHLBI), a part of the US National Institutes of Health (NIH). The study is being conducted under an investigational device exemption granted by the Food and Drug Administration (FDA).

Approximately 374 adult patients with moderate or severe PTS and iliac vein obstruction are being randomised to receive endovascular stent therapy + standard PTS therapy versus standard PTS therapy alone. The primary study hypothesis is that the use of endovascular stent therapy will reduce the severity of PTS at 6 months, assessed by a blinded examiner using the VCSS measure. Secondary outcomes assessed over 24 months include PTS severity, QOL, ulcer healing, safety, valve reflux and cost-effectiveness. The study enrolled its first patient in July 2018 and is currently active in 30 US clinical centres.

## Modelling Quality Venous Clinical Practice

High-quality data will benefit future care, but there is an equally pressing need for an immediate elevation of general clinical practice awareness and standards around PTS care. Worldwide, and even within local clinical practices, PTS care is highly variable: few providers are well-educated on the nature of this condition or the various modes of therapy that can be used to help patients. Against this background, the C-TRACT trial can be a compelling vehicle to improve PTS care.

Because publicly funded studies require robust multidisciplinary expertise, community input and extensive peer review prior to funding, the resulting study protocols often provide excellent examples of expert consensus on best practices for disease management. This is certainly true of C-TRACT, which was developed via an organised multi-specialty process with active NHLBI support.[5] In a number of areas, this study can be used to model the delivery of high-quality PTS care, including endovascular intervention.

## Improving Patient Selection

The recent dramatic increase in the number of stent placements, endovascular operators and complications has prompted concern among venous experts and societies about current patient selection practices.[13] C-TRACT restricts study inclusion to patients with sufficient life impact from PTS to justify a permanent device implant, and a strong potential to respond to stent recanalisation. Study patients must have PTS that is causing substantial limitation of daily activities or work capacity due to venous symptoms or a venous ulcer. Patients who do not have a VCSS score ≥8, a Villalta score ≥10, or an open venous ulcer are excluded.[14]

Study patients must also have ipsilateral iliac vein obstruction, as shown by occlusion or ≥50% stenosis on venogram, CT venogram, MRI venogram or intravascular ultrasound (IVUS); or a combination of reduced venous outflow fraction on air plethysmography and abnormal duplex ultrasound. Patients with poor inflow to the common femoral vein are excluded. Hence, patients with mild PTS, mild stenosis or a low likelihood of favourable stent patency are excluded from study participation and the risks of stent placement. Were these or similar criteria to be followed in clinical practice, the number of unnecessary or ineffective stent placements might be reduced.

## Encouraging Quality Conservative Therapy

Traditional medical training can be criticised for a failure to view venous disease through a holistic lens. Indeed, many providers are trained to think about treating 'chronic occlusions' rather than 'patients with a serious condition that is amenable to risk factor modification and multi-modality therapies'. The C-TRACT trial plan instructs research teams to counsel patients in both treatment groups on lifestyle-related measures that they can take to reduce PTS severity. Compression therapy appropriate to the presence or non-presence of an open ulcer is routinely prescribed to study patients.

At each visit, the value of compression is reinforced and adjustments are made to address residual symptoms or intolerance. Anticoagulant therapy is reviewed and modified to follow published clinical practice guidelines for DVT care. The use of venoactive drugs that have been evaluated for chronic venous disease is encouraged, including pentoxyfilline for venous ulcers. Patients with ulcers are managed in specialised wound ulcer care facilities that adhere to published guidelines.[15] Endovenous ablation is encouraged for patients in either arm who have saphenous reflux and a venous ulcer.[16] In this way, C-TRACT proposes a conservative multimodality regimen that, if used in clinical practice, may enable some PTS patients to improve and be spared an irreversible stent implantation. Conversely, persistent disability after institution of the above organised program can strengthen the justification to consider endovascular options.

## Advancing Best Practices for Endovascular Therapy

The C-TRACT endovascular therapy protocol embeds a number of good practices that can enhance safety and efficacy. The use of ultrasound guidance for venous access is required, as is the use of venography and IVUS to define the extent of the obstructive process.[17,18] After crossing the obstruction, predilatation is required to optimise the potential for maximum stent expansion.

Self-expandable bare stents made of elgiloy or nitinol that are legally marketed in the United States (but not under recall) may be used, with the use of FDA-approved dedicated venous stents encouraged. Stents must be dilated to at least 12 mm (for the iliac vein, at least 14 mm is strongly encouraged). Post-stenting venogram and IVUS must be performed. Patients should receive anticoagulation and antiplatelet therapy daily for at least 6 months after the procedure, with low-molecular-weight heparin strongly recommended for the first 3 months if possible. General adoption of these practices to ensure optimal venous imaging, device selection and sizing, and follow-up care seems likely to enhance the likelihood of achieving durable stent patencies.

## COVID-19 Pandemic: Adaptations and Opportunities

In-person follow-up visits of patients enrolled in the C-TRACT trial were initially planned for 2, 4, 6, 12, 18 and 24 months after randomisation. However, the onset of the COVID-19 pandemic in early 2020 resulted in near-complete cessation of in-person study activity for several months, with an incomplete and heterogeneous recovery thereafter. In March 2020, the C-TRACT investigators were provided written guidance on adapting the conduct of the study to the conditions imposed by the COVID-19 pandemic, which included allowance of remote visits when dictated by patient risk level and local requirements.

Coordinating centre staff applied enormous energy to actively engaging with study teams to guide them in implementing the study during the pandemic. Despite these efforts, it was observed that many participants were missing follow-up visits and that the complexities of arranging the visits were burdensome for study teams due to local COVID-19 restrictions on face-to-face visits and limitations on available staffing. Therefore, in January 2021 the protocol was amended to convert the 2-, 4-, 12-, 18- and 24-month visits into remote visits that could be performed with telemedicine tools.

Of note, although the study data capture at these time points is now conducted remotely, physicians are still encouraged to bring patients back for in-person clinical visits as needed to ensure quality PTS care, as is possible per local conditions and patient-specific risks: for example, to re-size compression therapy and maintain a high-quality relationship between the patient and the care team.

Importantly, to maintain the integrity of the study's primary outcome assessment, the baseline and 6-month visits and VCSS assessments have been retained as required in-person visits, per the study's original design. However, the Patient-Reported Villalta (PRV) scale has been substituted for the in-person VCSS and Villalta PTS Scale assessments that were required as secondary assessments at 12, 18 and 24 months, enabling remote data capture. The PRV, designed to permit patient self-assessment of the elements of the original Villalta PTS Scale, has been shown to have excellent agreement with the original scale when used with an accompanying visual aid (which is provided to study patients) to guide patients in self-assessing their visible PTS signs.[19] The PRV has been successfully used to enable remote assessment of PTS in a previous large clinical study.[20] The study's QOL questionnaires are now largely completed by participants at home and collected by mail.[21,22]

The C-TRACT investigators certainly did not foresee the possibility of being compelled to institute a mid-trial change in outcome assessment. However, the adaptations to the pandemic speak to new opportunities to revitalise the venous disease clinical trial enterprise. It has long been recognised that clinical trial conduct in the US can be inefficient and cumbersome, reducing the speed with which new therapies are translated into clinical practice; many of the same issues exist in other countries as well. The barriers are particularly high for investigator-initiated studies that evaluate complex (e.g. endovascular) interventions and that seek to compare treatment paradigms.

C-TRACT is already the largest RCT of its kind; however, despite starting more than 3 years earlier, the trial has enrolled less than one-third of its pre-planned patient sample. Of note, slow accrual was also observed with other major NIH endovascular trials (e.g. CORAL, ATTRACT, BEST-CLI).[23,24] In this sense, it is hoped that an important silver lining of the pandemic will be the accelerated integration of innovative technology to support remote clinical trial conduct. In response to the pandemic, C-TRACT incorporated electronic informed consent, telemedicine visits and patient-reported remote clinical assessments. Beyond improving data capture, it is hoped that the reduction in the participant burden to only 2–3 required in-person visits will increase enthusiasm among patients (especially those who live distant from a clinical centre) to be enrolled and followed in the study.

It is hoped that venous clinical trials will routinely include such modes of efficient trial conduct, and that there will be robust efforts to scientifically validate new venous outcome assessment tools that can be remotely administered using smartphones, wearables and other mobile tools, as is done for other diseases.[25] In addition to making trial participation easier for patients and less resource intensive for study teams, such tools have the potential to address a crucial current limitation of venous outcome assessment, namely, that despite the fact that PTS causes daily symptoms and life impact that fluctuates over time, patients are currently assessed only a few times during follow-up (e.g. every 6 months). The development and validation of remote venous assessment tools could enable a more complete capture of a patient's daily experience with PTS. Their use should not be limited to research studies, but could be applied in clinical practice to enhance the follow-up of patient status and improve the overall patient experience by improving the degree and quality of communication with the patient care team.

Given the ongoing challenges to study enrolment, technology is also being applied to connect potential study candidates to C-TRACT Trial research teams. An institutional review board (IRB)-approved mobile app has been developed for the C-TRACT trial, and is available on the Apple and Google Play stores. This app is designed to enable rapid, Health Insurance Portability and Accountability Act (HIPAA)-compliant referral of a potential patient to the study by a busy provider. The provider answers three quick questions via check-box and enters a provider (e.g. nurse coordinator) contact telephone number, then the app sends a HIPAA-compliant message to the study's clinical coordinating centre, whose staff then call the provided contact number to hear about the patient.

In addition, a number of barriers to study referral among endovascular providers have been recognised: first, within some surgical and interventional radiology practices the traditional culture is for a physician

to manage the patients referred to them, and the health system may reward providers with higher procedure volumes (these factors can deter physicians from referring patients even to providers within the same practice); second, referral to other (often competitive) local centres is often discouraged by division leaders and hospital systems, and there can also be insurance coverage barriers; and last, providers have different perceptions of the willingness of patients and caregivers to travel to more distant clinical sites for a clinical trial participation opportunity, which can reduce their inclination to refer patients. Hence, the C-TRACT investigators are now pursuing a social media campaign to directly target IRB-approved, study-related messaging to a target audience of DVT-interested laypersons (patients, family members and other caregivers). It is hoped that these technology-assisted strategies will pay major dividends in accelerating the pace of recruitment to this study, and that they can similarly support other studies and patient needs in clinical practice.

## Conclusion

The C-TRACT trial will rigorously characterise the risk–benefit ratio of endovascular stent therapy for PTS. From a patient's perspective, study enrolment enhances the likelihood of receiving high-quality expert-endorsed PTS care and affords them the benefits of independent safety oversight, which is valuable given the nature of the endovascular procedure being evaluated. In addition, C-TRACT provides a useful model from which to improve the global standard for PTS care and drive innovation in the implementation of pivotal venous clinical trials. ❑

## Clinical Perspective

- Endovascular stent placement has shown strong potential to improve clinical outcomes in patients with severe limb symptoms and disability from post-thrombotic syndrome (PTS), but also poses risks and costs.
- Selection of PTS patients for venous stent placement in clinical practice can be improved through careful patient evaluation and diligent application of conservative therapies, as modelled by the National Institutes of Health-sponsored C-TRACT trial and other studies.
- The application of modern technology to aid the implementation of the C-TRACT trial during the COVID-19 pandemic highlights the potential for technology adjuncts to improve the PTS patient experience and expedite the completion of pivotal clinical trials.


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