2019

Relationships between the use of pharmacomechanical catheter-directed thrombolysis, sonographic findings, and clinical outcomes in patients with acute proximal DVT: Results from the ATTRACT Multicenter Randomized Trial

Ido Weinberg  
*Massachusetts General Hospital*

Suresh Vedantham  
*Washington University School of Medicine in St. Louis*

Amber Salter  
*Washington University School of Medicine in St. Louis*

Gail Hadley  
*Vascular Ultrasound Core-Laboratory*

Noor Al-Hammadi  
*Washington University School of Medicine in St. Louis*

Follow this and additional works at: [https://digitalcommons.wustl.edu/icts_facpubs](https://digitalcommons.wustl.edu/icts_facpubs)  
*See next page for additional authors*

**Recommended Citation**  
Authors
Relationships Between the Use of Pharmacomechanical Catheter-Directed Thrombolysis, Sonographic Findings, and Clinical Outcomes in Patients with Acute Proximal DVT: Results from the ATTRACT Multicenter Randomized Trial

Running Head: Sonographic Findings and Clinical Outcomes ATTRACT

Ido Weinberg¹,²*, Suresh Vedantham³, Amber Salter⁴, Gail Hadley², Noor Al-Hammadi⁴, Clive Kearon⁵, Jim A. Julian⁵,⁶, Mahmood K. Razavi⁷, Heather L. Gornik⁸, Samuel Z. Goldhaber⁹, Anthony J. Comerota¹⁰, Andrei L. Kindzelski¹¹, Robert M. Schainfeld¹, John F. Angle¹², Sanjay Misra¹³, Jonathan A. Schor¹⁴, Darren Hurst¹⁵, Michael R. Jaff¹⁶ for the ATTRACT Trial Investigators

Author Affiliations

1 – Vascular Medicine Section, Cardiology Division, Massachusetts General Hospital, Boston, MA, USA. @Angiologist
2 – Vascular Ultrasound Core-Laboratory (VasCore), Boston, MA, USA
3 – Mallinckrodt Institute of Radiology, Washington University in St. Louis, St. Louis, MO, USA
4 – Division of Biostatistics, Washington University in St. Louis, St. Louis, MO, USA
5 – McMaster University, Department of Oncology, Hamilton, Ontario, Canada
6 – Juravinski Hospital and Cancer Centre, Hamilton, Ontario, Canada
7 – St Joseph's Hospital, Orange, CA, USA
8 – Vascular Center, University Hospitals Harrington Heart & Vascular Institute, Cleveland, OH
9 – Brigham and Women's Hospital, Division of Cardiovascular Medicine, and Harvard Medical School, Boston, MA, USA
10 – Inova Heart and Vascular Institute, Inova Alexandria Hospital, Alexandria, VA, USA
11 – Division of Blood Diseases & Resources, National Heart, Lung, and Blood Institute, National Institutes of Health (NIH), Bethesda, MD, USA
12 – Department of Radiology, University of Virginia, Charlottesville, VA, USA
13 – Department of Radiology, Mayo Clinic, Rochester, MN, USA
14 – Staten Island University Hospital, New-York, NY, USA
*Corresponding author*

Ido Weinberg, MD

55 Fruit Street, GB852G

Boston, Massachusetts 02114

Phone: 617-726-2256

Fax: 617-726-3971

E-Mail: iweinberg@mgh.harvard.edu
Abstract

Few studies have documented relationships between endovascular therapy, duplex ultrasonography (DUS), post thrombotic syndrome (PTS), and quality of life (QOL). The Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial randomized 692 patients with acute proximal deep vein thrombosis (DVT) to receive anticoagulation or anticoagulation plus pharmacomechanical catheter directed thrombolysis (PCDT). Compression DUS was obtained at baseline, 1-month and 12-months. Reflux DUS was obtained at 12-months in a subset of 126 patients. Clinical outcomes were collected over 24 months. At 1-month, patients who received PCDT had less residual thrombus compared to Control patients evidenced by non-compressible common femoral vein (CFV) (21% vs. 35%, p < 0.0001), femoral vein (51% vs. 70%, p < 0.0001) and popliteal vein (61% vs. 74%, p < 0.0001). At 12 months in the ultrasound substudy, valvular reflux prevalence was similar between groups (85% vs. 91%, p=0.35). CFV non-compressibility at 1 month was associated with higher rates of any PTS (61% vs. 46%, p<0.001), a higher incidence of moderate-or-severe PTS (30% vs. 19%, p=0.003), and worseQOL (difference 8.2 VEINES-QOL points; p=0.004) at 24 months. Valvular reflux at 12 months was associated with moderate-or-severe PTS at 24 months (30% vs. 0%, p=0.01), but not with any PTS (63% versus 53%, p=0.47). In summary, PCDT results in less residual thrombus but does not reduce venous valvular reflux. CFV non-compressibility at 1 month is associated with more PTS, more severe PTS, and worse QOL at 24 months. Valvular reflux may predispose to moderate-or-severe PTS.

Keywords: Deep vein thrombosis, thrombolytic therapy, ultrasound, post-thrombotic syndrome
Introduction

Post thrombotic syndrome (PTS) describes a spectrum of adverse clinical signs and symptoms that may develop after deep vein thrombosis (DVT). Clinical features range from minor limb discomfort to severe leg pain, intractable edema, irreversible skin changes, and ulceration. These sequelae often result in reduced quality of life (QOL) and financial burden. Unfortunately, PTS is common, developing in approximately 40% of patients after a first episode of symptomatic DVT. Once it develops, treatment of PTS is often ineffective. Little is known about how to prevent PTS once a DVT has occurred.

The natural history of DVT, the use of duplex ultrasonography (DUS) for the diagnosis of DVT, and longitudinal post-DVT DUS characteristics have all been described. Venous thrombus burden diminishes in most patients following DVT and often a lumen is re-established, a process known as recanalization. Proximal thrombus location and greater thrombus burden are associated with lower recanalization rates than thrombi that are confined to the distal venous segments. More rapid thrombus resolution may result in improved valvular function. In tandem, after DVT, the prevalence of venous reflux increases over time. Venous hypertension, vein wall inflammation and valvular reflux are considered central to the pathophysiology of PTS.

The Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial (ClinicalTrials.gov NCT00790335) randomized patients with acute proximal DVT to receive anticoagulation or anticoagulation plus pharmacomechanical catheter-directed thrombolysis (PCDT). In ATTRACT, patient outcomes were collected over 2 years, including the occurrence and severity of PTS and health-related QOL. The main study outcomes have been reported elsewhere. We performed the current analyses to describe the
extent of residual thrombus and valvular reflux during the 12 months after proximal DVT, to
determine if PCDT reduced residual thrombus and valvular reflux, and to determine if residual
thrombus and reflux in the first 12 months resulted in increased PTS and reduced QOL at 24
months.
Methods

This was a phase 3, multicenter, randomized, open-label, assessor-blinded, controlled clinical trial\textsuperscript{16}. The trial was approved by the institutional review boards at all participating centers, and all participants provided written informed consent.

Patients with acute symptomatic proximal DVT involving the femoral, common femoral, and/or iliac veins (with or without other involved ipsilateral veins) were enrolled at 56 centers in the United States. Participants were excluded if they had symptoms for more than 14 days. Complete inclusion and exclusion criteria have been previously published\textsuperscript{15}.

Patients were randomly assigned in a 1:1 ratio to receive anticoagulation (control) or anticoagulation and PCDT (intervention). Randomization was stratified according to clinical center and thrombus extent (i.e. iliofemoral DVT or femoral-popliteal DVT). All patients in both treatment groups were provided sized-to-fit 30-40 mmHg, knee-high, graduated elastic compression stockings and were instructed to wear them during the daytime throughout follow-up. Clinical follow-up was performed through 24 months post-randomization.

A study flow diagram is presented in Figure 1. In the overall trial, 692 patients were randomized (355 to Control, 337 to PCDT). One patient was found to not have qualifying proximal DVT immediately after randomization to PCDT and was excluded from all analyses. Five control arm patients crossed over to receive PCDT during the first 7 days post-randomization, and 11 patients randomized to the PCDT arm did not have the procedure within 7 days, leaving 350 patients in the control arm and 325 patients in the PCDT arm for the per-protocol data set that was used in these analyses.

Clinical outcomes
PTS was assessed at all scheduled follow-up visits by clinician examiners who were blinded to treatment allocation. The occurrence of PTS was counted when, in the index leg, a patient had a Villalta Scale score of 5 or greater or a venous stasis ulcer at one or more of the 6, 12, 18 or 24 month scheduled follow-up visits after randomization. PTS was also counted if a patient underwent an unplanned endovascular procedure during follow-up due to severe, progressive venous-related limb symptoms (unless a Villalta score within the previous 4 weeks was lower than 5). The severity of PTS was assessed using the continuous Villalta score and was also categorized as moderate-or-severe PTS if the Villalta score was ≥10 on any occasion. PTS severity was also measured by the venous clinical severity score (VCSS, score ranges from 0 to 27). For both scales, higher scores indicate more severe PTS.

In the study, venous disease-specific QOL was assessed at baseline and through 24 months post-randomization using the patient-reported Venous Insufficiency Epidemiological and Economic Study Quality of Life (VEINES-QOL) measure where lower scores indicated reduced QOL.

Ultrasound assessments

Prior to randomization, all patients were required to have baseline venous compression DUS that assessed the compressibility of the common femoral vein (CFV), femoral vein (FV), and popliteal vein (PV) in the index leg. To minimize barriers to enrollment, these exams could be done at external facilities. The exams had to be done within 7 days prior to randomization.

At the 30-day post-randomization visit, all patients were required to undergo bilateral venous DUS to evaluate residual thrombus extent. On these exams, the compressibility of the veins (CFV, FV, PV) was recorded as being either fully compressible (defined as complete apposition of the vein walls during application of external ultrasound probe pressure), or non-compressible
Ultrasound Substudy:

An ultrasound substudy, with enrollment of 142 consecutive patients in 5 designated clinical centers, was planned as part of the original study design. During the first 12 months of follow-up, 13 patients were lost to follow-up, and an additional 3 patients could not have their ultrasound examinations included in the analysis due to data transmission errors. Hence, a total of 126 patients (61 PCDT Arm, 65 Control Arm) had analyzable data from the 12-month ultrasound exams.

These patients underwent a detailed venous DUS of the index leg 12 months post-randomization with evaluation of thrombus extent and valvular reflux. The protocol for performing DUS was standardized across all sites by the ultrasound core laboratory. Briefly, patients were placed in a supine position with the leg externally rotated at the hip and slightly flexed at the knee. Veins were serially visualized from the CFV to the tibio-peroneal trunk. In each segment B-mode gray scale imaging was performed with and without compression maneuvers, as well as color and spectral Doppler imaging.

Reflux DUS was performed in the standing position. Using an automated cuff inflator/deflator with appropriately sized cuffs, the presence of reflux was assessed in the CFV, FV, profunda femoral vein, PV, great saphenous vein, and small saphenous vein. While insonating the vein, the cuff was rapidly inflated and then rapidly deflated. Spectral Doppler waveforms as well as
valve closure time following augmentation were recorded. Color Doppler was used to display presence or absence of flow reversal within the vein. Reversed flow >0.5 seconds was considered positive for reflux in any given deep or superficial vein segment. For purposes of this analysis, the outcome “any reflux” was defined as the presence of reflux in any of the veins evaluated, while “deep reflux” was defined as the presence of reflux in the CFV, FV, profunda femoral vein, or PV.

The ultrasound studies were performed in vascular laboratories that were accredited by the American College of Radiology or the Intersocietal Accreditation Commission – Vascular Testing Division. The exams were performed by registered vascular technologists who had completed an ultrasound protocol training session.

An independent core-laboratory (VasCore, the Vascular Ultrasound Core Laboratory, Massachusetts General Hospital, Boston, MA) credentialed the sonographers, led the ultrasound protocol training, provided ongoing quality oversight for the DUS exams, and adjudicated the ultrasound substudy 12-month compression and reflux DUS exams. Baseline and 1-month compression DUS exams were not routinely reviewed by the core laboratory.

A modified Venous Segmental Disease Score (VSDS) was calculated, as not all segments were available to report the original VSDS\textsuperscript{23}. Obstruction was scored in the CFV (2 points), FV (1 point), profunda femoral vein (1 point), PV (2 points), and great saphenous vein (1 point); the points were summed to calculate the VSDS obstruction score (total possible = 7 points). If any flow was present on color and/or spectral Doppler, a score of ‘0’ was assigned to the segment. If there was no flow present on color and spectral Doppler, the total possible points for that segment were assigned. Reflux was scored in the great saphenous vein (1 point), small saphenous vein (0.5 point), CFV (1 point), FV (1 point), profunda femoral vein (1 point), and PV
(2 points); the points were summed to calculate the VSDS reflux score (total possible = 6.5 points). If flow reversal was present for >0.5 seconds, the full possible score was counted for that segment. Missing segments were scored as ‘0’, for both the obstruction and reflux scores.

**Statistical Analysis**

Because the focus of these analyses was on disease mechanisms, the analysis population consisted of those patients who were randomized, had DVT at enrollment, and received the assigned treatment. Only the index leg was included in the analysis. Descriptive statistics were used to summarize demographic and clinical characteristics using mean (standard deviation) or median (25th, 75th) for continuous variables, and frequency (percentage) for categorical variables. Evaluation of differences in venous sonographic outcomes (non-compressible vs compressible vein segments) between the control and PCDT groups used multivariable logistic regression to adjust for baseline compressibility status. Differences in residual diameter between the control and PCDT groups were evaluated using multivariable linear regression to adjust for baseline compressibility status.

The association of compressibility status of vein segments (non-compressible vs compressible) with late clinical and anatomical outcomes used t-tests for continuous outcomes and chi square tests for categorical outcomes in the overall cohort. To examine if change in CFV compressibility from baseline to 1 month influenced late clinical and anatomical outcomes, these analyses were also done on the following mutually exclusive subgroups: those who had a compressible CFV at baseline and those who had a non-compressible CFV at baseline, using the same analysis methods.
In the ultrasound substudy, the association of compressibility status of vein segments (non-compressible vs compressible) and presence of any or deep reflux with late clinical and anatomical outcomes used Wilcoxon tests for continuous outcomes and chi square tests for categorical outcomes.

A two-sided P value of 0.01 or lower was considered statistically significant for all analyses to account for multiple testing. All analyses were conducted in SAS v9.4 (SAS Institute, Cary NC).
Results

Baseline thrombus distribution, as evident from the proportion of non-compressible venous segments, was similar in the PCDT and control arms (Table 1). The baseline characteristics of the ultrasound substudy patients were similar to the characteristics of the overall ATTRACT trial population (Table 1).

Effect of PCDT Treatment Upon DUS Outcomes

At 1 month, in the overall trial, patients in the PCDT arm had less residual thrombus as evidenced by: a lower proportion of non-compressible venous segments (Table 2) - CFV (21% PCDT vs. 35% Control, p<0.0001), FV (51% PCDT vs. 70% Control, p<0.0001), and PV (61% PCDT vs. 74% Control, p<0.0001); and smaller residual diameters of the CFV and PV (Table 2).

At 12 months, in the ultrasound substudy participants, patients in the PCDT arm also had less residual thrombus, which reached statistical significance for the proportion with FV non-compressibility (Table 2). The VSDS obstruction score at 12 months did not differ between groups. The distribution of completely obstructed venous segments at 12 months can be found in Supplemental Table S1.

At 12 months, in the ultrasound substudy, the proportions of patients with reflux in any vein (85% PCDT vs. 91% Control, p=0.35) and any deep vein (83% PCDT vs. 86% Control, p=0.71) were similar in both groups. The anatomical distribution of refluxing segments can be found in Supplemental Table S2. VSDS reflux score at 12 months was similar in both groups (Table 2).

Relationship of 1-month DUS findings to 12-month and 24-month outcomes
In the overall trial, CFV non-compressibility at 1 month was associated with a higher rate of PTS (61% vs. 46%, p<0.001), a higher rate of moderate-or-severe PTS (30% vs. 19%, p=0.003), and lower QOL scores (difference 8.2 VEINES-QOL scale units, p=0.004) at 24 months (Table 3). In contrast, the presence of either femoral vein or popliteal vein non-compressibility at 1 month was not associated with a lower rate of PTS (52% vs. 44%, p=0.07), moderate-or-severe PTS (23% vs. 19%, p=0.23), or better QOL (p=0.26). In the analysis that included only those patients with a non-compressible CFV at baseline, restoration of CFV compressibility at 1-month was associated with better clinical outcomes – this reached statistical significance for 24-month PTS (62% vs. 46%, p=.004) and QOL (difference 7.3 VEINES-QOL scale points, p=0.01), but not moderate-or-severe PTS (29% vs. 21%, p=0.07) (Supplemental Table S3). In the analysis that included only those patients with a compressible CFV at baseline, there continued to be no relationship between 1-month compressibility of the femoral and popliteal veins and late clinical outcomes (Supplemental Table S3).

In the ultrasound substudy, CFV non-compressibility at 1 month did not predict the presence of valvular reflux in the deep veins or any veins at 12 months. In contrast, FV or PV non-compressibility at 1 month appeared to be associated with more valvular reflux at 12 months which reached statistical significance for any reflux (93% vs. 70%, p=0.002) and the VSDS Reflux Score (3.2 [1.6] vs. 1.9 [1.7], p = 0.002) but not for deep reflux (88% vs. 70%, p = 0.02).

**Relationship of 12-month DUS findings to 24-month clinical outcomes**

In the ultrasound substudy, compressibility of the CFV at 12 months appeared to be associated with favorable clinical outcomes at 24 months – these relationships approached statistical
significance for any PTS (83% vs. 57%, p=0.02) but were less compelling for moderate-or-severe PTS (39% vs. 22%, p=0.09) and QOL (difference 7.5 VEINES-QOL scale points, p=0.08) (Table 4). Compressibility of both the femoral vein and popliteal vein (compared to non-compressibility of one or both) at 12 months was not associated with lower rates of PTS (56% vs. 64%, p=0.40) or with less moderate-or-severe PTS (21% vs. 27%, p=0.41) at 24 months. While reflux at 12 months was not associated with more any PTS (63% vs. 53%, p=0.47), it was associated with more moderate-or-severe PTS (30% vs. 0%, p=0.01) at 24 months. Similarly, there was no association of deep vein reflux with any PTS (63% vs. 58%, p=0.70), but deep vein reflux appeared to be associated with moderate-or-severe PTS (30% vs. 5%, p=0.02).

Of patients who had a compressible CFV and no valvular reflux at 12 months follow-up, 6/13 (46%) developed PTS but none (0%) developed moderate-or-severe PTS. Of patients who had both a non-compressible CFV and valvular reflux at 12 months follow-up, PTS developed in 16/20 (80%) and moderate-or-severe PTS developed in 9/20 (45%).
Discussion

In this large, randomized study of anticoagulation alone versus anticoagulation and PCDT for acute proximal DVT, our findings collectively suggest that: 1) the use of PCDT is associated with lower thrombus burden at 1-month and likely also at 12 months; 2) a thrombus-free CFV at 1 month is associated with improved 24-month clinical outcomes, including PTS, moderate-or-severe PTS, and QOL, but the same is not true for a thrombus-free femoral-popliteal venous segment; 3) in patients presenting with CFV thrombus, successful restoration of full CFV compressibility during the first month is associated with reduced PTS and improved QOL, and possibly also with reduced moderate-or-severe PTS; 4) the use of PCDT is not associated with less venous valvular reflux at 12 months; and 5) venous valvular reflux was not associated with any PTS but may have a role in progression to moderate-or-severe PTS.

Venous obstruction and valvular reflux contribute to venous hypertension, which has been considered a central component of the pathophysiology of PTS. The “open vein hypothesis” has posited that preservation of late venous patency and valvular competence may prevent PTS, and that early thrombus removal may assist this process\(^{24-26}\). In a series of ultrasound studies in anticoagulated DVT patients, Meissner et al. found that venous segments showing delayed thrombus clearance were more likely to develop valvular reflux, and that reflux developed more often if there was DVT propagation or re-thrombosis\(^{27}\). In a randomized trial evaluating compression therapy, Prandoni et al. found that PTS developed more frequently in proximal DVT patients with residual venous thrombus or popliteal valvular reflux at 6-month follow-up (\(n = 180, 47\% \text{ vs. } 23\%, p < 0.01\))\(^{28}\). In a prospective analysis of 93 patients who presented with iliofemoral DVT and underwent CDT, combining various DUS-derived measures including thrombus burden, venous obstruction, and venous valvular reflux was useful in PTS prediction\(^{29}\).
However, the relationships among thrombus burden, the presence and sites of valvular reflux, and PTS have not been consistent\textsuperscript{24}. Previous studies have demonstrated substantial rates of both residual thrombus and valvular reflux in patients with and without PTS. While the degree of initial venous occlusion may correlate with later reflux\textsuperscript{29}, the effect of treatment has remained uncertain.

**Role of Residual Thrombus Burden and Venous Obstruction**

In ATTRACT, PCDT resulted in reduced thrombus burden at 1 month and at 12 months in the lower extremity proximal veins. This finding is very similar to what was observed in a previous multicenter randomized trial that evaluated CDT in 189 patients with proximal DVT (the CaVenT study). In that study, iliofemoral venous obstruction at 2 years (assessed by a combination of DUS and air plethysmography) was less prevalent in patients who underwent CDT (25% vs. 40%)\textsuperscript{30}, to a similar degree as in ATTRACT. Furthermore, in CaVenT, iliofemoral venous obstruction was present in more patients who developed PTS (Villalta score $\geq$ 5) as compared with those without PTS (44% vs. 23%).

Of note, the proportion of patients with residual thrombus during follow-up was higher than one might expect given the extensive nature of the endovascular procedures in both studies. It is unclear if this is the result of venographically occult thrombus that remained after PCDT, versus later development of asymptomatic recurrent thrombosis, and if additional focus on minimizing recurrence in the early weeks after PCDT (e.g., with improved antiplatelet and anticoagulation strategies, improved PCDT technique up front, or additional imaging surveillance) may prove beneficial in increasing the effectiveness of PCDT in PTS prevention.
Role of Valvular Reflux

In the Control arm of the ultrasound substudy of the ATTRACT trial, 86% of patients had deep venous valvular reflux after 12 months follow-up. This finding is consistent with previous studies that have reported high rates of valvular reflux in patients who experienced a proximal DVT and were treated with either anticoagulation alone (including the randomized CaVenT study, 83% at 2 years)\textsuperscript{30} or with systemic thrombolysis (Laiho et al, 81%)\textsuperscript{31}.

However, in ATTRACT, PCDT did not reduce the occurrence of valvular reflux. This finding differs substantially from what has been observed in previous retrospective studies\textsuperscript{32} and smaller randomized trials\textsuperscript{30, 33}. In a randomized trial comparing pulse-spray CDT to anticoagulation alone for patients with iliofemoral DVT, results at 6 months were available in 35 patients and reflux was present in fewer patients in the pulse-spray CDT arm (11% vs. 41%)\textsuperscript{33}. In the CaVenT trial (n=189), femoral-popliteal reflux at 2 years was present in fewer patients who underwent CDT (66.7% vs. 83.2%, p = 0.009)\textsuperscript{30}. In that study, patients who developed PTS had more venous reflux at 2 years as compared with those who did not develop PTS (89.8% vs. 61.9%).

The reasons for the differences in the effect of catheter intervention upon valvular reflux between ATTRACT and CaVenT are unknown. In both studies the presence of reflux was adjudicated by an independent core-laboratory, but the thrombus removal method used (CDT in CaVenT, PCDT in ATTRACT) differed to an extent. One possibility is that the use of mechanical thrombectomy devices for PCDT may promote valve injury, which could be either macroscopic or related to aggravation of inflammation or other biological mechanisms. Another possibility is that a longer period of thrombolysis (e.g., the 48 hours in CaVenT versus the 20 hours in ATTRACT) could provide more complete thrombus clearance or improved inflow, contributing to restoration of normal vein function. Of course, it is also possible that the observed differences in valvular...
reflux between the studies are unrelated to the procedure type but stem more from differences in the conduct of the ultrasound assessments, differences in study size or location (Norway versus United States), or from the overall level of methodological rigor applied. Unfortunately, ATTRACT does not provide insight into how to minimize the development of valvular reflux.

**Study Limitations**

This study is not without limitations. For budgetary reasons, it was only possible to perform detailed ultrasound examinations at 12 months in 142 patients, which reduced our ability to assess inter-relationships with the 12-month ultrasound assessments. Baseline and 1-month compression ultrasound assessments were not routinely centrally interpreted. Information on the baseline presence of reflux was not available since the study patients were only identified after the diagnosis of acute DVT. Our analysis involved substantial multiple testing. Finally, while most of the design and outcomes were pre-specified, the sonographers did not use the defined VSDS venous obstruction criteria, which reduced the utility of that assessment.

**Conclusion**

In conclusion, residual thrombus and valvular reflux are present with high frequency after proximal DVT. PCDT leads to reduced late residual thrombus burden but does not prevent venous valvular reflux from developing. While less clot burden in the CFV is associated with less PTS, less moderate-or-severe PTS, and better QOL, that is not the case for clot burden in the FV and PV. Valvular reflux may have a role in progression to moderate-or-severe PTS. Thus, to reduce PTS, additional study of the open vein hypothesis in the iliofemoral venous segment may be helpful, but new insights into alternative mechanisms (biochemical, genetic, inflammatory, and/or microvascular) will likely be needed to fully elucidate the pathophysiology of PTS.
Acknowledgements

The authors wish to thank Victoria B. Sova, Sandra M. Croteau, and the entire network of investigators and study staff at the ATTRACT Trial coordinating centers, core laboratories, vascular ultrasound laboratories, and clinical centers (see Appendix).

Disclosures

Ido Weinberg – None; Suresh Vedantham – Grant support from Cook Medical; Amber Salter – None; Gail Hadley – None; Noor Al-Hammadi – None; Clive Kearon – None; Jim A. Julian – None; Mahmood K. Razavi – Consulting fees from Abbott, Boston Scientific, Medtronic, Veniti, and Volcano/Phillips; Heather L. Gornik – Research support from CVR Global, Flexlife Health/Zin Medical – Equity; Samuel Z. Goldhaber – Grant support from BiO2 Medical; grant support and consulting fees, Boehringer Ingelheim, BMS, Daiichi Sankyo, Janssen, Portola, Bayer, and BTG/Ekos; Anthony J. Comerota – Consulting fees from Medtronic; Andrei L. Kindzelski – None; Robert M. Schainfeld – None; John F. Angle – Consultant for Proteon Therapeutics; grant support from Siemens Medical; Sanjay Misra – Consultant for Medtronic, DSMB Chair for Flexstent and Cordis Johnson & Johnson; Jonathan A. Schor – None; Darren Hurst – None; Michael R. Jaff – Holds equity in Embolitech and Venarum; uncompensated advisor, Boston Scientific, Cordis Corporation; compensated advisor: Medtronic, Sanofi, BTG; consultant, Volcano/Phillips.

Sources of funding

The ATTRACT Trial was supported by grants from the National Heart, Lung, and Blood Institute (NHLBI) for the clinical coordinating center (U01-HL088476 to Washington University in St. Louis) and data coordinating center (U01-HL088118 to McMaster University, Hamilton,
ON); the Washington University Center for Translational Therapies in Thrombosis, which is supported by a grant from the NHLBI (U54-HL112303); the Washington University Institute of Clinical and Translational Sciences, which is supported by a grant from the National Center for the Advancement of Translational Sciences (UL1-TR00044810); Boston Scientific; Covidien (now Medtronic); Genentech; the Society of Interventional Radiology Foundation; the Canada Research Chairs Program (Tier 1 support to Dr. Susan Kahn); the CanVECTOR Network (funded by Canadian Institutes of Health Research CDT-142654, to Dr. Kahn); the Heart and Stroke Foundation of Canada (Investigator Award to Dr. Kearon); and a Jack Hirsh Professorship in Thrombosis (to Dr. Kearon). BSN Medical donated the compression stockings.
References


Table 1: Baseline characteristics for overall trial participants and ultrasound substudy participants

<table>
<thead>
<tr>
<th></th>
<th>Overall Trial</th>
<th>Ultrasound Substudy</th>
<th>Overall Trial</th>
<th>Ultrasound Substudy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total&lt;sup&gt;1&lt;/sup&gt; (N=675)</td>
<td>PCDT (N=325)</td>
<td>Control (N=350)</td>
<td>Total&lt;sup&gt;1&lt;/sup&gt; (N=126)</td>
</tr>
<tr>
<td>Age (years), median (SD)</td>
<td>52.0 (42.0, 62.0)</td>
<td>52.0 (41.0, 61.0)</td>
<td>53.0 (43.0, 62.0)</td>
<td>52.0 (41.0, 59.0)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>416 (62%)</td>
<td>197 (61%)</td>
<td>219 (63%)</td>
<td>76 (60%)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>528 (78%)</td>
<td>257 (79%)</td>
<td>271 (77%)</td>
<td>107 (85%)</td>
</tr>
<tr>
<td>Hispanic or Latino, n (%)</td>
<td>41 (6%)</td>
<td>15 (5%)</td>
<td>26 (7%)</td>
<td>9 (7%)</td>
</tr>
<tr>
<td>BMI, median (SD)</td>
<td>30.6 (26.8, 35.7)</td>
<td>30.9 (27.5, 36.0)</td>
<td>30.5 (26.2, 35.1)</td>
<td>31.4 (27.5, 35.6)</td>
</tr>
<tr>
<td>eGFR, median (SD)</td>
<td>84.2 (72.0, 98.0)</td>
<td>78.0 (70.0, 97.0)</td>
<td>88.0 (74.0, 102.0)</td>
<td>93.5 (70.0, 108.0)</td>
</tr>
<tr>
<td>DVT Left Leg, n (%)</td>
<td>416 (62%)</td>
<td>203 (63%)</td>
<td>213 (61%)</td>
<td>78 (62%)</td>
</tr>
<tr>
<td>Non-compressible CFV, n (%)</td>
<td>364/644 (57%)</td>
<td>179/308 (58%)</td>
<td>185/336 (55%)</td>
<td>67/122 (55%)</td>
</tr>
<tr>
<td>Non-compressible FV, n (%)</td>
<td>598/644 (93%)</td>
<td>286/308 (93%)</td>
<td>312/336 (93%)</td>
<td>116/122 (95%)</td>
</tr>
<tr>
<td>Non-compressible PV, n (%)</td>
<td>554/643 (86%)</td>
<td>267/308 (87%)</td>
<td>287/335 (86%)</td>
<td>108/121 (89%)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Treatment groups are per-protocol patients

BMI=Body Mass Index, eGFR=Estimated Glomerular Filtration Rate, DVT=Deep Vein Thrombus, CFV=Common Femoral Vein, FV=Femoral Vein, PCDT=Pharmacomechanical Catheter-Directed Thrombolysis, PV=Popliteal Vein, SD=Standard Deviation
Table 2. Effect of PCDT on Venous Sonographic Outcomes at 1 month and 12 months

<table>
<thead>
<tr>
<th>Overall Trial</th>
<th>Status at 1 Month</th>
<th>PCDT&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Control</th>
<th>p-value&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-compressible CFV, n (%)</td>
<td>63/307 (21%)</td>
<td>107/310 (35%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>CFV diameter (mm), mean (SD)</td>
<td>1.5 (4.3)</td>
<td>3.4 (7.3)</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>Non-compressible FV, n (%)</td>
<td>155/307 (51%)</td>
<td>218/312 (70%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Non-compressible PV, n (%)</td>
<td>185/306 (61%)</td>
<td>231/312 (74%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>PV diameter (mm), mean (SD)</td>
<td>4.1 (4.9)</td>
<td>6.4 (7.2)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ultrasound Substudy</th>
<th>Status at 12 Months</th>
<th>PCDT&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Control</th>
<th>p-value&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-compressible CFV, n (%)</td>
<td>8/60 (13%)</td>
<td>15/62 (24%)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>CFV diameter (mm), mean (SD)</td>
<td>0.5 (1.4)</td>
<td>1.2 (2.4)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Non-compressible FV, n (%)</td>
<td>27/61 (44%)</td>
<td>43/62 (69%)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Non-compressible PV, n (%)</td>
<td>28/61 (46%)</td>
<td>45/62 (73%)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>PV diameter (mm), mean (SD)</td>
<td>1.9 (2.4)</td>
<td>3.2 (2.3)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Obstruction score&lt;sup&gt;3&lt;/sup&gt;, mean (SD)</td>
<td>0.08 (0.4)</td>
<td>0.14 (0.4)</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Reflux score&lt;sup&gt;3&lt;/sup&gt;, mean (SD)</td>
<td>2.7 (1.7)</td>
<td>3.0 (1.7)</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Any reflux present, n (%)</td>
<td>51/60 (85%)</td>
<td>57/63 (91%)</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>Deep reflux present, n (%)</td>
<td>50/60 (83%)</td>
<td>54/63 (86%)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

<sup>1</sup> Treatment groups are per-protocol patients
<sup>2</sup> Comparisons adjusted for baseline compressibility status for CFV, PV and FV at 1 month and 1 year
<sup>3</sup> Scores are derived from the modified Venous Segmental Disease Scale (VSDS)

CFV=Common Femoral Vein, FV=Femoral Vein, PCDT=Pharmacomechanical Catheter-Directed Thrombolysis, PV=Popliteal Vein, SD=Standard Deviation
Table 3. Association of venous non-compressibility at 1 month with late clinical, anatomical, and physiological outcomes

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Status of CFV at 1 Month</th>
<th>Status of FV and PV at 1 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-compressible</td>
<td>Compressible</td>
</tr>
<tr>
<td>Any PTS, n (%)</td>
<td>104/170 (61%)</td>
<td>205/447 (46%)</td>
</tr>
<tr>
<td>Moderate-or-Severe PTS, n (%)</td>
<td>51/170 (30%)</td>
<td>85/447 (19%)</td>
</tr>
<tr>
<td>Villalta score at 24 months, mean (SD)</td>
<td>5.2 (5.8)</td>
<td>4.0 (4.6)</td>
</tr>
<tr>
<td>VCSS score at 24 months, mean (SD)</td>
<td>2.7 (3.3)</td>
<td>2.1 (2.7)</td>
</tr>
<tr>
<td>VEINES-QOL score at 24 months, mean (SD)</td>
<td>73.2 (24)</td>
<td>81.4 (20)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anatomical/Physiological Outcome</th>
<th>Status of CFV at 1 Month</th>
<th>Status of FV and PV at 1 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-compressible</td>
<td>Compressible</td>
</tr>
<tr>
<td>Non-compressible CFV at 12 months, n (%)</td>
<td>22/36 (61%)</td>
<td>1/83 (1%)</td>
</tr>
<tr>
<td>Non-compressible FV at 12 months, n (%)</td>
<td>23/36 (64%)</td>
<td>46/84 (55%)</td>
</tr>
<tr>
<td>Non-compressible PV at 12 months, n (%)</td>
<td>18/36 (50%)</td>
<td>53/84 (63%)</td>
</tr>
<tr>
<td>Obstruction score at 12 months, mean (SD)</td>
<td>0.2 (0.6)</td>
<td>0.1 (0.4)</td>
</tr>
<tr>
<td>CFV diameter (mm), mean (SD)</td>
<td>2.8 (2.8)</td>
<td>0.05 (0.4)</td>
</tr>
<tr>
<td>PV diameter (mm), mean (SD)</td>
<td>2.0 (2.5)</td>
<td>2.8 (2.4)</td>
</tr>
<tr>
<td>Reflux score at 12 months, mean (SD)</td>
<td>3.0 (1.8)</td>
<td>2.8 (1.7)</td>
</tr>
<tr>
<td>Any reflux present at 12 months, n (%)</td>
<td>31/36 (86%)</td>
<td>74/84 (88%)</td>
</tr>
<tr>
<td>Deep reflux present at 12 months, n (%)</td>
<td>30/36 (83%)</td>
<td>71/84 (85%)</td>
</tr>
</tbody>
</table>

CFV=Common Femoral Vein, FV=Femoral Vein, PTS=Post-thrombotic syndrome, PV=Popliteal Vein, SD=Standard Deviation, VCSS=Venous Clinical Severity Score, VEINES-QOL=Venous Insufficiency Epidemiological and Economic Study Quality of Life
<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Status of CFV at 12 Months</th>
<th>Status of FV and PV at 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-compressible</td>
<td>Compressible</td>
</tr>
<tr>
<td>Any PTS, n (%)</td>
<td>19/23 (83%)</td>
<td>56/99 (57%)</td>
</tr>
<tr>
<td>Moderate-or-Severe PTS, n (%)</td>
<td>9/23 (39%)</td>
<td>22/99 (22%)</td>
</tr>
<tr>
<td>Villalta score at 24 months, mean (SD)</td>
<td>6.4 (5.5)</td>
<td>4.2 (4.3)</td>
</tr>
<tr>
<td>VCSS score at 24 months, mean (SD)</td>
<td>2.8 (2.7)</td>
<td>1.9 (2.5)</td>
</tr>
<tr>
<td>VEINES-QOL score at 24 months, mean (SD)</td>
<td>72.2 (19)</td>
<td>79.7 (22)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Any Reflux at 12 Months</th>
<th>Deep Reflux at 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Any PTS, n (%)</td>
<td>68/108 (63%)</td>
<td>8/15 (53%)</td>
</tr>
<tr>
<td>Moderate-or-Severe PTS, n (%)</td>
<td>32/108 (30%)</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>Villalta score at 24 months, mean (SD)</td>
<td>4.9 (4.8)</td>
<td>2.7 (2.7)</td>
</tr>
<tr>
<td>VCSS score at 24 months, mean (SD)</td>
<td>2.3 (2.6)</td>
<td>1.3 (1.9)</td>
</tr>
<tr>
<td>VEINES-QOL score at 24 months, mean (SD)</td>
<td>77.3 (22)</td>
<td>82.0 (20)</td>
</tr>
</tbody>
</table>

CFV=Common Femoral Vein, FV=Femoral Vein, PTS=Post-thrombotic syndrome, PV=Popliteal Vein, SD=Standard Deviation, VCSS=Venous Clinical Severity score, VEINES-QOL=Venous Insufficiency Epidemiological and Economic Study Quality of Life
Figure 1: Consort diagram

692 patients randomized

1 patient excluded after randomization

336 were assigned to pharmacomechanical-thrombolysis group

11 did not receive pharmacomechanical thrombolysis in first 7 days

325 were included in the per-protocol analysis
- Baseline compression ultrasounds (n=309)
- Month 1 compression ultrasounds (n=304)

61 were included in the ultrasound sub-study
- Baseline compression ultrasounds (n=58)
- Month 12 compression ultrasounds (n=60)

355 were assigned to control group

5 received pharmacomechanical thrombolysis in first 7 days

350 were included in the per-protocol analysis
- Baseline compression ultrasounds (n=337)
- Month 1 compression ultrasounds (n=312)

65 were included in the ultrasound sub-study
- Baseline compression ultrasounds (n=64)
- Month 12 compression ultrasounds (n=61)
Figure 1 Legend: Study flow diagram for the overall ATTRACT Trial and the ultrasound substudy
### Supplemental Table S1

Percentage of Patients in Ultrasound Substudy with **Obstruction**

* in each evaluated venous segment at 12 months

<table>
<thead>
<tr>
<th>Venous Segment</th>
<th>Total (N=123)</th>
<th>PCDT (N=60)</th>
<th>Control (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFV Obstructed, n (%)</td>
<td>1 (0.8%)</td>
<td>0 (0.0%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>FV Obstructed, n (%)</td>
<td>8 (6.5%)</td>
<td>3 (5.0%)</td>
<td>5 (7.9%)</td>
</tr>
<tr>
<td>Profunda FV Obstructed, n (%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Popliteal Obstructed, n (%)</td>
<td>2 (1.6%)</td>
<td>1 (1.7%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>GSV Obstructed, n (%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Iliac Obstructed, n (%)</td>
<td>1 (0.8%)</td>
<td>0 (0.0%)</td>
<td>1 (1.6%)</td>
</tr>
</tbody>
</table>

* Complete absence of flow on color and spectral Doppler
CFV=Common Femoral Vein, FV=Femoral Vein, GSV=Great Saphenous Vein, SSV=Small Saphenous Vein

### Supplemental Table S2

Percentage of Patients in Ultrasound Substudy with **Reflux**

* in each evaluated venous segment at 12 months

<table>
<thead>
<tr>
<th>Venous Segment</th>
<th>Total (N=123)</th>
<th>PCDT</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFV Reflux, n (%)</td>
<td>46/123 (37%)</td>
<td>23/60 (38.3%)</td>
<td>23/63 (36.5%)</td>
</tr>
<tr>
<td>FV Reflux, n (%)</td>
<td>74/122 (61%)</td>
<td>33/60 (55.0%)</td>
<td>41/62 (66.1%)</td>
</tr>
<tr>
<td>Profunda FV Reflux, n (%)</td>
<td>21/123 (17%)</td>
<td>7/60 (11.7%)</td>
<td>14/63 (22.2%)</td>
</tr>
<tr>
<td>Popliteal Reflux, n (%)</td>
<td>84/123 (68%)</td>
<td>38/60 (63.3%)</td>
<td>46/63 (73.0%)</td>
</tr>
<tr>
<td>GSV Reflux, n (%)</td>
<td>29/123 (24%)</td>
<td>16/60 (26.7%)</td>
<td>13/63 (20.6%)</td>
</tr>
<tr>
<td>SSV Reflux, n (%)</td>
<td>30/123 (24%)</td>
<td>14/60 (23.3%)</td>
<td>16/63 (25.4%)</td>
</tr>
</tbody>
</table>
Supplemental Table S3

Association of restoration of venous non-compressibility at 1 month with late outcomes

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Status of CFV at 1 Month for Patients with Non-Compressible CFV at Baseline</th>
<th>Status of FV and PV at 1 Month for Patients with Compressible CFV at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Still Non-compressible</td>
<td>Became Compressible</td>
</tr>
<tr>
<td>Any PTS, n (%)</td>
<td>91/147 (62%)</td>
<td>82/179 (46%)</td>
</tr>
<tr>
<td>Moderate-Severe PTS, n (%)</td>
<td>43/147 (29%)</td>
<td>37/179 (21%)</td>
</tr>
<tr>
<td>Villalta score at 24 months, mean (SD)</td>
<td>5.2 (6.0)</td>
<td>4.3 (4.8)</td>
</tr>
<tr>
<td>VCSS score at 24 months, mean (SD)</td>
<td>2.7 (3.4)</td>
<td>2.3 (3.0)</td>
</tr>
<tr>
<td>VEINES-QOL score at 24 months, mean (SD)</td>
<td>73.0 (24)</td>
<td>80.3 (21)</td>
</tr>
</tbody>
</table>

CFV=Common Femoral Vein, FV=Femoral Vein, PV=Popliteal Vein, SD=Standard Deviation, VCSS=Venous Clinical Severity Score, VEINES-QOL=Venous Insufficiency Epidemiological and Economic Study Quality of Life, PTS=post-thrombotic syndrome
ATTRACT Study Leadership, Investigators, and Lead Sonographers

Steering Committee
Samuel Z. Goldhaber, MD (Chair) Harvard Medical School
David J. Cohen, MD, MSc St. Luke’s Mid America Heart Institute
Anthony J. Comerota, MD University of Michigan
Heather L. Gornik, MD, MHS, RVT Cleveland Clinic Heart & Vascular Institute
Michael R. Jaff, DO Harvard Medical School
Jim Julian, MMath McMaster University
Susan R. Kahn, MD, MSc McGill University, Jewish General Hospital
Clive Kearon, MB, PhD McMaster University
Stephen Kee, MD (SIR Foundation) UCLA Medical Center
Andrei L. Kindzelski, MD, PhD National Heart, Lung, and Blood Institute
Lawrence Lewis, MD Washington University in St. Louis
Elizabeth Magnuson, ScD St. Luke’s Mid America Heart Institute
Mahmood K. Razavi, MD St. Joseph’s Vascular Institute
Timothy P. Murphy, MD Brown University
Suressh Vedantham, MD (Principal Investigator) Washington University in St. Louis

Clinical Coordinating Center
Mallinckrodt Institute of Radiology, Washington University in St. Louis, United States

Data Coordinating Center
Ontario Clinical Oncology Group, McMaster University, Hamilton, Canada

Health Economic Core Laboratory
Mid America Heart Institute, St. Luke’s Hospital, Kansas City, United States

Vascular Ultrasound Core Laboratory
VasCore, Massachusetts General Hospital, Boston, United States
**ATTRACT Clinical Centers: Site Investigators**

**Adventist Midwest Health:** Michael Sichlau – site PI, Athanasios Vlahos, Steven Smith, Quinn Thalheimer, Nisha Singh, Rekha Harting, John Gocke, Scott Guth, Neel Shah

**Albert Einstein Medical Center:** Paul Brady – site PI, Marvin Schatz, Mindy Horrow, Peyman Markazi, Leli Forouzan, Terence A.S. Matalon, David Hertzog

**Allegheny General Hospital:** Swapna Goday – site PI, Margaret Kennedy – previous site PI, Robert Kaplan, Thomas Campbell, Jamie Hartman, Elmer Nahum, Arvind Venkat

**Ann Arbor VA Health Center:** Venkataramu Krishnamurthy – site PI, John Rectenwald, Peter Henke, Jonathan Eliason, Jonathon Willatt, Guillermo Escobar

**Baptist Cardiac and Vascular Institute:** Shaun Samuels – site PI, Barry Katzen, James Benenati, Alex Powell, Constantino Pena, Howard Wallach, Ripal Gandhi

**Central DuPage Hospital:** Joseph Schneider – site PI, Stanley Kim, Farrah Hashemi, Joseph Boyle, Nilesh Patel, Michael Verta

**Christiana Care Hospital:** Daniel Leung – site PI, Marc Garcia – previous site PI, Phillip Blatt, Jamil Khatri, Dave Epstein, Randall Ryan, Tom Sweeny, Michael Stillabower, George Kimbiris, Tuhina Raman, Paul Sierzenski, Lelia Getto, Michael Dignazio, Paul Sierzenski, Mark Horvath

**Cleveland Clinic Foundation:** Heather Gornik – site PI, John Bartholomew, Mehdi Shishehbor, Frank Peacock, Douglas Joseph, Soo Hyum Kim, Natalia Fendrikova-Mahlay, Daniel Clair, Sean Lyden, Baljendra Kapoor, Gordon McLennon, Gregory Pierce, James Newman, James Spain, Amanjiit Gill, Aaron Hamilton, Anthony Rizzo, Woosup Park

**Danbury Hospital:** Alan Dietzek – site PI, Ira Galin, Dahlia Plummer, Richard Hsu, Patrick Broderick, Andrew Keller, Sameer Sayeed

**Eastern Connecticut Hematology & Oncology Associates:** Dennis Slater – site PI, Herb Lustberg, Jan Akus, Robert Sidman, Mandeep Dhami, Phillip Kohanski, Anca Bulgariu, Renuka Dulanala, James Burch, Dinesh Kapur, Jie Yang

**Florida Hospital:** Mark Ranson – site PI, Alan Wladis, David Varnagy, Tarek Mekhail, Robert Winter, Manuel Perez-Izquierdo

**Forsyth Medical Center:** Stephen Motew – site PI, Robin Royd-Kranis, Raymond Workman, Scott Kribbs, Gerald Hogsette, Phillip Moore, Bradley Thomason, William Means, Richard Bonsall, John Stewart, Daniel Golwya

**Gundersen Clinic, Ltd.:** Ezana Azene – site PI, Wayne Bottner, William Bishop, Dave Clayton, Lincoln Gundersen, Jody Riherd, Irina Shakhnovich, Kurt Ziegelbein
Georgetown University: Thomas Chang – site PI, Karun Sharma – previous site PI, Sandra Allison, Fil Banovac, Emil Cohen, Brendan Furlong, Craig Kessler, Mike McCullough, Jim Spies

Henry Ford Health System: Judith Lin – site PI, Scott Kaatz, Todd Getzen, Joseph Miller, Scott Schwartz, Loay Kabbani, David McVinnie

Holy Name Medical Center: John Rundback – site PI, Joseph Manno, Richard Schwab, Randolph Cole, Kevin Herman, David Singh, Ravit Barkama, Amish Patel

Jobst Vascular Center: Anthony Comerota – site PI, John Pigott, Andrew Seiwert, Ralph Whalen, Todd Russell, Zakaria Assi, Sahira Kazanjian, Jonathan Yobbagy, Brian Kaminski, Allan Kaufman, Garett Begeman, Robert DiSalle, Subash Thakur

Maine Medical Center: Paul Kim – site PI, Marc Jacquet, Thomas Dykes, Joseph Gerding, Christopher Baker, Mark Debiasto, Derek Mittleider, George Higgins III, Steven Amberson, Roger Pezzuti, Thomas Gallagher PA-C


Mayo Clinic: Sanjay Misra – site PI, Haraldur Bjarnason – previous site PI, Aneel Ashrani, Michael Caccavale, Chad Fleming, Jeremy Friese, John Heit, Manju Kalra, Thanila Macedo, Robert McBane, Michael McKusick, Andrew Stockland, David Woodrum, Waldemar Wysokinski

Mease Countyside Hospital: Adarsh Verma – site PI, Andrew Davis – previous site PI, Jerry Chung, David Nicker, Brian Anderson, Robert Stein, Michael Weiss

Medical College of Wisconsin/Froedtert Hospital & Clinics: Parag Patel – site PI, William Rilling, Sean Tutton, Robert Hieb, Eric Hohenwalter, M. Riccardo Colella, James Gosset, Sarah White, Brian Lewis, Kellie Brown, Peter Rossi, Gary Seabrook

Medical University of South Carolina: Marcelo Guimaraes – site PI, J. Bayne Selby, William McGary, Christopher Hannegan, Jacob Robison, Thomas Brothers, Bruce Elliott, Nitin Garg, M. Bret Anderson, Renan Uflacker, Claudio Schonholz, Laurence Raney, Charles Greenberg

Oregon Health & Science University: John Kaufman – site PI, Frederick Keller, Kenneth Kolbeck, Gregory Landry, Erica Mitchell, Robert Barton, Thomas DeLoughery, Norman Kalbfleisch, Renee Minjarez, Paul Lakin, Timothy Liem, Gregory Moneta, Khashayar Farsad, Ross Fleischman, Loren French

Pepin Heart Hospital and Dr. Kiran C. Patel Research Institute: Vasco Marques – site PI, Yasir Al-Hassani, Asad Sawar, Frank Taylor

Phoenix Heart & Cardiovascular: Rajul Patel – site PI, Rahul Malhotra – previous site PI, Stanley Kim, Farah Hashemi, Joseph Boyle, Nilesh Patel, Marvin Padnick, Melissa
Gurley, Fred Cucher, Ronald Sterrenberg, G. Reshmaal Deepthi, Gomes Cumaranatunge

Riverside Methodist Hospital: Sumit Bhatla – site PI, Darick Jacobs, Eric Dolen, Pablo Gamboa, L. Mark Dean, Thomas Davis, John Lippert, Sanjeev Khanna, Brian Schirf, Jeffrey Silber, Donald Wood, J. Kevin McGraw, Lucy LaPerna, Paul Willette

Rhode Island Hospital: Timothy Murphy – site PI, Joselyn Cerezo, Rajoo Dhangan, Sun Ho Ahn, Gregory Dubel, Richard Haas, Bryan Jay, Ethan Prince, Gregory Soares, James Klinger, Robert Lambiase, Gregory Jay, Robert Tubbs, Michael Beland, Chris Hampson, Ryan O’Hara, Chad Thompson, Michael Beland, Aaron Frodsham, Fenwick Gardiner, Abdel Jaffan, Lawrence Keating, Abdul Zafar

Providence Sacred Heart Medical Center & Children’s Hospital: Radica Alicic – site PI, Rodney Raabe – previous site PI, Jayson Brower, David McClellan, Thomas Pellow, Christopher Zylak, Joseph Davis, M. Kathleen Reilly, Kenneth Symington, Cameron Seibold, Ryan Nachreiner, Daniel Murray, Stephen Murray, Sandeep Saha, Gregory Luna

Southern Illinois University: Kim Hodgson – site PI, Robert McLafferty – previous site PI, Douglas Hood, Colleen Moore, David Griffen

St. Elizabeth Healthcare Edgewood (KY): Darren Hurst – site PI, David Lubbers, Daniel Kim, Brent Warren, Jeremy Engel, D. P. Suress

St. Elizabeth Regional Medical Center (NE): Eric VanderWoude – site co-PI, Rahul Razdan – site co-PI, Mark Hutchins, Terry Rounsborg, Madhu Midathada, Daniel Moravec, Joni Tilford, Daniel Kim, Joni Beckman PA

St. Joseph Hospital: Mahmood Razavi – site PI, Kurt Openshaw, D. Preston Flanigan, Christopher Loh, Howard Dorne, Michael Chan

St. Luke’s Hospital and Health Network: Jamie Thomas – site PI, Justin Psaila, Michael Ringold, Jay Fisher, Any Lipcomb, Timothy Osmin

St. Luke’s Hospital: Brandt Wible – site PI, Brendan Coleman, David Elliott, Gary Gaddis, C. Doug Cochran

St. Vincent Medical Group: Kannan Natarajan – site PI, Stewart Bick, Jeffrey Cooke, Ann Hedderman, Anne Greist, Lorrie Miller, Brandon Martinez, Vincent Flanders, Mark Underhill

Stanford University Medical Center: Lawrence Hofmann – site PI, Daniel Sze, William Kuo, John Louie, Gloria Hwang, David Hovsepian, Nishita Kothary, Caroline Berube, Donald Schreiber, Brooke Jeffrey

Staten Island University Hospital: Jonathan Schor – site PI, Jonathan Deitch, Kuldeep Singh, Barry Hahn, Brahim Ardolic, Shilip Gupta

Temple University Hospital: Riyaz Bashir – site PI, Angara Koneti Rao, Manish Garg, Pravin Patil, Chad Zack, Gary Cohen, Frank Schmieder, Valdimer Lakhter
The Reading Hospital: David Sacks – site PI, Robert Guay, Mark Scott, Karekin Cunningham, Adam Sigal, Terrence Cescon, Nick Leasure, Thiruvenkatamsamy Dhurairaj

TriHealth/Good Samaritan Hospital: Patrick Muck – site PI, Kurt Knochel, Joann Lohr, Jose Barreau, Matthew Recht, Jayapandia Bhaskaran, Ranga Brahmamdam, David Draper, Apurva Mehta, James Maher

University of Iowa: Melhem Sharafuddin – site PI, Steven Lentz, Andrew Nugent, William Sharp, Timothy Kresowik, Rachel Nicholson, Shiliang Sun, Fadi Youness, Luigi Pascarella

University of Illinois- Chicago: Charles Ray – site PI, Martha-Gracia Knuttinen – previous site PI, James Bui, Ron Gaba, Valerie Dobiesz, Ejaz Shamim, Sangeetha Nimmagadda, David Peace, Aarti Zain, Alison Palumto

University of Maryland: Ziv Haskal – site PI, Jon Mark Hirshon, Howard Richard, Avelino Verceles, Jade Wong-You-Chong, Bertrand Othee, Rahul Patel, Bogdan Iliescu

University of Michigan Hospitals and Health Centers: David Williams – site PI, Joseph Gemmete, Venkataramu Krishnamurthy, Wojciech Cwikel, Kyung Cho, James Schields, Ranjith Vellody, Paula Novelli, Narasimham Dasika, Thomas Wakefield, John Rectenwald, Peter Henke, Jeffrey Desmond, James Froehlich, Minhajuddin Khaja

University of Minnesota: David Hunter – site PI, Jafar Golzarian, Erik Cressman, Yvonne Dotta, Nate Schmiechen

University of New Mexico: John Marek – site PI, David Garcia, Isaac Tawil, Mark Langsfeld

University of North Carolina: Stephan Moll – site PI, Matthew Mauro, Joseph Stavas, Charles Burke, Robert Dixon, Hyeon Yu, Blair Keagy, Kyuny Kim, Raj Kasthuri, Nigel Key

University of Pittsburgh: Rabih Chaer – site PI, Michael Makaroun, Robert Rhee, Jae-Sung Cho, Donald Baril, Luke Marone, Margaret Hseih, Kristian Feterik, Roy Smith, Geetha Jeyabal, Jennifer Rogers

University of Utah Medical Center: Russel Vinik – site PI, Dan Kinikini, Larry Kraiss, Michelle Mueller, Robert Pendleton, Matthew Rondina, Mark Sarfati, Nathan Wanner, Stacy Johnson, Christy Hopkins, Daniel Ihnat


Utah Valley Reginal Medical Center: Carl Black – site PI, Mark Asay, Daniel Hatch, Robert Smilanich, Craig Patten, S. Douglas Brown, Ryan Nielsen, William Alward, John Collins, Matthew Nokes
**Wake Forest Baptist Health:** Randolph Geary – site PI, Matthew Edwards, Christopher Godshall, Pavel Levy

**Weill Cornell Medical College:** Ronald Winokur – site PI, Akhilesh Sista – previous site PI, David Madoff, Kyungmouk Lee, Bradley Pua, Maria DeSancho, Raffaele Milizia, Jing Gao

**Western Penn Allegheny Health System:** Swapna Goday – site PI, Margaret Kennedy – previous site PI, Robert Kaplan, Thomas Campbell, Gordon McLean, Jamie Hartman, Elmer Nahum, Sanualah Khalid

**Washington University in St. Louis:** Suresh Vedantham – site PI, Larry Lewis, Nael Saad, Mark Thoelke, Robert Pallow, Seth Klein, Gregorio Sicard

**ATTRACT Ultrasound Substudy – Participating Sites and Lead Sonographers**

**Cleveland Clinic Foundation:** Alia G. Grattan, Kathleen MacDonald

**Jobst Vascular Center:** S. Masatkina, A. Wilson, Julie Mason

**Massachusetts General Hospital:** Kathryn Lane Contis, Kathleen Hannon, Andrea Mattoon, Caroline Yarnevich

**St. Joseph Hospital:** Keefe Baker, Eileen Halcrow, Brad Weiss

**Washington University in St. Louis:** John Gibson, Deborah Wehrle