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Author manuscript

N Engl J Med. Author manuscript; available in PMC 2026 April 14.

Endovascular Therapy for Post-Thrombotic Syndrome: A Randomized Trial

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Abstract

Background: Post-thrombotic syndrome (PTS) is common after deep vein thrombosis and can cause severe limb symptoms that impair patients' activity and quality of life (QOL). Endovascular therapy (EVT) can eliminate chronic venous obstruction and is hypothesized to reduce the severity of PTS.

Methods: We randomized 225 patients with moderate-or-severe PTS and imaging-confirmed iliac vein obstruction to receive EVT (iliac vein stent placement and enhanced anti-thrombotic therapy) plus standard PTS care or standard PTS care alone. PTS severity at 6 months (primary outcome) was assessed using the validated Venous Clinical Severity Score (VCSS) by evaluators who were blinded to treatment arm. Key secondary outcomes included venous disease-specific and overall physical QOL.

Results: At 6 months, PTS severity was lower in the EVT group (N=112) than the No-EVT group (N=112) -- mean VCSS 8.1 (standard deviation [SD] 5.1) points EVT, versus 10.0 (SD 4.9) points No-EVT (adjusted difference −2.0 points; p=0.001). Venous disease-specific QOL was higher (better) in the EVT group at 6 months (VEINES-QOL score: adjusted difference 14.5 points; p<0.001), as was generic QOL (SF-36 Physical Component Scale summary score: adjusted difference 6.1 points; p<0.001). Through 6 months, EVT led to more overall bleeding (11.6% versus 3.6%, p=0.03).

Conclusion: Among patients with moderate-or-severe PTS and iliac vein obstruction, EVT reduced PTS severity and improved health-related QOL over 6 months, but led to a higher risk of bleeding. Trial Registration: www.clinicaltrials.gov: NCT03250247

Introduction

Post-thrombotic syndrome (PTS) develops frequently after acute proximal deep vein thrombosis (DVT) (1). Relatively few affected patients receive focused PTS management due to lack of awareness of, and evidence for, available therapies (2). Venous hypertension plays a central role in PTS and stems from chronic venous obstruction, valvular reflux, central venous pressure elevation, calf pump impairment, and lymphatic dysfunction (2,3). PTS manifests across a broad severity spectrum; patients with PTS and iliac vein obstruction often experience chronic limb pain, swelling, skin changes, and/or venous leg ulcers, impairing function and quality of life (QOL) (4).

Previous studies suggest that image-guided endovascular placement of metallic stents may reduce iliofemoral venous obstruction and thereby improve venous physiology, PTS severity, and QOL (5–9). However, its benefits and risks have not been evaluated in a multicenter randomized controlled trial (RCT). We therefore conducted the Chronic Venous Thrombosis: Relief with Adjunctive Catheter-Directed Therapy (C-TRACT) Trial to determine if endovascular therapy (EVT) reduces PTS severity.

Methods

Study Organization

C-TRACT was an NIH-sponsored, Phase III, multicenter, randomized, open-label, assessor-blinded, controlled clinical trial (NCT03250247) (10,11). The study was approved by a central institutional review board; all patients provided informed consent. The C-TRACT Steering Committee and investigators were responsible for the study's design and conduct, respectively. The authors are solely responsible for the writing of this article and vouch for its accuracy. The first author created the first draft and the last author oversaw data analysis by staff biostatisticians (Supplementary Appendix).

Patient Population

Patients with moderate-or-severe PTS and iliac vein obstruction were enrolled at 29 U.S. clinical centers. PTS was defined as chronic venous disease in the ipsilateral leg of a patient with DVT ≥ 3 months before enrollment (12). PTS was considered "moderate-or-severe" if there was substantial limitation of daily activities or work capacity from venous symptoms that resulted in a Venous Clinical Severity Score (VCSS) ≥ 8, a Villalta PTS Scale score ≥ 10, or an open venous ulcer (12–16). Iliac vein obstruction was defined as occlusion or ≥ 50% stenosis on catheter venogram, intravascular ultrasound (IVUS), computed tomography venogram, or magnetic resonance venogram. Patients were excluded if they were <18 years old; pregnant; or had recent (<3 months) acute DVT, poor inflow to the common femoral vein (CFV), or previous stent placement. See Supplementary Appendix for full criteria.

Stratification and Randomization

Patients were allocated 1:1 to receive EVT (iliac vein stent placement and enhanced anti-thrombotic therapy) or No-EVT using web-based central randomization. Randomization was stratified by clinical center, by whether there was an open venous ulcer, and by

whether the CFV was normal on ultrasound (since CFV status affects PTS severity and stent patency) (1,17,18). The randomization sequence, computer-generated in advance by an independent statistician using varying block sizes, was not accessible to clinical center personnel. Allocation was concealed until treatment assignment release.

Treatments

Patients in both groups received standard PTS care including: (a) individualized compression therapy, starting with sized-to-fit, knee-high, 20–30 mmHg elastic compression stockings (Medi USA, Whitsett, NC) for compression-naïve patients, adjusted as needed to encourage compliance; (b) anticoagulation appropriate to the patient's DVT recurrence risk; (c) guidance on smoking cessation, leg elevation, exercise, and avoidance of limb trauma; and (d) for patients with an open venous ulcer, oral pentoxifylline and multilayer compression were encouraged and there was referral to a wound/ulcer care clinic for comprehensive evidence-based care (2,19–23).

EVT was performed per published guidelines by board-certified physicians whose credentials were approved by study leadership (5,23). Sterile technique, fluoroscopic guidance, and either general anesthesia or moderate sedation were used. The treating physician chose the access vein, the method of crossing the obstructed veins, and the stent type (required to be FDA-approved or cleared for any indication, made of nitinol or elgiloy, non-covered, and ≥12 mm diameter). After multiplanar catheter venography and IVUS (required), the veins were pre-dilated and stents were deployed and dilated to ≥12 mm. Repeat venography and IVUS were performed. If acute thrombus or inflow vein obstruction was present, standard endovascular methods were used to optimize flow. Patients received anticoagulation during EVT. After EVT, absent contraindications, therapeutic anticoagulation and daily aspirin (81 mg) were recommended for at least 6 months.

Outcome Assessments

The primary outcome was PTS severity at 6 months post-randomization, assessed with the VCSS by a clinician who was blinded to treatment arm allocation (13–15). The VCSS is a validated scoring system designed to assess clinical change in patients with chronic venous diseases. The VCSS scores 10 venous manifestations (8 clinical signs, 1 symptom, compression use) 0–3, yielding a total score 0–30. The VCSS, reported on a continuous scale and by severity categories that correlate with markers of disease severity, has been used as a key outcome in PTS investigations (8,9,14,24–27). Blinded assessment with the Villalta PTS Scale (score 0–33) was used as a secondary measure of PTS severity (12,16). On both scales, higher scores denote more severe PTS.

Patient-reported QOL was assessed at 6 months with the venous disease-specific Venous Insufficiency Epidemiological and Economic Study Quality of Life (VEINES-QOL) survey (scored 0–100, 4–6 points represents important clinical change) and generic Medical Outcomes Study 36-Item Short Form Health Status Survey (SF-36) (scored 0–100, 2.5 points represents important clinical change) (28–33). On both scales, higher scores denote better QOL.

Calf volume was estimated using the truncated cone formula from measurements of calf circumference and length that were obtained by a blinded assessor at 6 months (34). The presence of an open venous ulcer at 6 months was recorded by the blinded assessor.

Independent core laboratory readers graded the venograms and IVUS exams obtained during the EVT procedures before and after stenting as occluded, partially occluded (≥ 50% obstructed), or patent (< 50% obstructed).

Bleeding, recurrent venous thromboembolism (VTE), and deaths were adjudicated by an independent committee that was blinded to treatment allocation. Bleeding was “major” if it was overt and prompted a hemoglobin drop ≥ 2.0 g/dl, transfusion of ≥ 2 units red blood cells, or involved a critical site (35). Recurrent VTE diagnosis required new/worsened symptoms and imaging confirmation.

Sample Size

The primary outcome was the 6-month VCSS adjusted for baseline. Sample size was calculated using the change in VCSS from baseline to 6 months to test the hypothesis of no difference between groups. Based on previous trial data from patients with high baseline VCSS, we anticipated a 3-point decrease in the No-EVT group with SD=5.4, versus a 5-point decrease in the EVT group (8,24). With α=0.05 (two-sided) and 90% power to detect a 2-point difference, 155 patients per group were required. Accounting for expected loss to follow-up (<5%), crossover from No-EVT to EVT (<10%), and crossover from EVT to No-EVT (<3%), the target sample size was increased by 20.6% to 374 (187 per group). Although the minimal clinically important difference on the VCSS has not been formally established, the 2-point difference we aimed to detect was half the size of published VCSS score thresholds (4 points apart) that correlate with incremental gradations in clinical severity (14). In December 2023, an independent committee at NHLBI reviewed study progress without access to treatment arm-specific data. As observed crossovers and follow-up losses were fewer than originally expected, the investigators were instructed by NHLBI, with data safety monitoring board approval, to stop accrual in June 2025 or when a revised sample size of 250 patients was reached, which was estimated to provide >80% power under unchanged assumptions of treatment effect and variability.

Statistical Analysis

The modified intention to treat (ITT) set included all randomized patients analyzed by allocated treatment arm, excluding any who violated inclusion criteria (did not have moderate-or-severe PTS or iliac vein obstruction). The primary efficacy analysis was the comparison between groups of the mean 6-month VCSS using the modified ITT population and a linear mixed model adjusted for baseline VCSS, strata (normal/abnormal CFV, presence/absence of open venous ulcer) as fixed effects, and center as a random effect, with missing VCSS values imputed using multiple imputation (MI) (age, sex, body mass index [BMI], strata, baseline VCSS, 6-month Villalta score). Sensitivity and subgroup analyses are described in the Supplementary Appendix.

Analysis of VEINES-QOL scores using the Bland system was performed similarly and adjusted for baseline QOL, strata, age, sex, and BMI (MI additionally incorporated baseline

VCSS and valvular reflux) (30). The SF-36 was scored using standard algorithms; its Physical Component Scale (PCS) summary scores were analyzed using same approach as the VEINES-QOL (MI additionally included baseline VCSS and employment status) (36). Mean calf volume, adjusted for baseline volume, was compared between groups using methods similar to the primary outcome (MI additionally included age, sex, BMI, baseline valvular reflux). Villalta scale scores, adjusted for baseline score and strata, were summarized by means and 95% confidence intervals (MI additionally included age, sex, BMI, baseline VCSS and valvular reflux). The proportion of patients with active ulceration (persistent or new) was compared using Cochrane-Mantel-Haenszel test adjusted for CFV status (normal/abnormal) and presence/absence of an open venous ulcer.

Safety outcomes were summarized by incidence proportions and were compared between groups using Cochrane Mantel Haenszel test adjusted for CFV status (normal/abnormal) and presence/absence of an open venous ulcer. Risk ratios and corresponding 95% CIs and p-values were calculated.

The primary analysis of VCSS at 6 months was tested at two-sided alpha 0.05. To account for multiple comparisons, the VEINES-QOL and SF-36 PCS were tested at alpha 0.05 in hierarchical fashion. VEINES-QOL was tested first, and SF-36 PCS was tested only if the VEINES-QOL p-value <0.05. No multiplicity adjustments were made for calf volume, ulcer presence, or safety outcomes.

Results

Baseline Characteristics of Participants

From July 2018 to June 2025, 225 patients were randomized (113 EVT, 112 No-EVT) (Figure 1). One patient assigned to EVT was removed by the IRB and excluded from analysis by the blinded adjudication committee after being found to not have imaging-confirmed iliac vein obstruction. Baseline characteristics were similar between treatment groups (Table 1). The enrolled population was similar to the general population of patients with moderate-or-severe PTS (Supplementary Appendix).

Adherence to Protocol, Treatment, and Follow-Up

The use of compression was similar between groups (Table 2, Supplementary Appendix). Anti-thrombotic medications, particularly anti-platelet agents (71.3% versus 21.0%), were used more frequently in the EVT group. In the EVT group, EVT was performed at median 16 days (interquartile range 9–28) post-randomization. Stent deployment was successful in 98/102 (96%) patients. In 4 patients, the obstructed veins could not be crossed. On IVUS and venography, complete or partial obstruction was present in 101/101 (100%) and 14/101 (14%) patients at the start and end of EVT procedures, respectively. Complete occlusion was present in 52/101 (51%) and 5/101 (5%) patients at the start and end of EVT procedures, respectively.

Within 6 months, 1 patient assigned to No-EVT had EVT, and 4 patients assigned to EVT did not undergo EVT (Figure 1). Of these patients, 1 EVT group patient died before the 6-month assessment. Additional patients did not complete the 6-month assessment due to

loss to follow-up (n=12), withdrawal (n=6), or having the incorrect leg assessed (n=1, excluded by blinded adjudication committee).

Post-Thrombotic Syndrome Severity

In the primary analysis, PTS severity at 6 months was significantly lower in the EVT group than the No-EVT group (mean VCSS score 8.1 [SD 5.1] points EVT versus 10.0 [SD 4.9] points No-EVT, adjusted difference −2.0 points, 95% CI −3.2 to −0.8, p=0.001) (Table 3). Findings were similar in sensitivity analyses and across pre-specified subgroups (Supplementary Appendix). Point estimates of Villalta scores at 6 months also appeared lower in the EVT group. Figure 2 depicts the distribution of patients in the established VCSS and Villalta severity categories at baseline and 6 months.

Secondary Efficacy Outcomes

At 6 months, the mean VEINES-QOL score was 62.8 (SD 24.6) points for EVT versus 48.6 (SD 26.7) points for No-EVT (adjusted difference 14.5 points, 95% CI 9.5 to 19.4, p<0.001) (Table 3). The mean SF-36 PCS score was 56.0 (SD 16.4) points for EVT versus 49.9 (SD 17.1) points for No-EVT (adjusted difference 6.1 points, 95% CI 2.8 to 9.3, p<0.001). Mean calf volume (EVT 2442.1 cm^3, No-EVT 2392.2 cm^3) and open ulcer prevalence (EVT 8.9%, No-EVT 9.8%) were similar between groups.

Safety Outcomes

Bleeding (major + non-major) was more frequent in the EVT group (11.6%) than the No-EVT group (3.6%), driven mainly by non-major bleeds (9.8% versus 2.7%; Table 3). Major bleeds were infrequent (4 EVT, 1 No-EVT) and included 3 patients with gastrointestinal bleeds and 2 patients with intra-articular bleeds; all EVT group bleeds occurred more than 90 days after the EVT procedure. No bleeds were fatal or required surgical therapy (Supplementary Appendix). Rates of symptomatic VTE and death were similar between treatment groups. One patient died of unknown causes at 5 months (assigned to the EVT group, but did not undergo EVT due to personal choice and unrelated life events).

Additional procedure-related serious adverse events included 1 stent deformation addressed on-table with balloon angioplasty, and 1 hospital admission for groin pain (Supplementary Appendix).

Discussion

In this trial, a strategy of endovascular iliac vein stenting that included additional anti-thrombotic therapy reduced PTS severity and improved venous disease-specific and generic health-related QOL at 6 months compared to usual care in patients with moderate-or-severe PTS and iliac vein obstruction. The changes in VCSS and Villalta scores with use of EVT align with prospective single-arm studies (25–27). A 2018 Brazilian, single-center, double-blind RCT (n=51) reported more improvement in VCSS and SF-36 scores after iliac vein stenting versus a sham procedure (8). A 2023 European, single-center, open-label RCT (n=63) reported greater improvement in VCSS, VEINES-QOL, and Villalta scores with addition of iliac vein stenting to best medical therapy (9). C-TRACT confirms these findings

in a larger study with broad multisite involvement, precautions against bias, and focus on PTS (versus mixed venous disease in earlier trials). While the observed mean VCSS difference is of modest size, many patients shifted to lower severity categories on the PTS scales, indicative of reduced life interference from venous disease (12–16). The 14.5-point improvement in venous QOL exceeds the change observed for catheter intervention in acute iliofemoral DVT, and the 6.1-point improvement in SF-36 PCS compares favorably to beneficial interventions in other conditions (37–39). These findings highlight the value of iliac vein outflow after DVT, in alignment with the open vein hypothesis (40).

The high utilization of compression, anticoagulation, and on-label venous stents should increase confidence that contemporary PTS care was provided, although there was higher utilization of anti-thrombotic therapy in the EVT arm. Enhanced anti-thrombotic therapy to promote stent patency is common in real-world EVT care and was integrated into the protocol, resulting in combined anti-platelet and anticoagulant medication use in most EVT group patients. Although most bleeds were non-major and occurred months after EVT, increased bleeding risk from enhanced anti-thrombotic therapy represents a clinical trade-off of adopting a stent placement strategy.

This study has limitations. To enable quality standard PTS care and reflect real-world practice, the protocol provided guidance but allowed local physician-directed care. Variability in care delivered could have affected outcomes, including the higher utilization of anti-thrombotic medications and superficial vein treatments in the EVT group and the higher use of venoactive medications in the No-EVT group. C-TRACT included facilities of varying size but these findings may not apply to EVT performed by less experienced operators. Follow-up beyond 6 months is needed to characterize the extended risk-benefit ratio of EVT, elucidate relationships between anatomic and clinical outcomes, and further explore patients with venous ulcers. The target sample size was reduced after re-assessment indicated that initial assumptions were overly conservative; final enrollment reached 90% of the revised target. While C-TRACT is substantially larger than previous venous stent RCTs, the lower sample size reduced the precision of treatment effect estimates and could have overestimated benefit and under-detected low-frequency adverse events. In an open-label study, patient-reported QOL is susceptible to expectation/performance bias. However, bias was minimized by blinded assessment of the VCSS which is composed mostly of objectively evaluable clinical signs as opposed to subjectively reported symptoms. VCSS assessment was standardized through required assessor training and provision of the published scoring rubric (15).

In conclusion, in patients with moderate-or-severe PTS and iliac vein obstruction, the addition of EVT to standard PTS care reduced PTS severity and improved health-related QOL over 6 months, but increased the risk of bleeding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors express special thanks to Dr. Andrei Kindzelski from NHLBI for his support and guidance; to Dr. Clive Kearon (deceased) for his involvement in study design; to the investigators and research staff members at the clinical centers, core laboratories and coordinating centers (listed in the Supplementary Appendix); to the patients who generously volunteered to participate in the study; and to the following organizations that contributed to the study's success: American Venous Forum, American Vein and Lymphatic Society (formerly American College of Phlebology), National Blood Clot Alliance, Society of Interventional Radiology Foundation, Society for Vascular Medicine, Vascular Interventional Advances (VIVA) Foundation, and Vasculearn Network (formerly North American Thrombosis Forum).

Funding:

The C-TRACT trial is sponsored by the National Heart, Lung, and Blood Institute (NHLBI) of the U.S. National Institutes of Health (NIH) via grants UH3-HL138325 (clinical coordinating center, PI Dr. Suresh Vedantham) and U24-HL137835 (data coordinating center, PI Dr. Sameer Parpia). Study development was supported by NHLBI grants U34-HL123831 and UG3-HL138325 to Dr. Vedantham. Additional support was obtained from the Institute for Clinical and Translational Sciences at Washington University in St. Louis which is funded by the National Center for Advancing Translational Sciences (NCATS) via grant UL1-TR002345 to Dr. William Powderly. Medi USA donated compression garments to study patients. Dr. Kahn is a Tier 1 Canada Research Chair and receives support from the Canadian Institutes of Health Research.

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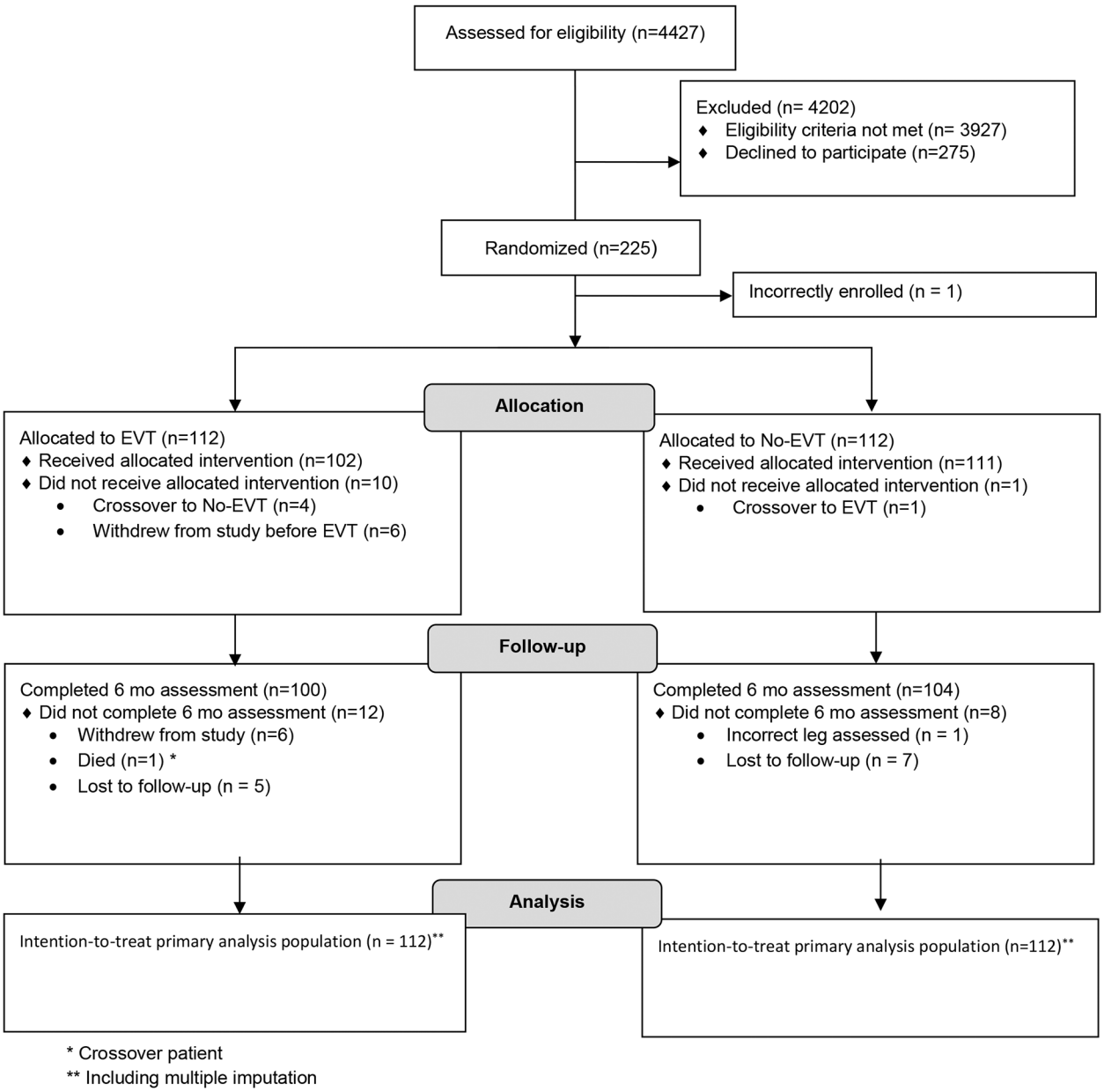

Figure 1 –. CONSORT Diagram

The diagram demonstrates the flow of C-TRACT participant randomization, adherence, and follow-up through 6 months by treatment group. The number of patients who met each inclusion and exclusion criterion are delineated in the Supplemental Appendix. EVT denotes endovascular therapy.

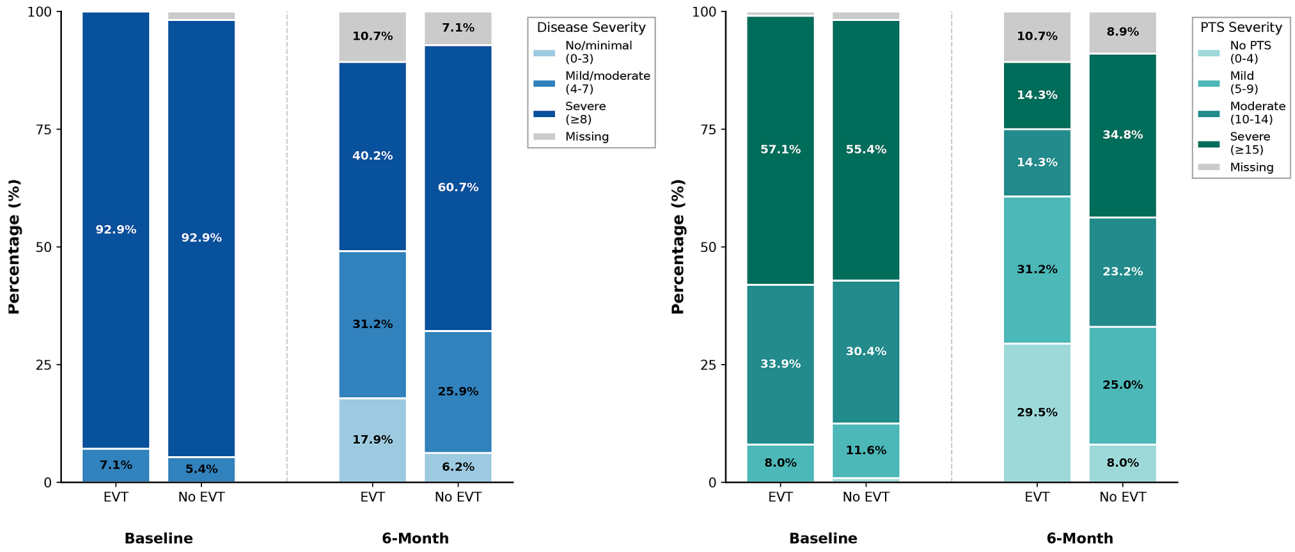

Figure 2 - Categorical Distribution of VCSS and Villalta Scores

The left panel demonstrates the distribution of C-TRACT patients by treatment group at baseline and 6 months follow-up across the 3 established post-thrombotic syndrome (PTS) severity categories on the Venous Clinical Severity Score (VCSS): no/minimal disease (0–3), mild/moderate disease (4–7), and severe disease (>8) (14). The right panel demonstrates the distribution of patients by treatment group at baseline and 6 months follow-up across the 4 established severity categories on the Villalta PTS Scale: no PTS (0–4), mild PTS (5–9), moderate PTS (10–14), and severe PTS (>15) (12,16). Patients entered the study with moderateor-severe PTS but over 6 months follow-up, many patients shifted to less severe categories, especially in the endovascular therapy (EVT) group.

Table 1.

Baseline Characteristics of Participants

Baseline Characteristics	EVT (n=112)	No EVT (n=112)
Age (years): mean (SD)	56.1 (12.7)	54.4 (14.2)
Sex - Female: n (%)	52 (46.4%)	54 (48.2%)
Race: n (%)		
Black	31 (27.7%)	23 (20.5%)
Other	2 (1.8%)	3 (2.7%)
White	73 (65.2%)	78 (69.6%)
Ethnicity - Hispanic or Latino: n (%)	12 (10.7%)	15 (13.4%)
BMI (kg/m^2): mean (SD)	35.0 (8.3)	35.3 (8.3)
Index Leg – Left: n (%)	75 (67.0%)	81 (72.3%)
CEAP Clinical Class: n (%)		
C2-C3	25 (22.3%) *	22 (19.6%)
C4	51 (45.5%) †	58 (51.8%)
C5	19 (17.0%)	16 (14.3%)
C6	17 (15.2%)	16 (14.3%)
CFV Normal: n (%)	40 (35.7%)	45 (40.2%)
VCSS: mean (SD)	12.5 (4.3)	12.3 (4.3)
VEINES-QOL Score: mean (SD)	38.9 (20.9)	39.6 (24.1)
Calf circumference (cm): mean (SD)	43.9 (8.3)	43.3 (6.0)
Receiving any anticoagulant drug: n (%)	90 (80.4%)	94 (83.9%)
Receiving any anti-platelet drug: n (%)	29 (25.9%)	20 (17.9%)
Using any compression therapy: n (%)	94 (83.9%)	83 (74.1%)
Valvular Reflux (any vein): n (%)	88 (78.57%)	92 (82.14%)

* Two patients were originally categorized as C0, corrected to C3 since edema sub-score on VCSS is non-zero

† One patient was originally categorized as C2, corrected to C4 since pigmentation sub-score on VCSS is non-zero

EVT = Endovascular therapy; BMI = body mass index; CEAP = Clinical-Etiological-Anatomical-Pathophysiological Classification System (C0–C6, higher categories have more severe clinical features); CFV = common femoral vein; VCSS = Venous Clinical Severity Score (0–30, higher scores indicate greater severity); VEINES-QOL = Venous Insufficiency Epidemiological and Economic Study Quality of Life (range approximately 0–100, higher scores indicate better quality of life); SD = standard deviation

Table 2.

Treatments after Randomization

Study Treatments	**EVT (n=112)**	**No EVT (n=112)**
Treatments at 6 Months		
Any anticoagulant drug	95/101 (94.1%)	87/105 (82.9%)
Any anti-platelet drug	72/101 (71.3%)	22/105 (21.0%)
Any compression therapy	93/99 (93.9%)	97/103 (94.2%)
Pentoxifylline	1/101 (1.0%)	5/105 (4.8%)
Any other venoactive drug	5/101 (5.0%)	10/105 (9.5%)
Any analgesic drug	26/101 (25.7%)	28/105 (26.7%)
Any superficial vein treatment (Up to 6 months)	6/112 (5.4%)	0/112 (0.0%)
Index EVT Procedure		
Patients with Index EVT Procedure started: n / total n (%) *	102/112 (91.1%)	-
Patients stented in Index EVT Procedure: n / total n (%) †	98/102 (96.1%)	-
Number of stents per patient: mean (min, max)	2.1 (1.0, 7.0)	-
Maximum stent diameter: (mm): mean (SD)	15.4 (2.0)	
Minimum stent diameter: (mm): mean (SD)	14.0 (2.0)	-
Patients with IVC stented: n / total n (%) †	19/102 (18.6%)	-
Patients with CIV stented: n / total n (%) †	84/102 (82.4%)	-
Patients with EIV stented: n / total n (%) †	78/102 (76.5%)	-
Patients with CFV stented: n / total n (%) †	51/102 (50.0%)	-
Patients with FV stented: n / total n (%) †	1/102 (1.0%)	-
Additional thrombolysis/thrombectomy: n / total n (%) †	3/102 (2.9%)	-
Type of stent: n ‡		
Abre (Medtronic)	81	-
SMART (Cordis)	13	-
Venovo (Becton Dickinson)	53	-
Vici (Boston Scientific)	12	-
WallStent (Boston Scientific)	28	-
Zilver Vena (Cook Medical)	22	-
Unknown	3	-

* Did not capture EVT procedure data for patient who crossed over from No EVT to EVT

† Denominator is number of patients who had Index EVT procedure started

‡ Patients could have multiple of the same or different stents

EVT = Endovascular Therapy; IVC = inferior vena cava; CIV = Common iliac vein; EIV = External Iliac Vein; CFV = Common femoral vein; FV = Femoral vein

Table 3.

Outcomes

Outcomes	**EVT (n=112)**	**No EVT (n=112)**			
Continuous	**mean (SD)**	**mean (SD)**	**Adjusted Difference**	**95% CI**	**p-value**
VCSS ‡	8.1 (5.1) †	10.0 (4.9) †	−2.0	−3.2, −0.8	0.001
VEINES-QOL‡	62.8 (24.6) †	48.6 (26.7) †	14.5	9.5, 19.4	<0.001
SF-36 PCS‡	56.0 (16.4) †	49.9 (17.1) †	6.1	2.8, 9.3	<0.001
Villalta Score‡	8.2 (5.7) †	12.3 (6.4) †	−4.1	−5.5, −2.7	
Calf volume (cm^3) ‡	2442.1 (907.0) †	2392.2 (849.6) †	−21.6	−152.0, 108.7	
Binary	**Number of Patients with events (%)**	**Number of Patients with events (%)**	**Risk Ratio**	**95% CI**	**p-value**
Open venous ulcer	10 (8.9%)	11 (9.8%)	0.84	0.42, 1.71	
New ulcer	4 (3.6%)	1 (0.9%)			
Persistent ulcer	6 (5.4%)	10 (12.2)			
Symptomatic VTE	3 (2.7%)	4 (3.6%)	0.76	0.17, 3.28	
Stent thrombosis and other proximal DVT	3 (2.7%)	0 (0.0%)			
Stent thrombosis only	1 (0.9%)	0 (0.0%)			
Other proximal DVT only	0 (0.0%)	4 (3.6%)			
Symptomatic PE	0 (0.0%)	1 (0.9%)			
All bleeding	13 (11.6%)	4 (3.6%)	3.22	1.07, 9.69	0.03
Major bleeding	4 (3.6%)	1 (0.9%)	4.01	0.46, 34.97	
Non-major bleeding	11 (9.8%)	3 (2.7%)	3.64	1.02, 12.93	
Death	1 (0.9%)	0 (0.0%)			

† Outcome summaries were pooled across multiply imputed datasets by averaging arm-specific means and within-imputation variances

‡ Analysis results are derived from multiply imputed datasets, with missing values imputed using multiple imputation (MI) methods.

The Venous Clinical Severity Score (VCSS) ranges from 0 to 30 with higher scores indicating more severe post-thrombotic syndrome. (MI model included age, sex, BMI, strata, baseline VCSS score, Villalta score at 6 months).

The Venous Insufficiency Epidemiological and Economic Study Quality of Life (VEINES-QOL) measure score ranges from 0 to 100, with higher scores indicating better quality of life (MI model included baseline QOL score, strata, age, sex, and BMI, baseline VCSS, baseline valvular reflux).

The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) includes a physical component summary score (PCS). Score ranges from 0 to 100, with higher scores indicating better quality of life (MI model included baseline QOL score, strata, age, sex, and BMI, baseline VCSS, employment status).

The Villalta scale is an assessment of five patient-reported symptoms and six venous disease signs reported by clinicians who were unaware of the treatment assignments; a leg with an ulcer was assigned a minimum score of 15 points. Total scores range from 0 to 33, with higher scores indicating more severe post-thrombotic syndrome (MI model included baseline Villalta and strata, age, sex, and BMI, baseline VCSS score, baseline valvular reflux).

Calf volume was calculated using formula for a truncated cone (MI model included baseline volume and strata, age, sex, and BMI, baseline valvular reflux).

VCSS, Villalta and calf volume analysis were adjusted for baseline value and strata (normal/abnormal CFV, presence/absence of open venous ulcer). VEINES-QOL and SF-36 PCS were adjusted by baseline QOL score, strata, age, sex, and BMI. Center has been treated as a random effect on all the models.

VTE = Venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism; ITT = Intention-to-treat