

Rationale and design of the ATTRACT Study: A multicenter randomized trial to evaluate pharmacomechanical catheter-directed thrombolysis for the prevention of postthrombotic syndrome in patients with proximal deep vein thrombosis

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Background Current standard therapy for patients with acute proximal deep vein thrombosis (DVT) consists of anticoagulant therapy and graduated elastic compression stockings. Despite use of this strategy, the postthrombotic syndrome (PTS) develops frequently, causes substantial patient disability, and impairs quality of life. Pharmacomechanical catheter-directed thrombolysis (PCDT), which rapidly removes acute venous thrombus, may reduce the frequency of PTS. However, this hypothesis has not been tested in a large multicenter randomized trial.

Study design The ATTRACT Study is an ongoing National Institutes of Health–sponsored, Phase III, multicenter, randomized, open-label, assessor-blinded, parallel two-arm, controlled clinical trial. Approximately 692 patients with acute proximal DVT involving the femoral, common femoral, and/or iliac vein are being randomized to receive PCDT + standard therapy versus standard therapy alone. The primary study hypothesis is that PCDT will reduce the proportion of patients who develop PTS within 2 years by one-third, assessed using the Villalta Scale. Secondary outcomes include safety, general and venous disease-specific quality of life, relief of early pain and swelling, and cost-effectiveness.

Conclusion ATTRACT will determine if PCDT should be routinely used to prevent PTS in patients with symptomatic proximal DVT above the popliteal vein. (Am Heart J 2013;165:523-530.e3.)

The postthrombotic syndrome (PTS) develops in approximately 40% of patients within 2 years after a first episode of lower extremity deep vein thrombosis (DVT).¹ Clinical manifestations of PTS commonly include chronic pain, swelling, heaviness, and/or fatigue of the

affected limb. Patients with advanced PTS can develop venous claudication, stasis dermatitis, subcutaneous fibrosis, and skin ulceration. Postthrombotic syndrome impairs quality of life (QOL) significantly and imposes a major economic burden upon patients, health care providers, and society.^{2,3}

Anticoagulant drugs, the standard treatment of DVT, prevent pulmonary embolism and thrombus extension but do not actively remove venous thrombus.⁴ Because the persistence of thrombus within the venous system has been linked to the development of PTS, it is hypothesized that early, active elimination of venous thrombus in DVT patients may prevent PTS. This “Open Vein Hypothesis” is supported by (a) studies linking poor thrombus clearance to venous valve dysfunction and recurrent venous thromboembolism (VTE)^{5,6}; (b) studies finding an association between residual venous thrombus or valve incompetence and PTS⁷; and (c) clinical trials suggesting that systemic thrombolysis, surgical thrombectomy, or catheter-directed thrombolysis (CDT) reduces PTS.⁸⁻¹¹

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Pharmacomechanical catheter-directed thrombolysis (PCDT) refers to catheter-directed administration of a fibrinolytic drug directly into the venous thrombus with concomitant use of catheter-based device(s) to macerate the thrombus and speed thrombus removal.¹² It is currently used as a second-line treatment of DVT that progresses despite anticoagulation. However, the first-line use of PCDT for PTS prevention is controversial because, without evidence from a multicenter randomized controlled trial (RCT), it is uncertain if PCDT reduces clinically important PTS with acceptable safety and cost-effectiveness. The need for such a RCT has been endorsed by multidisciplinary expert panels and the US Surgeon General.¹³ We therefore developed the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) Trial to address this controversy.

Study objectives

The primary study objective is to determine if the initial use of PCDT along with standard DVT therapy reduces the proportion of patients who develop PTS during 24 months of follow-up compared with standard DVT therapy alone in patients with symptomatic acute proximal DVT. Secondary objectives include the following: (a) comparing the proportions of patients who develop major bleeding, symptomatic VTE, and death; venous disease-specific and general QOL; and relief of acute DVT symptoms between the 2 treatment arms; (b) identifying pretreatment predictors of therapeutic response to PCDT in the prevention of PTS; (c) comparing the short-term and long-term medical care costs of treatment and evaluating the incremental cost-effectiveness of PCDT compared with standard therapy alone; and (d) determining the posttreatment anatomic/physiologic conditions that need to be achieved (ie, removal of thrombus, restoration of venous patency, prevention of valvular incompetence) to prevent PTS.

Study design, organization, and regulatory status

ATTRACT is an ongoing, investigator-initiated, Phase III, multicenter, randomized, open-label, assessor-blinded, parallel two-arm, controlled clinical trial that is sponsored by the National Heart, Lung, and Blood Institute (NHLBI) of the US National Institutes of Health (NIH) (www.attract.wustl.edu; NCT00790335). Four companies (Bayer Healthcare, BSN Medical, Covidien, and Genentech) provide additional support but play no role in the study design, execution, or data analysis. The authors are solely responsible for the design and conduct of this study, all analyses, and the drafting and editing of this article.

Participants are enrolled in 40 to 60 US Clinical Centers and are followed for 24 months (Figure). The study's

conduct is approved by the Institutional Review Boards of Washington University in St Louis and all participating Clinical Centers. The study is conducted under an investigational drug exemption (IND) granted by the US Food and Drug Administration. To date (January 10, 2013), 392 patients have been enrolled. The study is led by a multidisciplinary Steering Committee (online Appendix A) and is monitored by an independent, NHLBI-appointed Data Safety Monitoring Board.

Patient population

The study includes patients with symptomatic proximal DVT that involves the iliac, common femoral, and/or femoral vein (with or without other involved veins) because these patients are at high risk for PTS.^{1,11} Patients who are outside the 16- to 75-year age range; who are pregnant; or who have active cancer, recent major surgery or obstetrical delivery, an intracranial lesion, or established PTS are excluded (see online Appendix B for full criteria).

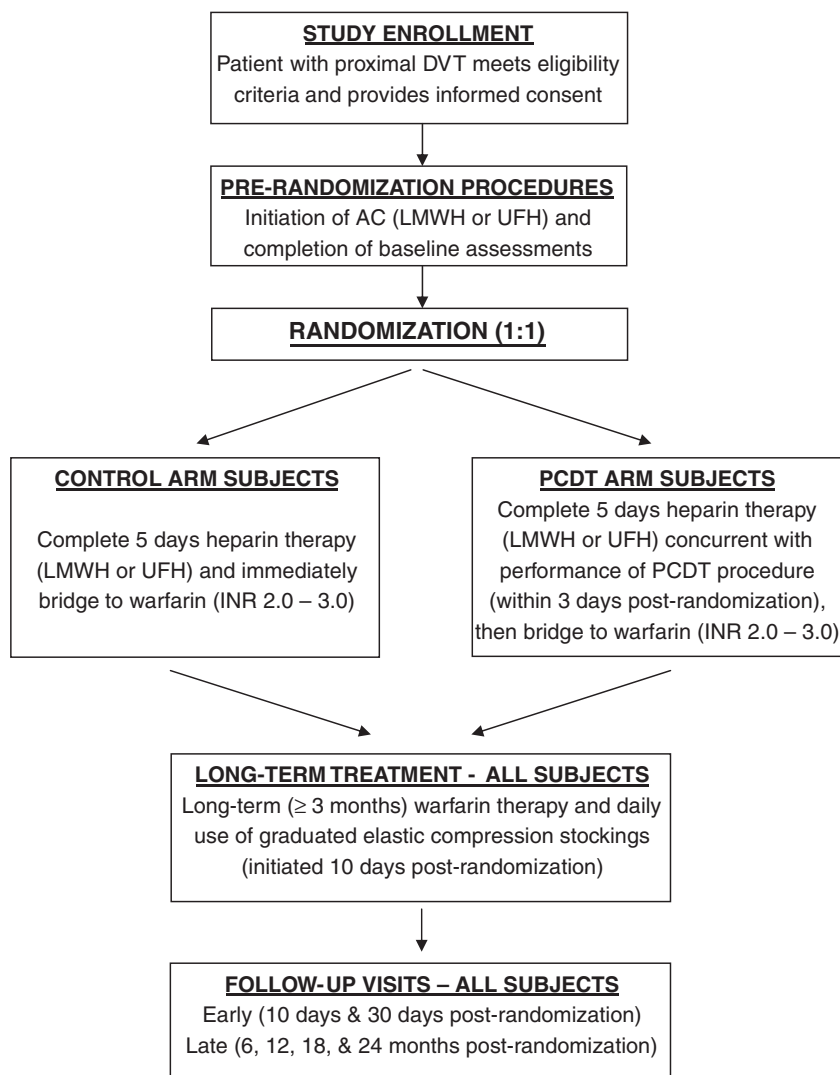
Randomization and stratification

Patients who meet the eligibility criteria and provide informed consent are randomized in a 1:1 ratio to receive either PCDT + standard DVT therapy or standard DVT therapy alone. Central automated randomization is performed using a Web-based system at the study's Data Coordinating Center (DCC) (Ontario Clinical Oncology Group, Hamilton, Ontario) that leads the investigator or coordinator through questions related to patient eligibility and stratification category and then provides treatment group allocation, thereby ensuring concealment. Randomization is stratified on 2 factors: (a) anatomical extent of the DVT (whether or not the common femoral vein and/or iliac vein is involved, because studies have observed PTS to be more frequent and more severe for iliofemoral DVT^{1,10}) and (b) Clinical Center. The complete randomization sequence, blocked in randomly varying block sizes, was computer generated by a DCC statistician who is otherwise uninvolved with the study.

Standard DVT therapy

Participants in both treatment arms receive initial weight-based anticoagulant therapy with low-molecular-weight heparin (LMWH) or intravenous unfractionated heparin (UFH) (per local hospital nomogram) for at least 5 days and until the international normalized ratio (INR) ≥ 2.0 on 2 consecutive draws on different days.⁴ Warfarin is started the day of randomization in Control arm participants or after PCDT is completed in PCDT arm participants. The recommended intensity (target INR 2.0-3.0) and duration (≥ 3 months, per international guidelines) of therapy are the same for participants in the 2 arms.⁴ Before startup, the credentials of coinvestigators overseeing medical

Figure



ATTRACT study schema.

therapy, and each site's anticoagulation monitoring procedures, are reviewed and approved by a Medical Therapy Credentialing Committee.

Participants in both treatment arms are provided sized-to-fit, knee-high, 30- to 40-mm Hg, graduated elastic compression stockings at the 10-day follow-up visit. We do not initiate compression therapy earlier because leg swelling can decrease markedly during the first 10 days, which makes it difficult to fit the stockings. In addition, some patients' legs are very tender initially; and published studies differ on whether very early compression influences the risk of developing PTS.¹⁴ A new pair of stockings is provided every 6 months. Initially and at each visit, the importance of daily stocking use is reinforced.

PCDT intervention

PCDT is performed by a board-certified endovascular physician whose credentials and experience are reviewed and approved by an Interventions Credentialing Committee, using a protocol that is based upon published practice guidelines.¹⁵ Venous access is established using ultrasonographic guidance, and a venogram is performed. The initial delivery of recombinant tissue plasminogen activator (rt-PA) (Activase, Genentech, South San Francisco, CA) may occur using 1 of 3 methods. If there is good inflow to the popliteal vein (ie, the lower half of the popliteal vein and at least 1 major calf vein tributary are free of occlusive thrombus), one of the following techniques is used: (a) "Isolated Thrombolysis"

Table. Schedule of outcome assessments

Assessment	Baseline	Initial Tx	10 d	30 d	6 m	12 m	18 m	24 m
Leg pain (Likert)	X		X	X				
Leg circumference	X		X	X				
Venous QOL (VEINES)	X			X	X	X	X	X
General QOL (SF-36 version 2)	X			X	X	X	X	X
Duplex ultrasonography	X			X		X*		
Venogram (PCDT arm only)		X†						
Cost diary review			X	X	X	X	X	X
Villalta Scale to assess PTS	X		X	X	X	X	X	X
VCSS					X	X	X	X
CEAP classification					X	X	X	X

Abbreviations: VEINES, Venous insufficiency epidemiological and economic study; SF-36, short-form 36; VCSS, venous clinical severity score; CEAP, clinical-etiological-pathophysiological-anatomic classification.

*Performed in a subgroup of patients.

†Performed pre- and post-PCDT.

using the Trellis Peripheral Infusion System (Covidien, Inc, Mansfield, MA)—2 catheter-mounted balloons on the Trellis catheter are inflated to “isolate” a thrombus-bearing venous segment, rt-PA is delivered into the thrombus via sideholes in the catheter, and an oscillating wire within the catheter provides intrathrombus drug dispersion; or (b) “PowerPulse Thrombolysis” using the AngioJet Rheolytic Thrombectomy System (MEDRAD Interventional-Bayer, Minneapolis, MN)—rt-PA is delivered and rapidly dispersed within the thrombus via a powerful pulse-spray from the AngioJet catheter. A maximum of 25 mg of rt-PA may be delivered during the initial procedure. If there is poor inflow to the popliteal vein, a third technique (“Infusion-First Thrombolysis”) is used—this entails placement of a multisidehole catheter across the venous thrombus and rt-PA infusion at 0.01 mg/(kg h), up to a maximum of 1 mg/h, for up to 30 hours.

After initial rt-PA delivery, investigators may tailor subsequent adjunctive therapy to individual patient circumstances. The physician may use additional rt-PA boluses (≤ 5 mg), balloon maceration, aspiration thrombectomy, and/or mechanical thrombectomy to eliminate residual thrombus. Continued infusion of rt-PA via a multisidehole catheter (0.01 mg/[kg h]) may also be used after any of the above initial PCDT techniques; but for the entire treatment, the maximum allowable rt-PA dose is 35 mg. Treatment is discontinued when (a) $\geq 90\%$ thrombus removal has been achieved with restoration of flow; (b) the 35-mg rt-PA maximum dose or 30-hour maximum infusion duration is reached; or (c) the patient suffers clinically overt bleeding or another complication that mandates cessation of therapy. Obstructive lesions in the iliac or common femoral vein may be treated with balloon angioplasty and/or stent placement; femoral vein obstructive lesions may be treated with balloon angioplasty.

Concomitant anticoagulation

The INR is required to be ≤ 1.6 when PCDT is started. For the on-table parts of the initial PCDT session and any

follow-up sessions, patients receive full therapeutic anticoagulation with twice-daily weight-based LMWH injections or intravenous unfractionated heparin (target partial thromboplastin time corresponding to 0.3-0.7 IU/mL anti-Xa activity on the site's heparin assay). During continuous rt-PA infusions, patients receive either twice-daily weight-based LMWH injections (full therapeutic dose) or intravenous UFH at 6 to 12 U/(kg h) (maximum allowed 1000 U/h) to maintain a subtherapeutic partial thromboplastin time (less than twice control).

Periprocedure use of retrievable caval filters

Inferior vena cava filter placement is discouraged in patients undergoing Infusion-First Thrombolysis. For patients treated with Isolated Thrombolysis or PowerPulse Thrombolysis, a retrievable filter may be used at physician discretion if there is thrombus in the inferior vena cava or iliac vein, and is removed as soon as possible.

Outcome assessments

Patients return for follow-up at 10 days, 30 days, 6 months, 12 months, 18 months, and 24 months postrandomization (Table).

Efficacy outcomes

The study's primary efficacy outcome is PTS, defined as a score of ≥ 5 on the Villalta PTS Scale (online Appendix C) in the leg with the index DVT, or an ulcer in that leg, at any time from the 6-month postrandomization follow-up visit to the 24-month visit (inclusive).

Postthrombotic syndrome is a “syndrome” that produces a range of symptoms and clinical signs that differ in character and severity among patients. Because there is no criterion standard objective test for PTS, validation of PTS measures has relied upon showing that they correlate with important health outcomes such as QOL and with known anatomic/physiologic findings of chronic venous disease.¹⁶ The Villalta PTS Scale combines patient self-

assessment of 5 common symptoms of PTS (pain, cramps, heaviness, paresthesias, pruritus) with clinician assessment of 6 common clinical signs of PTS (pretibial edema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia, redness), with each scored as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). The points are added to reach a total score.

We chose the Villalta PTS Scale as the study's primary measure to diagnose and grade PTS for the following reasons: (a) It is reliable, valid, and responsive to change.^{17,18} The presence of PTS by a Villalta score >5 is a better predictor of clinically important QOL impairment than imaging criteria.¹⁶ (b) It evaluates both symptoms and clinical signs. (c) It allows PTS severity to be assessed on a continuum (total score 0-33) and by category (present or absent; mild, moderate, severe). (d) It has been used successfully in previous PTS research, including multicenter trials.^{1,11,17-20} (e) Villalta scores correlate with anatomic/physiologic measures of chronic venous disease including abnormal venograms and venous pressures.^{21,22} (f) the Villalta PTS Scale is endorsed by the International Society of Thrombosis and Haemostasis as the standard to assess the presence and severity of PTS.¹⁷

A double-blinded design with sham PCDT procedures was considered; but this approach was rejected because (a) catheter placement for a sham procedure would increase the risk of bleeding and recurrent VTE in Control arm patients, (b) it would be complex and unlikely to reliably achieve blinding, and (c) it would cause patient hardship and interfere with QOL and cost-effectiveness assessments. Because patients are not blinded, high priority has been attached to blinding and standardized training of the clinicians evaluating PTS signs. The day before follow-up visits, participants receive a telephone reminder to not wear compression stockings on the visit day and to not reveal to study staff whether they received PCDT. The Villalta assessment is performed on each leg, and assessors are blinded as to which leg had the DVT. Site personnel are asked to schedule follow-up visits for as late as possible in the afternoon to allow PTS symptoms and signs to manifest.

The Villalta assessment is supplemented by the blinded administration of 2 additional measures, the Clinical-Etiologic-Anatomic-Pathophysiologic (CEAP) Classification System and the Venous Clinical Severity Score (VCSS), at the 6-, 12-, 18-, and 24-month follow-up visits.^{23,24} Also at these visits (and at baseline), health-related QOL is assessed with patient self-completion of the generic Short Form-36 (SF-36) QOL measure and the venous disease-specific venous insufficiency epidemiological and economic study-QOL measure.²⁵

To evaluate if PCDT speeds relief of acute DVT symptoms, patients are also assessed using a 7-category Likert scale to describe leg pain severity, the Villalta Scale, and standardized measurement of calf circumference at baseline and at the 10- and 30-day follow-up visits.

Safety outcomes

Investigators are required to report episodes of suspected clinically overt bleeding, recurrent VTE, or death. The primary safety outcome is the proportion of patients with major bleeding within 10 days postrandomization. Clinically overt bleeding is classified as "major" if it is associated with a hemoglobin drop of ≥ 2.0 g/dL, transfusion of ≥ 2 U of red blood cells, or involvement of a critical site (eg, intracranial). Less severe clinically overt bleeding is classified as "minor." Episodes of suspected symptomatic recurrent VTE are assessed and reported in a standardized way during follow-up.

Independent adjudication

Data on suspected clinical outcome events are reviewed at the DCC by an Independent Central Adjudication Committee of thrombosis clinicians who are blinded to patients' treatment allocation.

Imaging outcomes

Quantitative assessment of pre- and post-PCDT venograms, using the components of the Marder score that describe the proximal veins, is done to estimate the amount of thrombus removed.²⁶

At 1-year follow-up, venous Duplex ultrasonography is performed in a consecutive subgroup of 142 patients in both treatment arms in 7 participating Clinical Centers to assess for the presence of venous valvular reflux and to quantify residual deep vein thrombus. The goal of this substudy is to determine if prevention of valvular reflux and/or venous obstruction is a key mechanism underlying any effect of PCDT upon development of PTS. The examinations are performed in standardized fashion by Clinical Center sonographers blinded to treatment allocation and are analyzed by blinded examiners in an independent Ultrasound Core Laboratory (VasCore, Massachusetts General Hospital, Boston, MA).

Economic outcomes

The goals of the health economic study are to compare 2-year DVT-related medical care costs between the 2 treatments groups and, if PCDT + standard therapy is found to be both more effective and more costly than standard therapy alone, to evaluate the incremental cost per quality-adjusted life-year gained from a US societal perspective. Data relating to direct and indirect costs are collected from study intake through the 2-year follow-up period. Hospitalization costs are estimated using a combination of (a) procedural resource use data and standard resource-based costing methods and (b) hospital billing data, with charges converted to costs using department-level cost-to-charge ratios. Indirect costs are estimated from data relating to lost time from work, decreased productivity, and informal caregivers' time. Assessment of outpatient resource utilization and indirect costs is aided by use of a "cost diary" in which participants

record outpatient medical encounters, travel time, and out-of-pocket expenses related to their DVT. For the cost-effectiveness analysis, preference-based utility scores will be calculated from the SF-36 data collected using a validated US-specific scoring algorithm.²⁷

Because the clinical impact and costs associated with PCDT may accrue beyond 2 years, a Markov model²⁸ will be used by the Economic Core Laboratory (Mid-America Heart Institute, Kansas City, MO) to evaluate the long-term cost-effectiveness of PCDT. Data from ATTRACT and other studies, including a large prospective North American study on the natural history of DVT, will inform the model.³

Sample size determination

Based on previous studies, we estimated that 30% of Control arm participants will develop PTS between 6 and 24 months.^{1,19} Based on PTS reductions achieved in earlier studies,^{8-11,15} we hypothesized that PCDT would reduce the proportion of patients who develop PTS by at least 33%. Accepting a 5% chance of incorrectly concluding there is a difference in the proportion of participants with PTS at 24 months (α error = .05, 2-sided) and the requirement that the study has an 80% chance (β error = 0.2) of detecting a true difference if PCDT truly reduces PTS by 33%, and assuming a maximum 10% loss to follow-up, we plan to randomize 346 participants to each group for a total of 692 participants.

Data analysis

Two data sets will be considered: (a) a full-analysis set that consists of all participants randomized and (b) a per-protocol set that includes everyone in the full-analysis set, except for any participants who (1) was randomized to PCDT but did not receive endovascular therapy, (2) was randomized to Control but had skin puncture for PCDT or any thrombolytic therapy, or (3) received <4 weeks of anticoagulation.

The primary analysis, using the full-analysis set and analyzed per the intention-to-treat principle, is a comparison of the proportion of participants in each arm who developed *PTS*, defined as a total Villalta score of ≥ 5 or the presence of ulcer in the limb with the index DVT at the 6-month follow-up visit or subsequently during the 24 months after randomization (stratum-adjusted Cochran-Mantel-Haenszel test). Testing will be 2-sided. A *P* value $\leq .05$ will be considered statistically significant.

Secondary analyses will be performed using both analysis sets. To account for multiple testing, a 2-sided *P* value $\leq .01$ will be considered statistically significant. The stratum-adjusted Cochran-Mantel-Haenszel test will be used to compare the proportions of participants in each group with (a) major or any (major + minor) bleeding during the 10 days after randomization, and between 11 days and 24 months; (b) symptomatic VTE

within 24 months; and (c) death within 1 month or within 24 months.

Changes in QOL scores between baseline and 24 months will be compared between the 2 treatment groups using a linear regression model to adjust for the strata. The PTS severity classification (none, mild, moderate, severe) at 24 months will be compared between the 2 arms (4×2 table) using an exact Kruskal-Wallis nonparametric test with severity as a single ordered factor. The mean absolute change in leg pain severity (Likert scores) from baseline to 10 days and to 1 month postrandomization will be compared using analysis of covariance. Measured and percentage change in leg circumference from baseline to 10 and 30 days will be compared using linear regression modeling.

The extent of residual thrombosis and venous reflux will be compared between the 2 groups using the obstruction and reflux scores of the Venous Segmental Disease Scale.²⁹ These scores, and the post-PCDT Marder scores, will be correlated with the presence and severity of PTS at 24 months.

Discussion

Clinical practice guidelines of the Society of Interventional Radiology (2006) and the American Heart Association (2011) suggest consideration of adjunctive CDT or PCDT for selected patients with extensive proximal DVT, whereas the 2012 American College of Chest Physicians' guidelines suggest anticoagulant therapy alone over CDT.^{4,17,30} However, these suggestions are not based on data from rigorously performed RCTs. A recent multicenter RCT (CaVenT) found a 26% relative reduction (41% vs 56%, $P = .047$) in PTS at 2 years in proximal DVT patients who received CDT.¹¹ The investigators reported 3% major bleeds and 6% "clinically relevant" bleeding events in CDT-treated patients, with no bleeding events in the Control arm. Although CaVenT was well-performed, its influence on practice may be limited because of the following: (a) the study reported outcomes data on just 189 patients, making its findings imprecise; (b) the study evaluated CDT rather than PCDT, which may be more effective (from the added mechanical component of thrombus removal) and associated with less bleeding (because of reduced rt-PA dose and exposure duration) than CDT; and (c) in CaVenT, CDT was performed in just 4 treatment centers in Southern Norway. With >50 treatment centers across the United States, the results of ATTRACT will be more generalizable to a broader range of DVT patients and PCDT operators.

We selected the proportion of patients with PTS over 2 years as our primary outcome because most patients who ultimately develop PTS manifest the condition within 2 years.^{1,7,11} To minimize the potential for bias from differential application of cointerventions, there is standardization of anticoagulant therapy and compression therapy in

both groups. To minimize bias from the open-label design, clinical outcome evaluators and event adjudicators are blinded to treatment allocation; and a number of objective secondary outcome assessments (VCSS, CEAP, venograms, ultrasonograms) are being performed.

After reviewing the literature and surveying our investigators, we concluded that (a) no single PCDT method was clearly superior to others, (b) drug-only CDT with long rt-PA infusions was likely to be less efficient and less safe than PCDT, (c) most endovascular physicians preferred “faster” PCDT methods that use lower doses of rt-PA and facilitate outpatient or short-stay inpatient DVT treatment, and (d) physicians were most likely to achieve representative clinical results if permitted to use PCDT methods with which they were familiar. We therefore allow the use of multiple PCDT methods and encourage the use of fast PCDT when good venous inflow favors completion of clot removal in a single procedure.

In conclusion, ATTRACT will be the first US multicenter RCT to determine the long-term clinical impact of endovascular thrombolysis in proximal DVT. This study will greatly aid patients, physicians, payors, and policy-makers who face decisions on the use of catheter-based DVT therapy.

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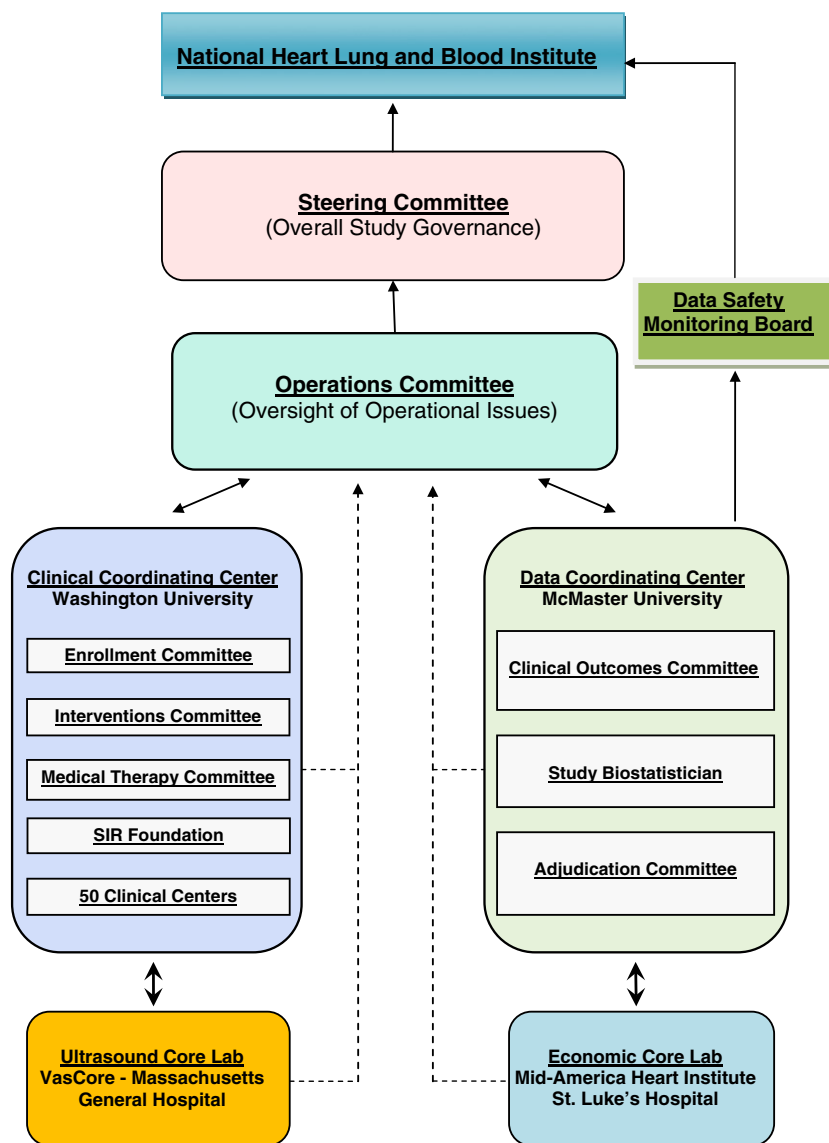
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Appendix A. ATTRACT Study organization



ATTRACT Steering Committee

David J. Cohen, MD, MSc Cardiology
 Anthony Comerota, MD Vascular Surgery
 Samuel Z. Goldhaber, MD (Chair) Cardiology
 Heather L. Gornik, MD Vascular Medicine
 Michael R. Jaff, DO Vascular Medicine
 Jim Julian, MMath Biostatistics
 Susan R. Kahn, MD, MSc Internal Medicine and Epidemiology
 Clive Kearon, MB, PhD Clinical Thromboembolism
 Stephen Kee, MD SIR Foundation Representative
 Andrei Kindzelski, MD, PhD NHLBI Project Officer
 Lawrence Lewis, MD Emergency Medicine
 Elizabeth A. Magnuson, ScD Economics
 Timothy P. Murphy, MD Interventional Radiology

Mahmood K. Razavi, MD Interventional Radiology
 Suresh Vedantham, MD (PI) Interventional Radiology

Collaborating Institutions

1. Clinical Coordinating Center
 Mallinckrodt Institute of Radiology at Washington University in St Louis, MO (USA)
 Responsible for enrollment, protocol adherence, regulatory compliance, site selection and monitoring, credentialing of medical and interventional investigators
2. Data Coordinating Center
 Ontario Clinical Oncology Group at McMaster University in Hamilton, Ontario (Canada)

Responsible for providing methodological and biostatistical expertise, monitoring data capture and quality control, managing study database, blinded outcome adjudication

3. Vascular Ultrasound Core Laboratory
VasCore, Massachusetts General Hospital in Boston, MA (USA)
Responsible for site ultrasonography laboratory credentialing, image analysis for recurrent DVT, coordination of ultrasonography substudy
4. Health Economic Core Laboratory
Mid America Heart Institute at St Luke's Hospital in Kansas City, MO (USA)
Responsible for quality control of economic data, direct collection of hospital bills and UB92 summary bills, coordination of cost comparison and cost-effectiveness evaluation
5. Society of Interventional Radiology Foundation
Responsible for identification of new sites, advertising of study to physicians

Appendix B. Eligibility criteria for the ATTRACT Study

Inclusion criterion

Symptomatic proximal DVT involving the iliac, common femoral, and/or femoral vein

Exclusion criteria

1. Age <16 years or >75 years
2. Symptom duration >14 days for the index DVT
3. In the index leg: established PTS, or previous symptomatic DVT within the last 2 years
4. In the contralateral leg: symptomatic acute DVT (*a*) involving the iliac and/or common femoral vein or (*b*) for which thrombolysis is planned as part of initial therapy
5. Limb-threatening circulatory compromise
6. Pulmonary embolism with hemodynamic compromise (ie, hypotension)
7. Inability to tolerate PCDT procedure due to severe dyspnea or acute systemic illness
8. Allergy, hypersensitivity, or thrombocytopenia from heparin, rt-PA, or iodinated contrast material, except for mild to moderate contrast material allergies for which steroid premedication can be used
9. Hemoglobin <9.0 mg/dL, INR >1.6 before warfarin was started, or platelets <100,000/mL
10. Moderate renal impairment in diabetic patients (estimated glomerular filtration rate <60 mL/min) or severe renal impairment in nondiabetic patients (estimated glomerular filtration rate <30 mL/min)
11. Active bleeding, recent (<3 months) gastrointestinal bleeding, severe liver dysfunction, bleeding diathesis
12. Recent (<3 months) internal eye surgery or hemorrhagic retinopathy; recent (<10 days) major surgery, cataract surgery, trauma, cardiopulmonary resuscitation, obstetrical delivery, or other invasive procedure
13. History of stroke or intracranial/intraspinal bleed, tumor, vascular malformation, aneurysm
14. Active cancer (metastatic, progressive, or treated within the last 6 months). Exception: patients with nonmelanoma primary skin cancers are eligible to participate in the study.
15. Severe hypertension on repeated readings (systolic >180 mm Hg or diastolic >105 mm Hg)
16. Pregnancy
17. Recently (<1 month) had thrombolysis or is participating in another investigational drug study
18. Use of a thienopyridine antiplatelet drug (except clopidogrel) in the last 5 days
19. Life expectancy <2 years or chronic nonambulatory status
20. Inability to provide informed consent or to comply with study assessments

Appendix C. Assessment of symptoms and clinical signs of PTS (Villalta)

SYMPTOMS (complete for both legs):

Q.1 In general, how would you rate the following SYMPTOMS in your **RIGHT** leg?
(please check one response for each symptom)

	No or				
	Minimal	Mild	Moderate	Severe	
Cramps	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	RIGHT LEG
Itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pins and needles	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Leg heaviness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Q.2 In general, how would you rate the following SYMPTOMS in your **LEFT** leg?
(please check one response for each symptom)

	No or				
	Minimal	Mild	Moderate	Severe	
Cramps	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	LEFT LEG
Itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pins and needles	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Leg heaviness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

SIGNS (complete for both legs):

This form is to be completed by the blinded clinician performing the assessment for PTS. The blinded clinician must be blind to the patient's responses to previous Symptoms questions

Q.1 Rate the following SIGNS for the **RIGHT** leg (please check one response for each sign)

	No or				
	Minimal	Mild	Moderate	Severe	
Pretibial edema	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	RIGHT LEG
Skin induration	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Hyperpigmentation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Venous ectasia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Redness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pain during calf compression	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is an ulcer present?	No <input type="checkbox"/>	Yes <input type="checkbox"/>			

Q.2 Rate the following SIGNS for the **LEFT** leg (please check one response for each sign)

	No or				
	Minimal	Mild	Moderate	Severe	
Pretibial edema	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	LEFT LEG
Skin induration	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Hyperpigmentation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Venous ectasia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Redness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pain during calf compression	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is an ulcer present?	No <input type="checkbox"/>	Yes <input type="checkbox"/>			