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Endovascular therapy for advanced post-thrombotic syndrome: Proceedings from a multidisciplinary consensus panel

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Abstract

Patients with advanced post-thrombotic syndrome (PTS) and chronic iliac vein obstruction suffer major physical limitations and impairment of health-related quality of life. Currently there is a lack of evidence-based treatment options for these patients. Early studies suggest that imaging-guided, catheter-based endovascular therapy can eliminate iliac vein obstruction and saphenous venous valvular reflux, resulting in reduced PTS severity; however, these observations have not been rigorously validated. A multidisciplinary expert panel meeting was convened to plan a multicenter randomized controlled clinical trial to evaluate endovascular therapy for the treatment of advanced PTS. This article summarizes the findings of the panel, and is expected to assist in

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developing a National Institutes of Health-sponsored clinical trial and other studies to improve the care of patients with advanced PTS.

Keywords

deep vein thrombosis; endovascular therapy; post-thrombotic syndrome; quality of life; stent

Introduction

The post-thrombotic syndrome (PTS) is a common late complication of lower extremity deep vein thrombosis (DVT).[1] Although many patients experience PTS as a manageable combination of chronic leg heaviness, fatigue, swelling, and/or aching that requires moderate lifestyle changes, patients with advanced PTS suffer profound physical limitations and quality of life (QOL) impairment.[2] Patients who have chronic iliac vein obstruction are especially susceptible to severe PTS that includes severe pain, short-distance venous claudication, uncontrolled edema, and/or venous ulcers. Venous ulcers markedly impair QOL, escalate healthcare costs, predispose the patient to infection, and can require surgical therapy.[3] Unfortunately, there is a lack of evidence-based treatment options that reliably produce clinical improvement in this patient population.

Preliminary studies suggest that image-guided, catheter-based endovascular therapy can eliminate iliac vein obstruction (with stent placement) and saphenous venous valvular reflux (with endovenous thermal ablation), and thereby reduce PTS severity and improve health-related QOL.[4–6] However, these interventions are associated with substantial risks and costs, and their effectiveness has not been prospectively validated. We therefore plan to conduct a multicenter randomized clinical trial (RCT) to evaluate the relative benefit of endovascular therapy versus optimal conservative management for the management of advanced PTS associated with chronic iliac vein obstruction. Because such a trial will be a complex undertaking, we felt that its design would benefit from discussion with a broad range of experts who manage and study PTS. To this end, we convened a multidisciplinary meeting of venous disease experts on 29–30 April 2015 with support from a clinical trial planning grant (U34-HL123831) from the National Heart, Lung, and Blood Institute (NHLBI). In this article, we summarize the discussions held at that meeting. Our objectives are to call attention to this important but unmet clinical need, to stimulate further conversation, and to assist healthcare providers who manage PTS and investigators who seek to conduct PTS treatment studies.

Meeting organization

Thirty leading DVT/PTS researchers and scientists from the following disciplines attended the meeting: vascular surgery ($n = 7$), interventional radiology ($n = 6$), cardiovascular medicine ($n = 5$), thrombosis medicine/epidemiology ($n = 2$), biostatistics ($n = 3$), health economics ($n = 1$), dermatology ($n = 1$), clinical trial methodology and coordination ($n = 4$), and a regulatory compliance expert ($n = 1$) (see Appendix). This roster included representatives from Research Triangle International (RTI), a research company that was

selected by the NHLBI to assist investigators to develop clinical trial proposals to address hematological disorders and their consequences (NHLBI grant U24-HL114577).

Before the meeting, we surveyed 75 physicians about their preferences for the lifestyle, medical, compressive, endovascular, and surgical treatments they prescribe for their patients with advanced PTS, and their level of confidence in the efficacy of these interventions. We used the 35 responses that were received from physicians in diverse medical subspecialties to frame the discussion at the meeting.

Prior to the meeting, the discussants were informed that a multicenter RCT was being developed to compare an 'endovascular-including strategy' versus a 'best non-invasive therapy strategy' for the management of advanced PTS. They were told that the primary goal of the meeting was to define the specific elements of PTS care for the intervention and control arms of the study that should be: (a) required; (b) recommended but not required; (c) discouraged but allowed; or (d) forbidden. They were instructed to consider each element's expected efficacy, safety, tolerability, feasibility of use, accessibility to patients in various practice settings (considering coverage and procurement issues and the implications to a study's budget), and the ability of the study to standardize administration. The participants were also asked their opinions on: how long it would be acceptable to withhold endovascular therapy from non-improving control arm patients; regulatory issues; and the best ways to obtain strong community engagement in the study.

The meeting was structured into four moderated roundtable panel discussions: (1) study design and general methodological issues; (2) medical and compressive therapies; (3) endovascular therapies; and (4) venous ulcer care. Each component began with a brief presentation to frame the discussion, including information from the clinical practice survey (Tables 1 and 2). After the meeting, the organizers distributed a written summary to outline areas of consensus and debate, and then revised it in response to feedback from the participants. Below we summarize the major discussion points.

Study design and methodology

First, there was broad agreement that endovascular therapy had matured sufficiently to merit systematic study as a way to reduce the morbidity of PTS, and that a RCT would provide the best way to undertake such an evaluation. The ability of the multidisciplinary community to complete the targeted accrual in the NHLBI-sponsored ATTRACT study (which evaluates catheter-directed thrombolysis for PTS prevention in proximal DVT) was noted as proof of the existence of the requisite medical community motivation and clinical trial infrastructure to succeed in a trial of PTS treatment.[7]

Second, it was noted that endovascular therapy presents immediate and long-term risks. Hence, there was agreement that the study population should be confined to patients with advanced PTS and iliac vein obstruction, since they appear to have the greatest potential for benefit. The group agreed that patients should meet the objectively applied criteria of PTS severity. Most participants agreed that to be potentially eligible, patients should have a Villalta score $\geqslant 10$ or a Venous Clinical Severity Score (VCSS) $\geqslant 8$, since these criteria

have been correlated with poorer QOL in PTS patients.[8–11] On the other hand, the panelists also agreed that it would be important to limit the number of exclusion criteria so as to optimize the study's external validity and its potential for participant enrollment, and to carefully document the characteristics of excluded patients on a screening log.

Third, the complexities of diagnosing iliac vein obstruction were discussed. Duplex ultrasound abnormalities in the common femoral vein (CFV) or iliac vein can identify many patients, but cross-sectional imaging (computed tomography (CT) venography, magnetic resonance (MR) venography) may be needed to identify others.[12,13] The limited accuracy of Duplex ultrasound for iliac vein assessment in many patients (due to overlying bowel gas or adipose tissue) was cited. Intravascular ultrasound (IVUS), though invasive, cost-additive, and not uniformly utilized by practitioners, was considered by many panel members to offer greater sensitivity in identifying iliac vein lesions compared with Duplex ultrasound, CT, MR, and venography.[14] There was consensus that a variety of imaging modalities should be acceptable for pre-randomization confirmation of the presence of iliac vein obstruction (complete obstruction or > 50% diameter stenosis).

Fourth, it was agreed that patients with multi-segment chronic occlusive disease that includes the inferior vena cava (IVC) are a particularly challenging patient subgroup for recanalization. Some such patients have occluded IVC filters for which management strategies are complex (e.g. stent placement through filter, or challenging filter retrieval methods).[15,16] After discussion, most members agreed that patients with occluded IVC filters were a distinct group that should be excluded from the study.

Fifth, the challenges of managing patients with chronic iliac vein obstruction extending into the common femoral vein (CFV) tributaries (femoral vein, deep femoral vein) were discussed. Exclusion of these patients was considered since they are difficult to treat, they experience poorer outcomes with any available therapy, and there is no uniform approach to treatment. However, because they constitute a substantial proportion of PTS patients, most participants favored including them. Stratification of randomization by this factor can assure a comparable distribution of these patients in the two arms.

Sixth, there was discussion on how long a non-improving patient could be asked to remain in the control arm without crossing over to receive endovascular therapy, and about related implications for the optimal timing of the primary outcome assessment. Unlike in usual clinical practice where many PTS patients are not aware of endovascular treatment options, all control arm patients in a randomized trial are informed about (and some may have a preference for) endovascular therapy. The group agreed that patient blinding by performing sham procedures was not justified; it is burdensome for patients and, by potentially increasing bleeding and thrombotic complications, might distort the comparison between the two treatment strategies. Hence, an open-label study with blinding of assessors and adjudicators was favored. Based on their clinical and research experiences, most participants thought it was reasonable to discourage non-improving control arm patients (with rare exceptions) from having endovascular therapy for the first 6 months while standard PTS care was being optimized. There was consensus that the primary outcome should not be assessed

before 3 months since it can take some patients that long to improve after endovascular therapy.

Seventh, it was noted that the quality of previous PTS care would have varied substantially among patients. One well-received proposal was to have a 1–2 month run-in period in which patients would receive optimal non-invasive PTS therapy and have concomitant medical issues addressed. For patients who still met the eligibility criteria, randomization would occur after the run-in period. The run-in period would help to avoid enrolling patients who were no longer eligible, or who were not prepared to receive only non-invasive therapy or to complete study assessments.

Eighth, because the hardship that patients experience with PTS is often not adequately reflected by the physician's assessment of physical signs of disease, it was felt that a patient-reported outcome (PRO) measure would be important to use to assess clinical improvement. Since QOL is a concept that is readily understandable to the medical and lay communities, it was decided that a validated, patient-reported, venous disease-specific measure of QOL (the VEINES-QOL) would be ideal to utilize as the study's primary outcome measure.[17,18] This 25-item measure queries venous symptoms, limitations in daily activities due to chronic venous disease, psychological impact, and change over time; has undergone comprehensive psychometric evaluation first in 1531 patients with chronic venous disease (including PTS) and subsequently in studies of elderly and non-elderly patients with DVT, PTS, and venous ulcers; and has been used in RCTs and cohort studies.[2,7,19–22] It was noted that VEINES-QOL scores in PTS patients have been published, which will be helpful for sample size calculations.[23] In the absence of a formal sample size calculation at the time of the expert panel meeting, there was general consensus that the study would likely need to include between 200 and 300 patients.

Of note, it was also considered desirable to have physical findings of PTS assessed and documented on other PTS scales (e.g. VCSS), since this information (e.g. venous ulcer healing, regression of skin changes) will be clinically relevant and can be obtained by blinded assessors. It was also agreed that use of ultrasound imaging by operators blinded to treatment allocation might provide important mechanistic information, since venous obstruction and valvular reflux are the physiological targets of endovascular intervention.

Finally, consistent with the need for community engagement, the meeting attendees uniformly agreed that incorporating patient input and obtaining endorsements from patient advocacy organizations and health professional organizations will promote the study's success.

Medical and compressive therapies

A number of medical and compressive approaches to the management of PTS are relevant to the management of all study patients.[24]

Many PTS patients will have co-morbid conditions that may contribute to their PTS symptoms. Aside from PTS, contributors to lower extremity edema might include right-sided congestive heart failure, pulmonary hypertension, lymphedema, sleep apnea, obesity,

inactivity, and/or renal or hepatic dysfunction. Also, neurological conditions and peripheral arterial disease can cause lower extremity pain or ulceration. It was agreed that treating chronic arterial limb ischemia would be the initial priority before addressing venous obstruction and reflux in a patient with a venous ulcer. Therefore, it was agreed that patients should have an ankle–brachial index of greater than 0.5 to be study-eligible. It was felt that patients with neurological conditions should be eligible since treatment of the venous component might still be expected to provide some degree of clinical improvement.

Regarding **lifestyle modifications**, our clinical practice survey revealed strong support that the proposed general measures had potential for benefit and low risk of harm, especially for patients without a venous ulcer (Tables 1 and 2). The expert panel agreed that study patients should be educated on avoiding injury to the involved extremity and on the benefits of including regular periods of leg elevation in their daily routines. Staying active and exercising should be recommended, if feasible. The use of supervised exercise programs was thought to be of possible benefit based upon one small randomized study, but there was consensus that a supervised exercise protocol should not be required for either group because of its uncertain efficacy, cost, and restricted availability.[25] Smoking cessation and weight loss, when relevant, will be encouraged to improve general health but few participants believed this to be likely to substantially impact PTS in many patients within the study's timeframe.

Survey respondents reported limited use of **medical interventions** beyond anticoagulation in their PTS patients, and limited confidence in the effectiveness of therapy directed against PTS specifically (Tables 1 and 2). In the study, appropriate thromboprophylaxis for high-risk situations and optimal treatment for venous thromboembolism (VTE) with anticoagulation will be encouraged. There was no consensus on the value of extending anticoagulation beyond the durations recommended in consensus guidelines. Mandating specific anticoagulant or antiplatelet medications was not felt to be justified or feasible, given differences in institutional and regional use and insurance coverage.[26,27] However, it is anticipated that the use of anticoagulant and antiplatelet therapy may differ between the two study arms, with more aggressive use of anti-thrombotic therapy in patients who have received stents; this was felt to be appropriate and reflects that additional anti-thrombotic therapy is part of the 'package' of endovascular care. While the benefit-to-risk ratio of aspirin therapy was believed to be favorable for most patients receiving stents, differences in aspirin use were considered unlikely to affect PTS severity during the study's timeline. The use of pentoxifylline to promote healing in patients with venous ulcers (only) was favored.[28] The use of diuretics was not favored as a PTS treatment. The use of venoactive medications (e.g. aescin, rutosides) was felt by some practitioners to be of benefit in selected patients, but there was no consensus that any single agent should be recommended or required. Topical and oral NSAIDs and oral narcotic agents for severe pain were considered acceptable on an as-needed basis.

Regarding **compressive interventions**, the use of graduated compression stockings in all study patients was favored by both the survey respondents and the expert panelists, but there was no consensus on whether 20–30 mmHg or 30–40 mmHg should be employed. Most participants believed that knee-high stockings were sufficient but that stocking length and

pressure could be tailored to clinical presentation and to patient and physician preferences. The potential benefits and limitations of other forms of compression (home edema pumps, wearable compression devices, other bandaging systems) were discussed, but the survey results and panel discussion did not support any specific type. The consensus was that these methods should be allowed but not required.

Endovascular therapy

As we expected, most of the survey respondents reported using iliac vein stents and endovenous saphenous ablation regularly, but there was no consensus on the preferred endovascular methods to treat chronic femoropopliteal DVT (Tables 1 and 2). This was true both for patients with, and without, active venous ulcers.

Extensive discussion centered around whether endovenous saphenous vein ablation should be allowed in one or both treatment arms and, by corollary, whether the study intervention was really ‘iliac/CFV stent placement’ or ‘an endovascular strategy including iliac/CFV stent placement and saphenous ablation when indicated’. Concern was expressed that allowing saphenous ablation in the endovascular therapy arm but not the control arm could introduce a confounding variable and/or bias. To address this, the question was posed as to whether closure of an incompetent saphenous vein would be considered standard care for a patient with advanced PTS and either (a) a newly recanalized (successfully stented) iliac/CFV, such as is expected in the endovascular treatment arm patients; or (b) a chronically occluded iliac/CFV, as would be present in the control arm patients.

Nearly all endovascular physicians present said they considered ablation of a major refluxing saphenous vein to be standard care for a patient with a venous ulcer or severe symptoms of chronic venous disease, assuming the iliac/CFV outflow tract was open, and that not allowing saphenous ablation as a component of endovascular therapy could artificially reduce its effectiveness. That said, it was estimated that only 10–30% of patients would require saphenous ablation after stent placement since some would not have saphenous reflux and others might no longer be sufficiently symptomatic to justify the procedure.

The endovascular physicians were asked if they would be comfortable ablating a refluxing great saphenous vein in the presence of ongoing iliac vein obstruction. The consensus response was no, since this approach would have limited efficacy and could pose safety issues (e.g. increased risk of peri-procedure DVT). Ultimately, the majority concluded that saphenous ablation should be part of the ‘package’ of endovascular therapy but should not be offered in the control arm. It was agreed that the patient’s clinical status could be documented using the study outcome measures after stent placement and before subsequent saphenous ablation, to enable later estimation of the relative importance of the two components. However, it was agreed that the study’s main goal should be to determine if an endovascular care strategy improves PTS, not to validate specific elements of care.

The participants discussed the current use of venous stents in the United States. No stent has a US Food and Drug Administration (FDA) indication for iliac vein use, but stents approved

for other indications have been used off-label for venous disease for many years.[6] Most of the published venous experience is with the use of Wallstents (Boston Scientific, Boston, MA, USA) due partly to their availability in large sizes, but other devices have also been used. Two stents engineered for venous use are currently undergoing investigational device exemption (IDE) trials. It was suggested that although an IDE will likely be required, requesting an IDE waiver from the FDA might be worthwhile since the study will be an investigator-initiated National Institutes of Health (NIH) study evaluating health outcomes rather than device safety/efficacy, and it could reduce study complexity.

The challenges of, and options for, managing patients with chronic obstruction extending into the femoral and/or deep femoral veins were discussed. The possibility of using thrombolytic therapy, either with a standard multi-sidehole catheter or an ultrasound catheter, to improve inflow was discussed. However, the general ineffectiveness of thrombolytic drugs for chronic occlusions and the risk of bleeding were cited as reasons not to incorporate this as a routine element of therapy.[29] It was noted that available stents have not demonstrated major problems when extended into the CFV. Several operators stated that when needed to establish inflow, they perform balloon angioplasty or extend stents into the deep femoral vein or the most cephalad segment of the femoral vein. Stents extended through long segments of the femoral vein were thought to be associated with poor patency. Some participants preferred open surgical methods (e.g. thromboendovenectomy) to disobliterate the inflow veins, often with concomitant construction of an arteriovenous fistula.[30] However, they acknowledged that only a limited number of sites will have access to a surgeon with this specialized expertise.

Venous ulcer care

Extensive discussion was held concerning whether patients with venous ulcers should be excluded from the study. Very large venous ulcers can take many months to heal and for pain to resolve, and are more likely to contribute to complications (e.g. systemic infection) and to have multi-factorial etiology.[31,32] Overall, the group had little confidence that non-improving, slowly-improving, or worsening control arm patients and their providers would be willing to forego crossover to the endovascular therapy arm for the duration required to heal a large ulcer. Hence, most participants agreed that patients with very large ulcers (area > 50 cm^2) should be excluded, but that patients with smaller ulcers should be eligible. The group agreed that mandating particular elements of ulcer care was less important than ensuring that ulcers were cared for in dedicated wound/ulcer care clinics. Engagement of the ulcer/wound care community in the investigative teams will help to ensure strong accrual and provision of quality ulcer care. There was consensus that compression is the principal component of care for patients with an active venous ulcer, and that the 2014 Venous Ulcer Care Guidelines of the American Venous Forum and Society for Vascular Surgery will serve as an excellent resource for the provision of optimal ulcer care in study patients.[24,33,34]

Conclusion

A multidisciplinary expert panel meeting was held to discuss the optimal ways of evaluating an endovascular treatment strategy for patients with advanced PTS and iliac vein

obstruction. The discussion was informed by the results of a clinical practice survey, in which physicians reported having confidence in the effectiveness of very few of the 24 different PTS interventions that were considered. The panel considered questions pertaining to study design and methodology, endovascular therapy, medical and compressive therapies, and ulcer care. The panel's recommendations are summarized in Table 3. This discussion will assist in developing a NIH-sponsored clinical trial and other collaborative studies directed at improving the care of advanced PTS.

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Appendix: PTS Expert Panel Members

Study design and methodology

Anthony Comerota, MD – Jobst Vascular Institute

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Table 1

Clinical practice survey: Treatment of advanced post-thrombotic syndrome (PTS) with no ulcer.

Treatment modality	Respondents (of 35 total)[a,b]					Mean score
	1	2	3	4	5	
Lifestyle interventions						
Periodic planned leg elevation	0	5	3	13	11	3.94
Education – avoid leg trauma	0	1	1	14	17	4.45
Supervised exercise program	0	3	6	16	7	3.84
Weight loss program	2	6	5	10	7	3.47
Smoking cessation program	0	2	12	15	5	3.67
Medical therapies						
Anticoagulation beyond DVT care	10	5	6	6	5	2.72
Antiplatelet therapy	14	7	2	8	1	2.22
Pentoxifylline	16	12	2	2	0	1.69
Venoactive medications	20	9	1	1	1	1.56
Diuretics	20	5	6	2	0	1.70
Oral NSAIDs	9	7	10	4	0	2.30
Topical NSAIDs	15	10	6	0	1	1.81
Compressive therapies						
Graduated elastic stockings	0	0	3	8	21	4.56
Home edema pump	4	9	12	5	2	2.75
Wearable intermittent compression	11	9	8	2	2	2.22
Inelastic compression	10	6	10	2	4	2.50
ACE™ wraps	12	4	8	2	0	2.00
Endovascular therapies						
Stent iliac/CFV	2	5	6	3	14	3.73
Extend stents into chronic FP DVT	10	9	6	4	2	2.32
EVTA refluxing saphenous	2	6	6	1	15	3.70
CDT for chronic FP DVT	10	8	5	6	3	2.50
US-CDT for chronic FP DVT	11	9	5	4	2	2.25
Angioplasty for chronic FP DVT	7	10	9	2	2	2.40

[a] Respondents were asked to rate each modality using these categories. It was recognized that this is a non-validated, non-ordinal system, but means were calculated to try to summarize the information.

1 = I don't believe this works and recommend it rarely or never; 2 = I believe this could be beneficial but recommend it rarely or never; 3 = I believe this could be beneficial and recommend it occasionally; 4 = I use this regularly but am not sure if it's really working; 5 = I use this regularly and am reasonably confident it works.

[b] All rows do not add up to 35 since some questionnaires were incomplete.

NSAID, non-steroidal anti-inflammatory drug; CFV, common femoral vein; FP, femoropopliteal; DVT, deep vein thrombosis; EVTA, endovenous thermal ablation; CDT, catheter-directed thrombolysis; US-CDT, ultrasound-assisted catheter-directed thrombolysis.

Table 2

Clinical practice survey: Treatment of advanced post-thrombotic syndrome (PTS) with active venous ulcer.

Treatment modality	Respondents (of 35 total)[a,b]					Mean score
	1	2	3	4	5	
Lifestyle interventions						
Periodic planned leg elevation	2	6	2	13	9	3.66
Education – avoid leg trauma	0	1	2	11	18	4.44
Supervised exercise program	1	3	8	16	4	3.59
Weight loss program	1	3	8	16	4	3.59
Smoking cessation program	3	1	6	18	5	3.63
Medical therapies						
Anticoagulation beyond DVT care	10	5	3	9	5	2.81
Antiplatelet therapy	14	7	3	6	2	2.21
Pentoxifylline	12	7	8	3	2	2.25
Venoactive medications	17	8	6	1	0	1.71
Diuretics	18	6	5	3	0	1.78
Oral NSAIDs	11	3	9	4	1	2.32
Topical NSAIDs	14	9	6	1	2	2.00
Compressive therapies						
Graduated elastic stockings	1	0	1	11	19	4.47
Home edema pump	5	7	12	5	3	2.81
Wearable intermittent compression	9	10	6	6	1	2.38
Inelastic compression	9	7	6	2	8	2.78
ACE™ wraps	11	7	9	3	2	2.31
Multilayer compression	4	3	6	3	15	3.71
Endovascular therapies						
Stent iliac/CFV	2	5	3	3	17	3.93
Extend stents into chronic FP DVT	10	10	6	4	4	2.47
EVTA refluxing saphenous	3	4	6	1	16	3.77
CDT for chronic FP DVT	10	7	6	6	1	2.37
US-CDT for chronic FP DVT	12	8	3	4	3	2.27

Treatment modality	Respondents (of 35 total)[a,b]					Mean score
	1	2	3	4	5	
Angioplasty for chronic FP DVT	7	12	5	3	2	2.34

[a]Respondents were asked to rate each modality using these categories. It was recognized that this is a non-validated, non-ordinal system, but means were calculated to try to summarize the information.

1 = I don't believe this works and recommend it rarely or never; 2 = I believe this could be beneficial but recommend it rarely or never; 3 = I believe this could be beneficial and recommend it occasionally; 4 = I use this regularly but am not sure if it's really working; 5 = I use this regularly and am reasonably confident it works.

[b]All rows do not add up to 35 since some questionnaires were incomplete.

DVT, deep vein thrombosis; NSAID, non-steroidal anti-inflammatory drug; CFV, common femoral vein; FP, femoropopliteal; EVTA, endovenous thermal ablation; CDT, catheter-directed thrombolysis; US-CDT, ultrasound-assisted catheter-directed thrombolysis.

Table 3

Expert panel recommendations for post-thrombotic syndrome (PTS) clinical trial.

Item	Recommendation
1	Perform multicenter RCT to assess EVT for iliac-obstructive PTS
2	Include patients with advanced PTS on Villalta or VCSS scales
3	Open-label study with blinded assessors and adjudicators
4	Primary outcome: change in VEINES-QOL measure at 6 months
5	Utilize run-in period to boost adherence, discourage crossover
6	Engage patient advocacy and health professional organizations
7	Encourage physical activity and risk factor modification
8	Non-proscriptive approach to medical PTS therapy
9	All patients use compression therapy (mainly graduated stockings)
10	Patients with active ulcer to be managed in specialized clinic
11	EVT = iliac vein stent placement followed by ablation of saphenous reflux
12	Early engagement of FDA around off-label use of stents

RCT, randomized controlled trial; EVT, endovascular therapy; VCSS, Venous Clinical Severity Score; VEINES-QOL, venous insufficiency epidemiological and economic study quality of life; FDA, Food and Drug Administration.