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Abstract

Background: The ATTRACT Trial previously reported that pharmacomechanical catheter-directed thrombolysis (PCDT) did not prevent the post-thrombotic syndrome (PTS) in patients with acute proximal deep vein thrombosis (DVT). In the current analysis, we examine the effect of PCDT in ATTRACT patients with iliofemoral DVT.
Methods: Within a large multicenter randomized trial, 391 patients with acute DVT involving the iliac and/or common femoral veins were randomized to PCDT with anticoagulation versus anticoagulation alone (No-PCDT) and were followed for 24 months to compare short-term and long-term outcomes.
Results: Between 6 and 24 months, there was no difference in the occurrence of PTS (Villalta scale $\geq$5 or ulcer: 49% PCDT versus 51% No-PCDT; risk ratio (RR)=0.95; 95% confidence interval (CI), 0.78–1.15; p=0.59). PCDT led to reduced PTS severity as shown by: lower mean Villalta and Venous Clinical Severity Scores [VCSS] (p<0.01 for comparisons at 6, 12, 18, and 24 months); and fewer patients with moderate-or-severe PTS (Villalta scale $\geq$10 or ulcer: 18% versus 28%; RR 0.65; 95% CI 0.45–0.94, p=0.021) or severe PTS (Villalta scale $\geq$15 or ulcer: 8.7% versus 15%; RR 0.57; 95% CI 0.32-1.01, p=0.048; and VCSS $\geq$8: 6.6% versus 14%; RR 0.46; 95% CI 0.24-0.87, p=0.013). From baseline, PCDT led to greater reduction in leg pain and swelling (p<0.01 for comparisons at 10 and 30 days) and greater improvement in venous disease-specific QOL (VEINES-QOL unit difference 5.6 through 24 months, p=0.029), but no difference in generic QOL (p > 0.2 for comparisons of SF-36 mental and physical component summary scores through 24 months). In patients having PCDT versus No-PCDT, major bleeding within 10 days occurred in 1.5% versus 0.5% (p=0.32), and recurrent VTE over 24 months was observed in 13% versus 9.2% (p=0.21).
Conclusions: In patients with acute iliofemoral DVT, PCDT did not influence the occurrence of PTS or recurrent VTE. However, PCDT significantly reduced early leg symptoms and, over 24 months, reduced PTS severity scores, reduced the proportion of patients who developed moderate-or-severe PTS, and resulted in greater improvement in venous disease-specific QOL.
Clinical Trial Registration: URL: www.clinicaltrials.gov Unique Identifier: NCT00790335

Key Words: deep vein thrombosis; iliofemoral; thrombolysis; post-thrombotic syndrome

Clinical Perspective

What is new?

- Outcomes are reported on a subgroup of 391 patients with acute iliofemoral DVT in whom pharmacomechanical catheter-directed thrombolysis (PCDT) was evaluated within a large multicenter randomized controlled trial (ATTRACT).
- In patients with acute iliofemoral DVT, PCDT does not influence the occurrence of the post-thrombotic syndrome (PTS) or recurrent venous thromboembolism through 24 months.
- In patients with acute iliofemoral DVT, PCDT does appear to provide greater reduction in acute leg pain and swelling through 30 days follow-up, as well as reduced PTS severity, reduced moderate-or-severe PTS, and greater improvement in venous disease-specific quality of life through 24 months.

What are the clinical implications?

- The findings support early use of PCDT in patients with acute iliofemoral DVT who have severe symptoms, low bleeding risk, and who attach greater importance to a reduction in early and late symptoms than to the risks, costs, and inconvenience of PCDT.

Introduction

Iliofemoral deep vein thrombosis (DVT), defined as DVT that involves the iliac and/or common femoral vein (with or without involvement of additional veins), often causes functional obstruction of venous outflow of the involved leg (1,2). These patients are phenotypically distinct from patients with calf or femoral-popliteal DVT, based on more frequent recurrent venous thromboembolic events, more frequent post-thrombotic syndrome (PTS), and more severe PTS (1,3-7). Preliminary studies of catheter-directed thrombolysis and related methods have suggested that these strategies may be most useful in patients with iliofemoral DVT compared to those with less extensive proximal DVT, and that the occurrence and degree of thrombus clearance may correlate with clinical outcome (8-13).

The biological plausibility that iliofemoral DVT should be recognized as a distinct entity in the anatomic spectrum of acute DVT is rooted in the anatomy and physiology of lower extremity venous return and the observation that venous recanalization occurs less often in patients with iliofemoral versus more distal DVT who were treated with anticoagulation alone or systemic thrombolysis (14,15). As the entire volume of venous blood return is directed through the common femoral and iliac veins, obstruction of this channel results in marked post-thrombotic venous hypertension (16) and severe post-thrombotic morbidity (3-7).

The main results of the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) Trial, the largest randomized trial evaluating catheter based intervention for acute proximal DVT, were recently reported (17,18). This study found no reduction of 2-year PTS frequency (the study's primary outcome) or improvement in health-related quality of life (QOL) in patients treated with pharmacomechanical catheter-directed thrombolysis (PCDT) compared with those treated with anticoagulation alone, although

there was a reduction in the severity of PTS in the PCDT-treated group. Importantly, patients in this study were stratified by the most proximal extent of their DVT (iliofemoral versus femoral-popliteal) prior to randomization, permitting a valid analysis of the outcomes of these two distinct anatomic-clinical presentations. The purpose of this analysis is to report the benefits and risks of PCDT in the patients in the ATTRACT Trial who presented with acute iliofemoral DVT.

Methods

Study Organization

The study design and the main study results for the overall ATTRACT cohort have been previously described (17,18). In brief, this was a NIH-sponsored, Phase III, multicenter, randomized, open-label, assessor-blinded, parallel two-arm, controlled clinical trial (www.attract.wustl.edu; NCT00790335). All patients provided written informed consent. The study was approved by the Institutional Review Boards at all participating centers. The authors and Steering Committee are solely responsible for the design and conduct of the study, all analyses, and the writing of this article. The data and study materials will be made available to other researchers in accordance with the NIH Public Access Policy, at www.clinicaltrials.gov or by contacting the Corresponding Author.

Patient Population, Stratification, and Randomization

Patients presenting with DVT in the femoral or a more proximal vein with symptoms of 14 days or less were enrolled from 56 centers in the United States (U.S.). Patients were stratified by clinical center and by the most proximal extent of their DVT, that is, whether the DVT involved the iliac and/or common femoral vein ("iliofemoral DVT"; this term applied whether or not more caudal veins were also involved), or not ("femoral-popliteal DVT") (1,2). After stratification,

patients were randomized in a 1:1 ratio to receive either PCDT with anticoagulation (PCDT Arm), or anticoagulation alone (No-PCDT Arm), and followed for 2 years. In this analysis, we report exclusively on the 391 patients with iliofemoral DVT; the patients with femoral-popliteal DVT are reported elsewhere.

Treatments

All patients were treated with initial and long-term anticoagulation consistent with published guidelines (19,20), and were provided knee-high 30 – 40 mm Hg ankle gradient elastic compression stockings (BSN Medical, Charlotte, NC) at their 10 day follow-up visit and every 6 months.

PCDT was performed as described elsewhere by board-certified physicians whose credentials were approved by the trial leadership, using methods consistent with published guidelines (21,22). Recombinant tissue plasminogen activator (rt-PA) (alteplase, Activase®, Genentech, South San Francisco, CA) was infused into the thrombus using one of three methods: a standard multi-sidehole catheter ("infusion-first"); the AngioJet Rheolytic Thrombectomy System (Boston Scientific, Malborough, MA) (“power pulse-spray” or “rapid lysis” method); or the Trellis Peripheral Infusion System (Covidien, Inc., Mansfield, MA [now Medtronic], “isolated thrombolysis”). Rt-PA dosing limits were: 1) 0.01 mg/kg/hr, not to exceed 1.0 mg/hr; 2) no more than 30 hours infusion; 3) no more than 25 mg in any one procedure session; and 4) no more than 35 mg total. After initial rt-PA delivery, physicians could use balloon maceration, catheter aspiration, thrombectomy devices, and/or balloon angioplasty to clear residual thrombus. Stent placement was encouraged for obstructive lesions in the iliac vein and/or common femoral vein causing $\geq$ 50% diameter narrowing, > 2 mmHg mean pressure gradient, or

robust collateral filling on venography. Patients received heparin-based anticoagulation during PCDT, as previously described (17,18).

Outcome Assessments

Patient outcomes were assessed at 10 and 30 days, and at 6, 12, 18, and 24 months following randomization, by clinicians who were blinded to treatment allocation. The adjudicators of safety and efficacy outcomes were also unaware of the treatment assignments.

PTS, defined as a Villalta score of $\geq$ 5 or a venous ulcer in the leg with the index DVT that occurred at any one or more assessments between the 6 month and 24 month follow-up visits (inclusive), was the study's primary efficacy outcome (23,24). The Villalta scale rates the severity of five patient-reported symptoms (pain, cramps, heaviness, pruritus, paresthesia) and six clinician-observed signs (edema, skin induration, hyperpigmentation, venous ectasia, redness), with each item scored from 0-3. Points for symptoms and signs are summed into a total score (range 0-33), and patients can be categorized as having no PTS (score 0-4), mild PTS (score 5-9), moderate PTS (score 10-14) or severe PTS (score $\geq$15, or presence of ulcer). Development of PTS was also attributed to patients if they underwent an unplanned endovascular procedure to treat severe venous symptoms beyond 6 months after randomization, unless there was a Villalta score < 5 in the previous 4 weeks.

The severity of PTS was evaluated at 6, 12, 18, and 24 months using the Villalta score and the Venous Clinical Severity Score (VCSS) (25) as continuous measurements. In addition, using the Villalta score, the presence of moderate or severe PTS (Villalta score $\geq$10, or an ulcer), or severe PTS (Villalta score $\geq$15, or an ulcer) were assessed as secondary outcomes. Using the VCSS (ranges from 0 to 27, with higher scores indicating more severe PTS), the presence of PTS

(VCSS score ≥4) and severe PTS (VCSS score ≥8) were also assessed using previously published criteria (26).

Generic health-related quality of life (QOL) was assessed with the SF-36 Health Status Survey (27), and venous disease-specific QOL was assessed with the Venous Insufficiency Epidemiological and Economic Study Quality of Life (VEINES-QOL) measure (28).

Leg pain and leg swelling were assessed at baseline, 10 days, and 30 days using a 7-point Likert pain scale and by measuring calf circumference (29).

Patients receiving PCDT had the amount of thrombus removal quantified by independent central readers using the proximal-vein components of the Marder score (30).

Safety outcomes included bleeding, recurrent venous thromboembolism, and death, which were recorded throughout follow-up and summarized through 10 days and 24 months. Clinically overt bleeding was classified as "major" if it was associated with a fall in the hemoglobin level of at least 2.0 g/dl, transfusion of ≥ 2 units of red blood cells, or involvement of a critical site (e.g., intracranial, intraspinal) (31). Less severe clinically overt bleeding was classified as "minor".

Sample Size

Sample size for the entire ATTRACT study was 692 proximal DVT patients based on these assumptions: 30% of control patients would develop PTS between 6 and 24 months; PCDT would reduce PTS by at least 33%; 10% loss to follow-up; need to have 80% power to detect the hypothesized treatment effect; acceptance of a two-side α error of 0.05. We did not estimate the sample size for the iliofemoral DVT subgroup, pre-specify the proportion of patients expected to have iliofemoral DVT, or require a minimum number of patients with iliofemoral DVT. A sample size of 391, corresponding to the number of patients in the current analysis, provides

approximately 80% power to detect (i) a 41% PTS reduction assuming a control proportion of 30%, and (ii) an effect size (i.e. mean difference divided by the SD) of at least 0.28, assuming a two-sided α error of 0.05 with each type of analysis.

Statistical Analysis

Two types of analyses were performed: a modified intention-to-treat analysis (primary analysis) that included all randomized patients except those who did not have DVT at enrollment; and a per-protocol analysis (secondary analyses) that excluded patients who, within 7 days post-randomization, were randomized to PCDT but did not receive it, or who were randomized to control but had skin puncture for PCDT thrombolysis or any thrombolytic therapy.

Cumulative proportions were compared using the Cochran-Mantel-Haenszel test adjusted for clinical center. Treatment effects are summarized using stratum-adjusted risk ratios (RR) with their corresponding 95% confidence intervals (CI).

The mean Villalta,VCSS, and QOL assessments at each visit were estimated using piece-wise linear regression growth curve models adjusting for clinical center and pre-specified baseline covariates (age, sex, body-mass index, race). Changes from baseline to 10 days and from baseline to 30 days for leg pain scores and calf circumferences in the index leg were compared using multiple linear regression, adjusted for clinical center. A supportive analysis modeled the values at 10 days and 30 days with the baseline value as a covariate. For the binary outcomes, interaction tests for subgroups were conducted using a logistic model with treatment, subgroup, and an interaction term as factors, with interaction p-values calculated using Wald joint tests. The risk ratios and 99% confidence intervals derived from the models were used to create the forest plots.

The analyses in this report are considered exploratory because, although they were pre-specified, they are confined to a subgroup of the main trial.

Results

Baseline Characteristics of Participants

Of the 692 patients in ATTRACT, 391 (57%) had iliofemoral DVT of whom 196 were randomized to PCDT and 195 were randomized to No-PCDT (**Figure 1**). Median age was 52 years, 53% were male, the index DVT was in the left leg in 64%, and symptoms were present for a median of 6 days (**Table 1**). Baseline characteristics were well balanced between the two treatment groups (**Table 1**)

Protocol and Treatment Adherence

Within 7 days after randomization, 4 patients assigned to No-PCDT had PCDT, and 6 patients assigned to PCDT did not have the procedure (**Figure 1**). These patients were excluded from the per-protocol analysis. PCDT was performed at a median one day post-randomization. Initial anticoagulant therapy, which was usually low molecular weight heparin or unfractionated heparin, was similar in the PCDT and No-PCDT patients (**Table 2**). The initial rt-PA delivery method in PCDT Arm patients was the "infusion first" method in 52% (median total rt-PA dose of 21 mg), the AngioJet method in 24% (median total rt-PA dose of 21 mg), and the Trellis method in 19% (median total rt-PA dose of 20 mg) (PCDT not performed in 5%; **Table 2**). After initial rt-PA delivery, additional endovascular methods were used in 91% of patients, as summarized in **Table 2**. Mean thrombus removal as assessed by pre and post PCDT venography was 86% (mean pre-procedure and post-procedure Marder scores 12.0 and 3.0, respectively, change -9.1; 95% CI, -8.2 to -10.0; $p < 0.001$). The mean duration of anticoagulation before first

permanent cessation during follow-up, use of antiplatelet therapy, and use of compression stockings were similar in the PCDT and No-PCDT patients (**Table 2**).

Development of Post-Thrombotic Syndrome

In the intention-to-treat analysis using the study's primary outcome measure (Villalta scale), PTS developed in 96 of 196 (49%) PCDT Arm patients and in 100 of 195 (51%) No-PCDT Arm patients (RR=0.95; 95% CI, 0.78-1.15; p=0.59) during 24 months follow-up (**Table 3**). In the per-protocol analysis and in all subgroups evaluated, the findings were similar (**Figure 2, Supplemental Table 1**). Using the VCSS scale, PTS developed in 30% of PCDT Arm patients and in 40% of No-PCDT Arm patients (RR=0.75; 95% CI, 0.57-0.98; p=0.034) (**Table 3**). In the per-protocol analysis, these findings were similar (29% PCDT versus 41% No-PCDT, RR=0.71, 95% CI, 0.54-0.94, p=0.015) (**Supplemental Table 1**).

Severity of Post-Thrombotic Syndrome

At 6, 12, 18, and 24 months, mean Villalta and VCSS scores were significantly lower in the PCDT Arm compared with the No-PCDT Arm ($p< 0.01$ at all time-points, both analysis sets) (**Table 4, Figure 3**) (32).

Moderate-or-severe PTS, as assessed by a Villalta scale score ≥10 or ulceration, developed in 36 (18%) patients assigned to PCDT and in 55 (28%) patients assigned to No-PCDT (RR=0.65; 95% CI, 0.45 to 0.94; p=0.021) (**Table 3**). The findings were similar in a per-protocol analysis (RR=0.63, p=0.013) (**Supplemental Table 1**). For this outcome, patients' sex, race, symptom duration (0-1 versus 1-2 weeks), side of DVT, and baseline symptom severity did not influence the effect of PCDT. However, patients < 65 versus ≥ 65 years old (p-interaction=0.04) and those with versus without a major reversible DVT risk factor at diagnosis

(p-interaction=0.05) appeared less likely to develop moderate-or-severe PTS with use of PCDT (**Figure 4**).

Severe PTS, as assessed by a Villalta score ≥15 or ulceration, developed in 17 (8.7%) patients assigned to PCDT and in 30 (15%) patients assigned to No-PCDT (RR=0.57; 95% CI, 0.32 to 1.01; p=0.048) (**Table 3**). Severe PTS, as assessed by a VCSS score ≥ 8, developed in 13 (6.6%) patients assigned to PCDT and 28 (14%) patients assigned to No-PCDT (RR=0.46; 95% CI, 0.24 to 0.87; p=0.013) (**Table 3**). These findings were similar in per-protocol analyses (**Supplemental Table 1**). Ulceration developed in 9 (4.6%) patients assigned to PCDT and in 12 (6.2%) patients assigned to No-PCDT (RR=0.75; 95% CI, 0.32 to 1.73, p=0.49).

Change in Presenting Symptoms and Health-Related Quality of Life

Mean change in leg pain from baseline for PCDT versus No PCDT was -1.76 versus -1.25 Likert points at 10 days (p=0.009), and -2.36 versus -1.80 Likert points at 30 days (p=0.008) (**Table 4**). Mean change in calf circumference from baseline for PCDT versus No PCDT was -0.79 cm versus +0.22 cm at 10 days (p=0.002) and -1.37 cm versus -0.10 cm at 30 days (p<0.001). The findings for these outcomes were similar in the per-protocol analyses **(Supplemental Table 2**).

Mean change in venous disease-specific quality of life from baseline to 24 months was 28.6 versus 23.0 VEINES-QOL scale units in the PCDT versus No-PCDT Arms (between-group difference 5.6 units, p=0.029). In the per-protocol analysis, this between-group difference was 5.3 units (p=0.04).

Mean change in the symptoms component of venous disease-specific quality of life from baseline to 24 months was 21.5 versus 16.2 VEINES-Sym scale units in the PCDT versus No-PCDT Arms (between-group difference 5.2 points, p=0.043). In the per-protocol analysis, this between-group difference was 5.1 units, p=0.012).

Mean change in generic quality of life (physical and mental component summary scores of SF-36 measure) from baseline to 24 months did not differ for the PCDT versus No-PCDT patients in either the intention-to-treat or per-protocol analyses (p>0.25 for all analyses, **Table 4, Supplemental Table 2**).

Safety Outcomes

Within 10 days, in PCDT versus No-PCDT patients, major bleeding occurred in three patients (1.5%) versus one patient (0.5%) (p=0.32), and any bleeding occurred in seven (3.6%) versus four (2.1%) patients (p=0.36) (**Table 3**). There were no fatal or intracranial bleeds. Recurrent venous thromboembolism within 24 months occurred in 26 (13.3%) PCDT versus 18 (9.2%) No-PCDT patients (p=0.21) (none were fatal). Of the six deaths in each group, none occurred within 10 days post-randomization (**Table 3**). Per-protocol analyses of the safety outcomes were similar (**Supplemental Table 1**).

Discussion

Contemporary clinical practice guidelines (including a Scientific Statement from the American Heart Association) recommend that studies of DVT therapy report outcomes separately for patients with iliofemoral versus less extensive DVT (1,2). These and other guidelines (19,20,22) also identify thrombus extent as a key factor to consider when deciding which patients should receive endovascular thrombus removal, which accounts for why some randomized trials have evaluated endovascular DVT therapies exclusively in patients with iliofemoral DVT (33-35). Consequently, this report focuses on findings in the iliofemoral DVT subgroup of the ATTRACT study.

Several studies have described favorable outcomes for aggressive thrombus removal therapies in comparison to anticoagulation alone in iliofemoral DVT, but each had major methodological limitations that undermine confidence in their findings. A small randomized trial evaluating surgical venous thrombectomy for acute iliofemoral DVT versus anticoagulation alone reported improved long term iliofemoral patency and reduced post-thrombotic morbidity in the surgically-treated patients (36). A post-hoc analysis of data from a prospective multicenter registry found that 68 CDT-treated patients had significantly fewer PTS symptoms, better physical functioning, less stigmata of chronic venous insufficiency, and less health distress ($p<0.05$ for all outcomes) at a mean follow-up of 16 months compared with 30 retrospectively "matched" patients who were treated with anticoagulation alone (9). A prospective non-randomized study (n=51) found better 6-month and 5-year venous patency and freedom from venous symptoms in patients who received CDT versus anticoagulation alone (37). Finally, a single-center randomized trial comparing streptokinase CDT versus anticoagulation alone observed a higher rate of normal venous function and less valvular reflux in CDT recipients (38). However, these studies were limited by potential selection bias and baseline differences between treatment groups due to their non-randomized design (9,37), small sample size (9,36-38), performance in a single center (37,38), and lack of rigorous PTS assessment with validated tools (38).

A recent multicenter randomized trial that evaluated CDT for proximal DVT above mid-thigh level (the CAVENT Trial) found that CDT reduced PTS, which significantly correlated with patency of the ipsilateral iliofemoral venous segment (11,13). Since CAVENT did not report outcomes separately for iliofemoral DVT and femoral-popliteal DVT patients, we are unable to combine data from the iliofemoral subgroups of the two trials. Although in the total

study population, CAVENT reported that CDT reduced any PTS, CDT did not improve long-term QOL and was associated with major and non-major bleeding complications. Consequently, we suggest that the findings of ATTRACT and CAVENT collective argue against routine first-line thrombolysis for proximal DVT, but that patients with iliofemoral DVT or more severe presentations may derive benefit and deserve further examination.

This exploratory analysis of the iliofemoral DVT subgroup in the ATTRACT Trial did not find an effect of PCDT upon the development of "any PTS" over 2 years using the pre-specified primary trial outcome (Villalta score threshold of 5), and did not find an effect upon bleeding. These findings were similar in the per-protocol analysis, and they are consistent with PCDT treatment effects for "any PTS" in the iliofemoral and femoral-popliteal subgroups that did not differ significantly (p-interaction=0.85) (18). Although PCDT reduced the occurrence of PTS in a pre-specified secondary assessment using the VCSS, we chose the Villalta scale as the trial's primary outcome measure based upon a more extensive body of literature and international societal recommendations supporting its use to detect incident PTS, including more rigorous assessment of the Villalta threshold score than the VCSS threshold score (23-26). Additional studies to compare the performance characteristics of these two PTS scales, using the ATTRACT and other datasets, would be worthwhile.

The data from this analysis collectively suggest that PCDT improves short-term recovery from DVT and reduces long-term progression of PTS severity in patients with iliofemoral DVT. Evidence favoring PCDT includes: 1) greater reduction in leg pain and swelling through 30 days ($p<0.01$); 2) reduced PTS severity ($p<0.01$ for Villalta and VCSS comparisons) at 6, 12, 18, and 24 months; 3) reduced occurrence of moderate-or-severe PTS ($p=0.021$ for comparison of proportion with Villalta $\geq$ 10) and severe PTS ($p<0.05$ for comparisons of proportions with

Villalta ≥ 15 and VCSS ≥ 8) through 24 months; and 4) greater improvement in venous disease-specific QOL from baseline to 24 months (5.6 points on VEINES-QOL scale, p=0.029). These findings were consistent in the per-protocol analyses.

However, the findings of this analysis should not be considered conclusive evidence that PCDT reduces the occurrence of moderate-or-severe PTS in patients with iliofemoral DVT. Moderate-or-severe PTS was one of a number of secondary outcomes. Although assessors were blinded to treatment arm, healthcare providers and patients were not blinded. Hence, further studies are recommended to determine whether PCDT truly reduces moderate-or-severe PTS in patients with iliofemoral DVT.

In this analysis, there was a suggestion that PCDT exerted a more positive effect upon the moderate-or-severe PTS outcome in iliofemoral DVT patients who were < 65 years of age versus those ≥ 65 years old (p-interaction = 0.04), and upon patients whose DVT was provoked by a major reversible risk factor (p-interaction = 0.05). However, as these two results are in subgroups within the iliofemoral subgroup, and as they are among many outcomes that were evaluated in the study, and as the tests of interaction were not strongly positive, these two findings may have occurred by chance (39,40).

Our analysis has several limitations. First, there was substantial loss to follow-up that was unbalanced between the treatment groups (more missed PTS assessments in the No-PCDT Arm), which influenced the study's estimates of treatment effects (18). As only 57% of ATTRACT Trial patients had iliofemoral DVT, power to detect differences in outcomes with PCDT versus No-PCDT in the iliofemoral DVT subgroup is substantially less than in the overall trial. Furthermore, in the absence of a statistically significant test of interaction to support a difference in the PCDT treatment effect upon moderate-or-severe PTS between the iliofemoral

and femoral-popliteal subgroups, the treatment effect estimate from the overall trial may be the most reliable estimate of the treatment effect in each of these two subgroups (39,40). This is also true for the assessment of bleeding, which was statistically higher with use of PCDT in the overall ATTRACT Trial. On the other hand, tests of interaction to detect differences in treatment effects between subgroups have low power in a medium-sized study such as ATTRACT. Strengths of this analysis include that it was pre-specified; that the presence of iliofemoral DVT was a stratification variable that was identified prior to randomization; and that the reduction in PTS severity with PCDT was a consistent finding across multiple venous outcome measures. We excluded patients with either asymptomatic DVT or DVT causing acute circulatory compromise since they could not be ethically randomized to one or the other treatment strategy, and we acknowledge that a) the enrolled patients had varying baseline symptom severity (and perhaps PTS risk); b) patients with recurrent ipsilateral DVT within the last 2 years (who are expected to have a high risk of PTS) were excluded; and c) site investigators could have chosen to bypass the study for selected patients at either end of the severity spectrum. However, throughout the study we provided detailed education to study centers that explicitly addressed this issue and strongly encouraged the enrollment of all willing iliofemoral DVT patients who met the study eligibility criteria. This analysis is also the largest report of randomized trial outcomes specifically in patients with iliofemoral DVT.

In conclusion, the findings of this exploratory analysis strongly suggest that PCDT reduces acute leg pain and swelling, reduces PTS severity, and improves venous QOL in patients with acute iliofemoral DVT. These findings support early use of PCDT in patients with acute iliofemoral DVT who have severe symptoms, low bleeding risk, and who attach greater importance to a reduction in early and late symptoms than to the risks, cost, and inconvenience

of PCDT. A decision to use PCDT should factor in this study's limitations (including the lack of patient blinding) and should be made only after a careful review of the bleeding risk in that individual patient. Further prospective study of PCDT and other endovascular therapies should be targeted to the subset of patients with iliofemoral DVT.

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Table 1. Baseline Characteristics by Treatment Group

Baseline Characteristic	**PCDT**	**No PCDT**	**Total**
	n = 196	n = 195	N = 391
Age, years: *median (IQR)*	51 (39, 62)	52 (42, 61)	52 (39, 62)
Male: *n (%)*	107 (55)	101 (52)	208 (53)
Race: *n (%)*			
White	158 (81)	148 (76)	306 (78)
Black/African-American	33 (17)	35 (18)	68 (17)
Other	5 (3)	12 (6)	17 (4)
Body mass index, kg/m^2: *median (IQR)*	31 (28, 37)	31 (26, 36)	31 (27, 37)
Symptom severity (Villalta[*]) class: *n (%)*[†]			
None or minimal (score 0-4)	24 (12)	31 (16)	55 (14)
Mild (score 5-9)	65 (33)	65 (33)	130 (33)
Moderate (score 10-14)	60 (31)	56 (29)	116 (30)
Severe (score ≥ 15)	47 (24)	42 (22)	89 (23)
Leg with index DVT, Left: *n (%)*	124 (63)	125 (64)	249 (64)
Previous DVT or PE: *n (%)*	48 (24)	45 (23)	93 (24)
Previous ipsilateral DVT: *n (%)*	3 (2)	10 (5)	13 (3)
DVT risk factors: *n (%)*[‡]			
Major surgery	19 (10)	21 (11)	40 (10)
Hospitalization	17 (9)	29 (15)	46 (12)
Plaster cast immobilization	7 (4)	3 (2)	10 (3)
Childbirth	3 (2)	5 (3)	8 (2)
Outpatient: *n (%)*	156 (80)	156 (80)	312 (80)
Days from start of DVT symptoms to rand: *median (IQR)*	6 (3, 9)	6 (3, 9)	6 (3, 9)
eGFR, mL/min: *median (IQR)*	84 (67, 103)	88 (72, 104)	86 (70, 103)
Leg pain severity: *n (%)*			
0-2	34 (17)	43 (22)	77 (20)
3-4	60 (31)	59 (30)	119 (30)
5-7	99 (51)	91 (47)	190 (49)
Unknown	3 (2)	2 (1)	5 (1)
Between-leg circumference difference[§], cm: *median (IQR)*	3 (2, 5)	3 (2, 4)	3 (2, 5)

Baseline Characteristic	PCDT	No PCDT	Total
	n = 196	n = 195	N = 391
Pre-randomization AC[ǁ] therapy: *n (%)*[‡]	180 (92)	184 (94)	364 (93)
LMWH	101 (56)	110 (60)	211 (58)
UFH	61 (34)	60 (33)	121 (33)
Rivaroxaban	7 (4)	7 (4)	14 (4)
Warfarin	89 (49)	98 (53)	187 (51)
Other	11 (6)	7 (4)	18 (5)

*** Villalta Scale**: 5 patient-reported signs (cramps, itching, pins & needles, leg heaviness, pain) and 6 blinded clinician-reported symptoms (pretibial edema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression) scored on a 4-point scale (0=none/minimal, 1=mild, 2=moderate, 3=severe) and summed into a total score, or the presence of an ulcer (score=15), for the leg with index DVT

† One patient in the No PCDT was not assessed

‡ Subjects may fit into more than one category

§ Leg circumference with index DVT minus Leg circumference of the other leg

ǁ Anticoagulant (AC) therapy that was given after DVT diagnosis and before randomization

IQR, inter-quartile range; DVT, deep vein thrombosis; PE, pulmonary embolism; rand, randomization; eGFR, estimated glomerular filtration rate; LMWH, low molecular weight heparin; UFH, unfractionated heparin

Table 2. Study Treatments Post Randomization

Treatment over Time	**PCDT** n = 196	**No PCDT** n = 195
Initial AC[*] therapy: *n (%)*[†]	*n = 194*	*n = 193*
UFH	73 (38)	42 (22)
LMWH	99 (51)	132 (68)
Other	29 (15)	28 (15)
At 30 days: *n (%)*[†]	*n = 183*	*n = 173*
Any AC Therapy	177 (97)	167 (97)
Antiplatelet Therapy	30 (16)	26 (15)
Compression stockings used ≥ 3 days per week	135 (74)	136 (79)
At 6 months: *n (%)*[†]	*n = 169*	*n = 150*
Any AC Therapy	136 (80)	126 (84)
Antiplatelet Therapy	34 (20)	23 (15)
Compression stockings used ≥ 3 days per week	111 (66)	108 (72)
At 24 months: *n (%)*[†]	*n = 141*	*n = 131*
Any AC Therapy	66 (47)	68 (52)
Antiplatelet Therapy	44 (31)	39 (30)
Compression stockings used ≥ 3 days per week	77 (55)	74 (56)
Duration of AC therapy: *n (%)*		
Never started	2 (1)	2 (1)
Not stopped during study period	106 (54)	108 (55)
Stopped during study period:	88 (45)	85 (44)
Days to stopping: *median (IQR)*	213 (182, 367)	270 (182, 395)
PCDT Procedure Details (PCDT Arm only)		
Initial rt-PA delivery method:		
Infusion-First: *n (%)*	102 (52)	
rt-PA total dose, mg: *median (IQR)*	21 (18, 26)	
rt-PA duration, hours: *% below 4h*, *mean (SD)*[‡]	0%,23 (7.2)	
AngioJet: *n (%)*	46 (24)	
rt-PA total dose, mg: *median (IQR)*	21 (15, 28)	
rt-PA duration, hours: *% below 4h*, *mean (SD)*[‡]	46%, 20 (5.5)	
Trellis: *n (%)*	38 (19)	
rt-PA total dose, mg: *median (IQR)*	20 (12, 30)	
rt-PA duration, hours: *% below 4h*, *mean (SD)*[‡]	58%, 20(4.6)	
Other[§]: *n (%)*	10 (5)	

Treatment over Time	**PCDT** n = 196	**No PCDT** n = 195
Additional endovascular methods used: *n (%)*		
None	18 (9)	
1 or more	178 (91)	
Type of additional method: *n (%)*[†]		
Balloon venoplasty	128 (72)	
Balloon maceration	105 (59)	
Rheolytic thrombectomy (AngioJet)	104 (58)	
Stent placement	70 (39)	
Large-bore catheter aspiration	44 (25)	
Isolated thrombolysis (Trellis)	11 (6)	
Veins that were accessed: *n (%)*[†]	192 (98)	
Ipsilateral Popliteal Vein	172 (90)	
Ipsilateral Tibial Vein	12 (6)	
Ipsilateral Common Femoral Vein	5 (3)	
Internal Jugular Vein	12 (6)	
Other Vein	17 (9)	
Marder scores: *median (IQR)*		
Pre-lysis (n=180)	11 (8, 16)	
Post-lysis (n=178)	2 (0, 4)	
Pre-post Decrease (n=176)	9 (4, 13)	

[*]Anticoagulation (AC) therapy given post randomization
[†] Subjects may fit into more than one category
[‡] Distributions are bimodal with spikes below 4 hours (means and SDs are for post 4-hour data)
[§] 6 PCDT procedures where there was no acute thrombus on venogram and 4 not attempted
IQR, Inter-quartile range; rt-PA, recombinant tissue plasminogen activator; SD, standard deviation

Table 3. Binary Study Outcomes by Treatment Group (Intention-to-Treat Analysis)

Outcome	PCDT n = 196		No PCDT n = 195		Risk Ratio		P Value
	Events	(%)	Events	(%)	Estimate	95% CI	
PTS*:							
Ulcer (any assessment)	9	(4.6%)	12	(6.2%)			
Villalta ≥ 5 (without ulcer)	86	(44%)	88	(45%)			
Late endovascular procedure only	1	(0.5%)	0	(0%)			
Total	96	(49%)	100	(51%)	0.95*	0.78, 1.15	0.59
PTS: VCSS ≥ 4*	59	(30%)	78	(40%)	0.75*	0.57, 0.98	0.034
PTS incidence proportion: †							
At 6 months	50/169	(30%)	68/149	(46%)	0.65	0.48, 0.87	
At 12 months	58/155	(37%)	49/137	(36%)	1.05	0.77, 1.42	
At 18 months	46/139	(33%)	47/123	(38%)	0.87	0.63, 1.20	
At 24 months	48/145	(33%)	52/133	(39%)	0.85	0.62, 1.16	
Moderate-severe PTS (Villalta ≥ 10) ‡	36	(18%)	55	(28%)	0.65*	0.45, 0.94	0.021
Moderate-severe PTS incidence proportion: §							
At 6 months	19/169	(11%)	29/149	(19%)	0.58	0.34, 0.99	
At 12 months	18/155	(12%)	24/137	(18%)	0.66	0.38, 1.17	
At 18 months	16/139	(12%)	23/123	(19%)	0.62	0.34, 1.11	
At 24 months	17/145	(12%)	25/133	(19%)	0.62	0.35, 1.10	
Severe PTS: Villalta ≥ 15 ‖	17	(8.7%)	30	(15%)	0.57*	0.32, 1.01	0.048
Severe PTS: VCSS ≥ 8 ‖	13	(6.6%)	28	(14%)	0.46*	0.24, 0.87	0.013
Major non-PTS treatment failure	4	(2.0%)	5	(2.6%)	0.80	0.22, 2.92	0.73
Any treatment failure **	97	(49%)	103	(53%)	0.93*	0.77, 1.13	0.47
Major bleeding in first 10 days	3	(1.5%)	1	(0.5%)	2.98	0.31, 28.4	0.32
Any bleeding in first 10 days	7	(3.6%)	4	(2.1%)	1.74	0.52, 5.85	0.36
VTE:							
First 30 days	11	(5.8%)	6	(3.1%)	1.82	0.69, 4.83	0.22
Total over 24 months	26	(13%)	18	(9.2%)	1.44	0.81, 2.53	0.21
Death	6	(3.1%)	6	(3.1%)	0.99	0.33, 3.03	0.99

*Cochran-Mantel-Haenszel (CMH) test adjusted for center, cumulative proportion of patients who developed PTS at any time between 6-24 months, inclusive. Villalta scores (0-33 range); VCSS scores (0-27 range), higher is worse for both.

† At each visit, the proportion of patients with any PTS according to the Villalta scale among those who had an assessment performed (denominator)

‡ Cumulative proportion with moderate or severe PTS (pre-specified analysis)

§ At each visit, the proportion of patients with moderate or severe PTS according to the Villalta scale among those who had an assessment performed (denominator)

‖ Cumulative proportion with severe PTS ** Composite of PTS or major non-PTS treatment failure.

PTS, post-thrombotic syndrome; CI, confidence interval; VTE, venous thromboembolism

Table 4. Continuous Study Outcomes by Treatment Group (Intention-to-Treat Analysis)

Outcome	PCDT n = 196		No PCDT n = 195		PCDT – No PCDT Difference	
	n	**mean** (SE)	**n**	**mean** (SE)	**Estimate** (SE)	**P-value**
Villalta mean scores*†:						
At 6 months	169	3.70 (0.51)	149	5.38 (0.50)	-1.68 (0.47)	<0.001
At 12 months	155	3.78 (0.50)	137	5.43 (0.49)	-1.65 (0.45)	<0.001
At 18 months	139	3.86 (0.52)	123	5.49 (0.50)	-1.62 (0.48)	<0.001
At 24 months	145	3.95 (0.54)	133	5.54 (0.54)	-1.60 (0.54)	0.0033
VCSS mean scores‡§:						
At 6 months	168	1.82 (0.32)	145	2.98 (0.32)	-1.16 (0.28)	<0.001
At 12 months	151	‖	134	‖	‖	‖
At 18 months	135	1.67 (0.35)	121	3.43 (0.35)	-1.76 (0.34)	<0.001
At 24 months	132	1.98 (0.35)	122	2.80 (0.35)	-0.82 (0.34)	0.018
SF-36 general Quality of Life‡: **						
PCS: Change, baseline to 24 months	141	10.65 (0.95)	128	11.43 (0.99)	-0.78 (1.17)	0.51
MCS: Change, baseline to 24 months	141	2.85 (0.82)	128	4.02 (0.86)	-1.17 (1.09)	0.28
VEINES disease-specific Quality of Life‡: ††						
Overall: Change, baseline to 24 months	141	28.63 (1.97)	128	23.02 (2.07)	5.61 (2.6)	0.029
Symptoms: Change, baseline to 24 months	140	21.45 (1.96)	128	16.24 (2.06)	5.21 (2.56)	0.043
Leg pain severity‡‡ (7-point scale): §§						
Change, baseline to Day 10	181	-1.76 (0.14)	177	-1.25 (0.14)	-0.51 (0.19)	0.0093
Change, baseline to Day 30	178	-2.36 (0.15)	171	-1.80 (0.15)	-0.56 (0.21)	0.0082
Index leg circumference‡‡ (cm): ‖						
Change, baseline to Day 10	175	-0.79 (0.23)	177	0.22 (0.23)	-1.00 (0.32)	0.0019
Change, baseline to Day 30	174	-1.37 (0.22)	170	-0.10 (0.23)	-1.27 (0.32)	<0.001

* Mean scores, standard errors (SE) and treatment differences estimated using growth curve models and piece-wise linear regression adjusted for center, and baseline covariates (age, sex, BMI, race)

† Villalta scores (0-33 range) – higher is worse

‡ Mean scores, standard errors (SE) and treatment differences estimated using growth curve models and piece-wise linear regression adjusted for center, and baseline covariates (age, sex, BMI, race, Villalta score)

§ VCSS scores (0-27 range) – higher is worse

‖ Model estimates are unchanged from month 6 to month 12 due to the lack of a significant time trend

** SF-36 major scales: physical component score (PCS, 0-100 range) and mental component score (MCS, 0-100 range) – higher is better, with a difference of 3 to 4 points considered clinically meaningful; †† VEINES overall score (0-100 range) and symptom specific score (0-100 range) – higher is better; ‡‡ Mean change scores, SEs, and treatment differences estimated using multiple linear regression adjusted for center; §§ patient-reported severity of pain in the index leg (0-7 range) – higher is worse; ‖ leg circumference measured at 10cm below tibial tuberosity of the index leg.

Figure Legends

Figure 1. Patient flow diagram for the iliofemoral DVT subgroup in the ATTRACT trial.

PCDT, pharmacomechanical catheter-directed thrombolysis; DVT, deep-vein thrombosis; LEP, Late Endovascular Procedure (not including inferior vena cava filter).

Figure 2. Subgroup analysis of PTS in patients with iliofemoral DVT.

Forest plot of risk ratios (PCDT versus No PCDT) for the occurrence of PTS from 6 to 24 months among subgroups of patients. The horizontal lines represent 99% confidence intervals.

PCDT, pharmacomechanical catheter-directed thrombolysis; DVT, deep vein thrombosis.

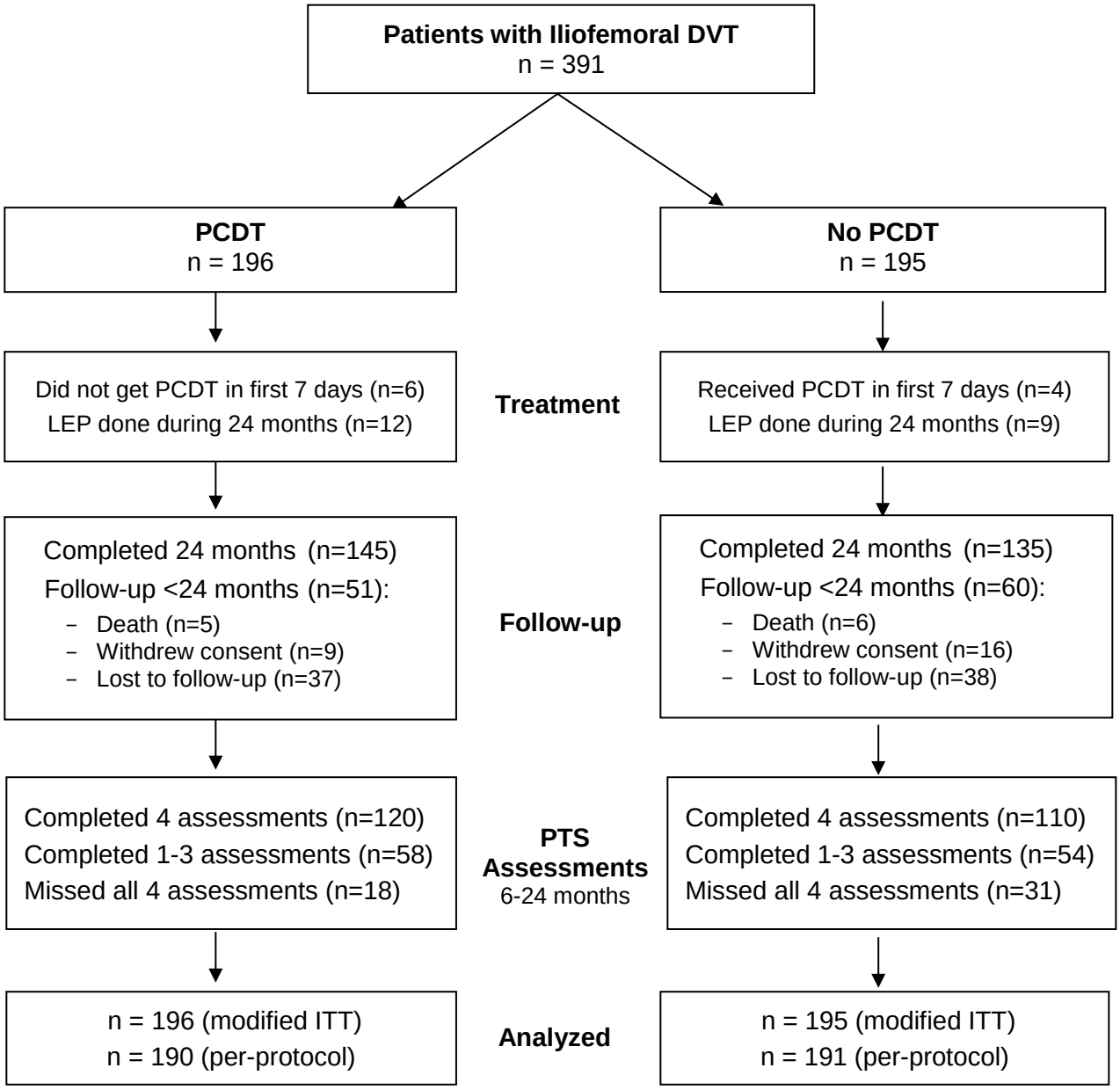
Figure 3: LOESS* of raw and predicted mean Villalta scores by treatment group

Graphical display (locally weighted scatterplot smoothing) of the Villalta Scores evaluating PTS severity by treatment arm, derived from piecewise-linear growth-curve models of the repeated assessments from baseline through 24 months.

Figure 4. Subgroup analysis of moderate-or-severe PTS in patients with iliofemoral DVT.

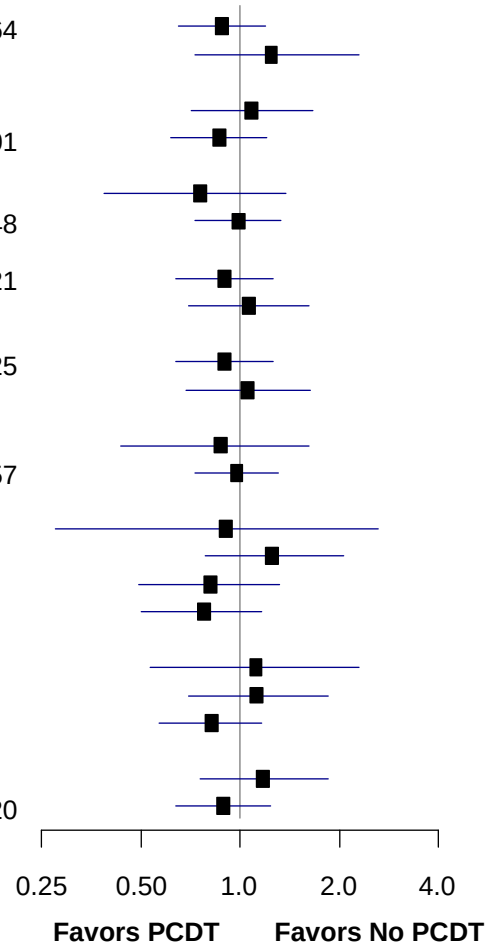
Forest plot of risk ratios (PCDT versus No PCDT) for the occurrence of moderate-or-severe PTS from 6 to 24 months among subgroups of patients. The horizontal lines represent 99% confidence intervals.

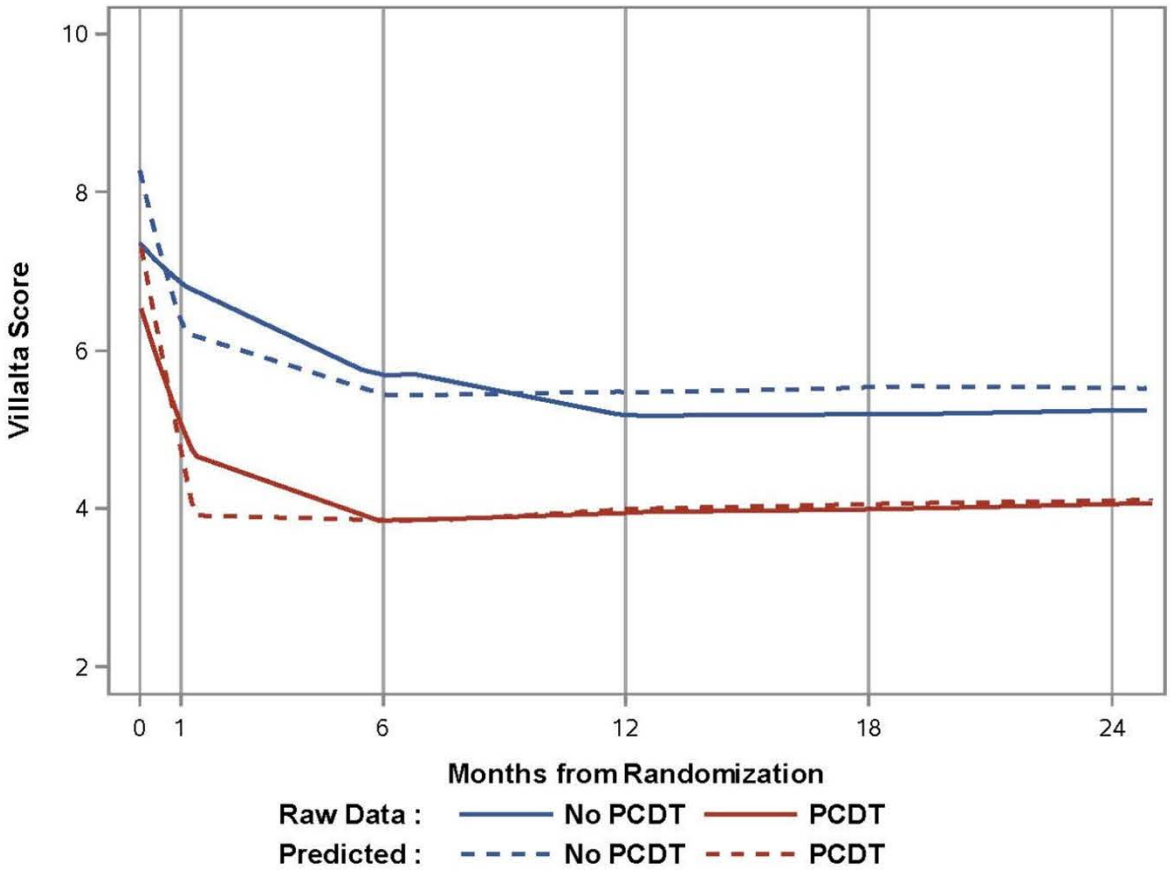
PCDT, pharmacomechanical catheter-directed thrombolysis; DVT, deep vein thrombosis.


Patients with Iliofemoral DVT
n = 391
PCDT
n = 196
No PCDT
n = 195
Did not get PCDT in first 7 days (n=6)
LEP done during 24 months (n=12)
Treatment
Received PCDT in first 7 days (n=4)
LEP done during 24 months (n=9)
Completed 24 months (n=145)
Follow-up <24 months (n=51):
- Death (n=5)
- Withdrew consent (n=9)
- Lost to follow-up (n=37)
Follow-up
Completed 24 months (n=135)
Follow-up <24 months (n=60):
- Death (n=6)
- Withdrew consent (n=16)
- Lost to follow-up (n=38)
Completed 4 assessments (n=120)
Completed 1-3 assessments (n=58)
Missed all 4 assessments (n=18)
PTS Assessments
6-24 months
Completed 4 assessments (n=110)
Completed 1-3 assessments (n=54)
Missed all 4 assessments (n=31)
n = 196 (modified ITT)
n = 190 (per-protocol)
Analyzed
n = 195 (modified ITT)
n = 191 (per-protocol)

PTS defined as Villalta score ≥ 5 or ulcer

Baseline Factor	Subgroup	PCDT vs No PCDT	Risk Ratio (99% CI)	P Interaction
Age	< 65	71/157 vs 84/164		0.15
	≥ 65	25/39 vs 16/31		
Sex	Female	42/89 vs 41/94		0.28
	Male	54/107 vs 59/101		
Race	African American	15/33 vs 21/35		0.43
	White	78/158 vs 74/148		
Leg symptom duration	< 1 week	59/128 vs 62/121		0.43
	≥ 1 week	37/68 vs 38/74		
Side of DVT	Left	58/124 vs 65/125		0.44
	Right	38/72 vs 35/70		
Major risk factor	Yes	14/29 vs 21/38		0.67
	No	82/167 vs 79/157		
Villalta severity score	0-4	7/24 vs 10/31		0.22
	5-9	35/65 vs 28/65		
	10-14	27/60 vs 31/56		
	≥ 15	27/47 vs 31/42		
Leg pain severity	1-2	15/34 vs 17/43		0.29
	3-4	32/60 vs 28/59		
	5-7	48/99 vs 54/91		
Between-Leg circumference difference	< 3 cm	37/68 vs 33/71		0.20
	≥ 3 cm	58/122 vs 64/120		





Moderate-or-severe PTS defined as Villalta score ≥ 10 or ulcer

Baseline Factor	Subgroup	PCDT vs No PCDT	P Interaction
Age	< 65	25/157 vs 49/164	0.04
	≥ 65	11/39 vs 6/31	
Sex	Female	16/89 vs 23/94	0.57
	Male	20/107 vs 32/101	
Race	African American	8/33 vs 12/35	0.98
	White	27/158 vs 39/148	
Leg symptom duration	< 1 week	21/128 vs 35/121	0.35
	≥ 1 week	15/68 vs 20/74	
Side of DVT	Left	22/124 vs 39/125	0.32
	Right	14/72 vs 16/70	
Major risk factor	Yes	3/29 vs 15/38	0.05
	No	33/167 vs 40/157	
Villalta severity score	0-4	2/24 vs 2/31	0.38
	5-9	11/65 vs 11/65	
	10-14	10/60 vs 19/56	
	≥ 15	13/47 vs 23/42	
Leg pain severity	1-2	4/34 vs 5/43	0.44
	3-4	13/60 vs 17/59	
	5-7	18/99 vs 33/91	
Between-leg circumference difference	< 3 cm	13/68 vs 21/71	0.85
	≥ 3 cm	22/122 vs 31/120