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## Correlation between post-procedure residual thrombus and clinical outcome in deep vein thrombosis patients receiving pharmacomechanical thrombolysis in a multicenter randomized trial

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**Correlation between Post-Procedure Residual Thrombus and Clinical Outcome in DVT  
Patients Receiving Pharmacomechanical Thrombolysis in a Multicenter Randomized Trial**

## **Abstract**

**Purpose:** To evaluate relationships between immediate anatomic outcomes and clinical outcomes of pharmacomechanical catheter-directed venous thrombolysis (PCDT).

**Materials and Methods:** Venograms from 317 proximal DVT patients who received PCDT in a multicenter randomized trial were reviewed. Quantitative thrombus resolution was assessed by independent readers using a modified Marder scale. The physician operators recorded their visual assessments of thrombus regression and venous flow. These immediate post-procedure anatomic outcomes were correlated with patient outcomes at 1, 12, and 24 months.

**Results:** PCDT produced substantial thrombus removal ( $p < 0.001$  for comparisons of pre-PCDT and post-PCDT thrombus scores in all segments evaluated). At procedure end, spontaneous antegrade venous flow was present in 99% of iliofemoral venous segments and in 89% of femoral-popliteal venous segments. For the overall proximal DVT population, and for the femoral-popliteal DVT subgroup, post-PCDT thrombus volume did not correlate with 1-month or 24-month outcomes. For the iliofemoral DVT subgroup, post-PCDT thrombus volume did not correlate with 24-month PTS occurrence but did correlate with 24-month Villalta PTS severity ( $p=0.0098$ ), with trends toward improved symptom status and venous disease-specific quality of life (QOL) over 1 and 24 months. Post-PCDT thrombus volume did not correlate with 12-month valvular reflux.

**Conclusion:** PCDT successfully removes thrombus in acute proximal DVT. However, the residual thrombus burden at procedure end does not correlate with the occurrence of PTS during the subsequent 24 months. In iliofemoral DVT, lower residual thrombus burden correlates with reduced PTS severity and probably also with improved venous QOL and fewer early symptoms.

## Introduction

Patients with proximal deep vein thrombosis (DVT) frequently develop the post-thrombotic syndrome (PTS) (1). PTS may cause daily limb pain, swelling, heaviness, and fatigue, with progression to stasis dermatitis and venous ulcers. These sequelae frequently impair patients' long-term health-related quality of life (QOL) (2).

The rationale for catheter-directed thrombolysis (CDT) for DVT has been largely predicated on the “open vein hypothesis”, which postulates that early thrombus removal may facilitate long-term venous patency, preserve venous valve function, reduce PTS, and improve QOL. However, of three recent randomized controlled trials (RCTs) that evaluated CDT and related therapies for proximal DVT, none provided strongly confirmatory findings (i.e., both prevention of PTS and improvement of long-term QOL) to justify widespread use of CDT as first-line therapy (3-6).

In the largest RCT, the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial, pharmacomechanical catheter-directed thrombolysis (PCDT) reduced the volume of thrombus but not the occurrence of PTS. However, PCDT did reduce PTS severity and improve QOL in the subgroup of patients with acute iliofemoral DVT (5,7-9). Substantial venous thrombus was present in both treatment groups on follow-up sonography at 1 month and 12 months post-randomization, and correlated with worse clinical outcomes (10). In the current analysis of the ATTRACT dataset, we evaluate and correlate the immediate venographic results of PCDT with subsequent clinical outcomes.

## **Materials and Methods**

### Study Design

The ATTRACT Trial was a Phase III, multicenter, open-label, assessor-blinded, randomized clinical trial. The study is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT007095). Patients provided written informed consent to participate. The study was approved by the institutional review boards of all participating clinical centers. Those who designed the study, collected/analyzed the data, drafted the paper, and decided to publish it will be specified in the final un-blinded version.

Patients with acute symptomatic proximal DVT extending above the popliteal vein were enrolled at 56 U.S clinical centers. The complete eligibility criteria and the main study outcomes for the overall cohort and major anatomic subgroups have been previously reported (5,7,8,11). Patients were randomly assigned in a 1:1 ratio to receive PCDT and standard anticoagulant therapy or anticoagulant therapy alone. Randomization was stratified according to clinical center and thrombus extent (specifically, whether or not the common femoral vein was compressible).

This analysis focuses exclusively on the patients who were assigned to, and actually received, PCDT therapy. Comparisons with the control arm could not be performed since those patients did not undergo venography. Methods of study conduct and clinical outcome data analysis have been previously published (5,7,8,11), but aspects relevant to this analysis are summarized below.

### Venography and PCDT Procedures

In the PCDT Arm patients, the procedure was performed at a median of 7 days after symptom onset. Patients underwent hand-injected catheter venography of the proximal veins of the index limb and pelvis immediately before PCDT and then immediately after PCDT and any adjunctive procedures were completed. If there was good inflow into the popliteal vein as assessed by the

treating physician on the day of the procedure, centers were required to start thrombolytic therapy using either the Trellis-8 device (Medtronic, Minneapolis, MN - Technique A) or the AngioJet device (Boston Scientific, Marlborough, MA – Technique B) to administer the drug (Activase, recombinant tissue plasminogen activator [rt-PA], Genentech, South San Francisco, CA). Patients with poor or absent inflow into the popliteal vein first underwent catheter-directed infusion (Technique C) using a multi-sidehole catheter at 0.01 mg/kg/hr rt-PA infusion, not to exceed 1.0 mg/hr. After initial thrombolysis as above, physicians were required to continue rt-PA infusion until either at least 90% of the thrombus was removed and there was antegrade flow by visual assessment, the protocol's dose limits (35 mg rt-PA total, 24-30 hours infusion) were reached, or a complication occurred.

Before, during, and after PCDT, patients were anticoagulated. However, during rt-PA infusions, unfractionated heparin was reduced to subtherapeutic levels (6-12 units/kg/hr). The duration of anticoagulant therapy followed clinical practice guidelines (12). All patients were provided sized-to-fit, 30-40 mmHg, knee-high, graduated elastic compression stockings (BSN Medical, Charlotte, NC) at 10 days follow-up, and were asked to wear them daily. Study follow-up visits were at 10 and 30 days, and 6, 12, 18, and 24 months post-randomization.

#### Assessment of Venograms

Static images of the pre-PCDT and post-PCDT venograms were transmitted by Clinical Center staff on digital media to an independent core laboratory at the study's data coordinating center, where experienced physician readers graded the venograms using the elements of the Marder score that correspond to the proximal veins (13). A "*total thrombus score*" was summed from component scores for the popliteal (4 points), femoral (10 points), common femoral (4 points), and iliac (6 points) veins (hence, total possible score for a limb with complete thrombosis was 24



points). We also calculated an “*iliofemoral segment sub-score*” (total possible 10 points, summed from the iliac and common femoral vein component scores) and a “*femoral-popliteal segment sub-score*” (total possible 14 points, summed from the femoral vein and popliteal vein scores).

In addition to these independent reader assessments, the endovascular operators were asked to document three items at the time of PCDT, based on visual assessment of the immediate-post-PCDT venograms: (a) whether there was spontaneous antegrade flow in the iliofemoral segment (iliac and common femoral veins); (b) whether there was spontaneous antegrade flow in the femoral-popliteal segment (femoral and popliteal veins); and (c) the proportion of thrombus removed (> 90%, 75-90%, 50-75%, or < 50%).

#### Assessment of Clinical Outcomes

As described elsewhere (5), PTS was assessed at follow-up visits between 6 and 24 months post-randomization by clinician examiners who were blinded to treatment allocation. The occurrence of *PTS* was counted if there was a Villalta Scale score of 5 or greater or a venous ulcer in the index leg at one or more of the 6, 12, 18 or 24 month scheduled follow-up visits, or if a patient had an unplanned endovascular procedure during follow-up to treat severe venous symptoms (14). The occurrence of *moderate-or-severe PTS* was defined as a Villalta score of 10 or greater or a venous ulcer during at least one visit. *PTS severity* was graded with the continuous Villalta Scale score [range 0-33] and the modified Venous Clinical Severity Scale [VCSS, range 0-27] score; for both scales, higher scores indicate more severe PTS (15). *Venous disease-specific QOL* was measured using the validated, patient-reported Venous Insufficiency Epidemiologic and Economic Quality of Life Survey (VEINES-QOL) at the follow-up visits (16). Resolution of *early DVT symptoms* was characterized by use of a Likert pain scale (range 0 to 7, higher being worse) and the Villalta and VEINES-QOL scales at baseline and at 1 month follow-up.

Study enrollees underwent compression ultrasound of the proximal veins at baseline (within 7 days prior to randomization) and at 1 month follow-up, aimed at delineating the thrombus extent. In addition, in 5 pre-selected Clinical Centers, an “ultrasound substudy” was conducted in 142 consecutive randomized patients (10). These patients had a detailed venous duplex ultrasound at 12 months follow-up, with assessment of thrombus extent and the presence of valvular reflux (defined as reversal of venous flow for > 0.5 seconds) in the deep and superficial veins.

### Statistical Analysis

Because the main focus of these analyses was on disease mechanisms, the analysis population consisted of those patients who had DVT at enrollment, were randomized to the PCDT Arm, had proximal vein thrombus identified on the pre-PCDT venogram, and received initial PCDT as assigned. Only the index leg was included in the analyses. Descriptive statistics were used to summarize demographic and clinical characteristics using mean (standard deviation) or median (range) for continuous variables, and frequency (percentage) for categorical variables. Since the venograms more accurately depicted the thrombus extent at the time of PCDT (compared with the pre-randomization ultrasounds done several days earlier), these analyses categorize patients in anatomic subgroups based on the pre-PCDT venogram status of the iliac and common femoral veins. Patients with any thrombus in these veins were categorized as “iliofemoral DVT”, and patients with no thrombus in these veins were categorized as “femoral-popliteal DVT” (17,18).

The differences in total and segmental thrombus scores and sub-scores between pre-PCDT and immediate-post-PCDT venograms were evaluated using paired t-tests for the overall cohort, iliofemoral DVT subgroup, femoral-popliteal DVT subgroup, and the three PCDT techniques. The associations between the continuous immediate-post-PCDT total thrombus scores, iliofemoral segment sub-scores, and femoral-popliteal segment sub-scores with outcomes used

analysis of covariance (ANCOVA) for continuous outcomes, adjusted for baseline status, and chi square tests for categorical outcomes. Testing for the overall cohort, and for the iliofemoral DVT and femoral-popliteal DVT subgroups, was conducted separately.

To further explore the relationships between residual thrombus and clinical outcomes, we reviewed the distribution of thrombus scores, considered the clinical relevance of potential cut-points, and categorized patients into three groups by their total thrombus score on the immediate-post-PCDT venograms: (a) complete lysis (total thrombus score 0); (b) mild residual thrombus occupying < 25% of the veins' volume ( $0 < \text{total thrombus score} < 6$ ); and (c) substantial residual thrombus occupying  $\geq 25\%$  of the veins' volume (total thrombus score  $\geq 6$ ).

Differences between these residual thrombus groups were evaluated using an ANCOVA for continuous clinical outcomes and chi square test for categorical outcomes. Pairwise comparisons were examined using a Tukey post-hoc adjustment if the overall F test was significant.

Additionally, subgroup comparisons in age (<65 years,  $\geq 65$  years), sex (male, female), ethnicity (Hispanic, non-Hispanic), race (African-American, White, Other), body-mass index (< 25, 25-30,  $> 30 \text{ kg/m}^2$ ), leg symptom duration (<1 week,  $> 1$  week), side of DVT (left, right), presence of major provoking DVT risk factor (yes, no), and history of previous DVT or PE (yes, no) for complete thrombus removal (immediate post-PCDT total thrombus score 0) versus incomplete removal (immediate post-PCDT total thrombus score  $> 0$ ) were conducted using separate logistic regression and the odds ratios (OR) and 95% confidence interval are reported. Differences in the percent thrombus removal between these subgroups were also evaluated using Wilcoxon tests.

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

A study flow diagram is presented in **Figure 1**. In the overall trial, 337 patients were randomized to the PCDT Arm. One patient was found to not have qualifying proximal DVT immediately after randomization and was excluded from all analyses. Eleven patients who were randomized to receive PCDT did not have the procedure within 7 days, and an additional eight patients did not undergo PCDT because the initial venogram was negative for proximal vein thrombus. Hence, 317 PCDT Arm patients had their venograms included in this per-protocol analysis. In **Table 1**, baseline characteristics are presented for participants in the overall analysis (n=317) and for participants in the iliofemoral DVT (n=200) and femoral-popliteal DVT (n=117) subgroups.

### *Thrombus Removal on Independently Adjudicated Venograms*

For all vein segments evaluated, PCDT led to substantial thrombus volume reduction, as shown by reduction of the iliofemoral segment sub-score ( $p < 0.001$ ), femoral-popliteal segment sub-score ( $p < 0.001$ ), and total thrombus score ( $p < 0.001$ ) (**Table 2**). This was true for the entire PCDT Arm cohort, for iliofemoral DVT and femoral-popliteal DVT, and for all three PCDT methods (**Table 3**). As reported previously, the mean immediate-post-PCDT total thrombus score was 2.7 points  $\pm$  3.6 (total possible 24 points) (5). For the iliofemoral segment, the mean immediate-post-PCDT total thrombus score was 0.7 points  $\pm$  1.6, corresponding to about 7% of the volume of that segment (total possible 10 points) (**Table 2**). For the femoral-popliteal segment, the mean immediate post-PCDT total thrombus score was 2.0 points  $\pm$  2.9, corresponding to about 14% of the volume of that segment (total possible 14 points) (**Table 2**).

Complete thrombolysis (immediate-post-PCDT Marder score of 0) was observed in 88/297 (30%) of the overall proximal DVT population, in 50/184 (27%) of patients in the iliofemoral DVT subgroup, and in 38/113 (34%) of patients in the femoral-popliteal DVT subgroup.

Other than a suggestion that patients with shorter (< 1 week) symptom duration may have had complete thrombolysis more frequently ( $p=0.04$ ), other baseline variables (age  $\geq 65$  years, sex, race, Hispanic ethnicity, body-mass index, side of DVT, major provoking DVT risk factor, history of previous DVT) did not significantly influence the proportion of patients who had complete thrombolysis (**Figure 2A**) or the percentage of thrombus removed (**Figure 2B**).

#### *Operator-Assessed Procedure Success*

After PCDT, the endovascular operators reported the presence of antegrade flow in the iliofemoral venous segments of 313/317 (99%) patients, and in the femoral-popliteal venous segments of 281/317 (89%) patients (**Table 2**). Achievement of  $\geq 50\%$  clot lysis was reported in 303/317 (96%) patients, with  $\geq 90\%$  clot lysis reported in 234/317 (74%) patients. The results were consistent across both anatomical subgroups and all three PCDT methods used (**Table 3**).

A total of 313 patients had a patent iliofemoral venous segment on the post-PCDT venogram. In **Table E1**, their 1-month and 12-month outcomes are descriptively presented by whether the femoral-popliteal venous segment was also patent at procedure end. Over 24 months, point estimates of the occurrence of PTS (46% versus 60%,  $p = 0.17$ ) and moderate-or-severe PTS (17% versus 31%,  $p = 0.06$ ) appeared lower in the patients who also had femoral-popliteal venous patency compared with those in whom femoral-popliteal venous segment patency was not achieved. However, these associations did not reach statistical significance and there was no effect upon venous disease-specific QOL (**Table E2**).

### *Relationship of Immediate Post-PCDT Residual Thrombus to Ultrasound Outcomes*

As shown in **Table 4**, patients with valvular reflux or residual venous non-compressibility at 1 month and 12 months follow-up did not have evidence of less effective PCDT (higher immediate post-PCDT total thrombus scores) than patients who had non-refluxing or compressible veins. An exception was that patients with compressibility of the femoral-popliteal veins at 1 month had a lower volume of immediate-post-PCDT residual thrombus in the same named veins ( $p=0.0006$ ).

### *Relationship of Immediate Post-PCDT Residual Thrombus to Clinical Outcomes*

**Figure 3** depicts the relationships between the post-PCDT residual thrombus score and 24-month clinical outcomes. For the overall study population, the residual thrombus score did not exhibit a statistically significant correlation with the 24-month mean Villalta, VCSS, or VEINES-QOL scores. PCDT Arm patients who developed PTS did not have more end-of-procedure residual thrombus than PCDT Arm patients who did not develop PTS (mean total thrombus score 2.7 points  $\pm$  3.3 versus 2.7 points  $\pm$  3.9,  $p = 0.95$ ). PTS developed in 46% of patients with complete thrombolysis, in 47% of patients with minor residual thrombus (post-PCDT thrombus score 1-5), and in 53% of patients with substantial residual thrombus (post-PCDT thrombus score  $\geq 6$ , corresponding to  $\geq 25\%$  of the vein segments' volume). Moderate-or-severe PTS developed in 13% of patients with complete thrombolysis, in 21% of patients with minor residual thrombus, and in 25% of patients with substantial residual thrombus (**Figure 4**).

For the femoral-popliteal DVT subgroup, the findings were similar, with no statistically significant relationships between the amount of immediate post-PCDT residual thrombus and either the 1-month clinical outcomes (leg pain, Villalta score, venous QOL score) (**Table 5**) or the 24-month clinical outcomes (scores on PTS severity and venous QOL scales) (**Figure 3**).

For the iliofemoral DVT subgroup, patients with higher immediate-post-PCDT total thrombus scores had higher (worse) 24-month Villalta scores ( $p=0.0098$ ). Specifically, iliofemoral DVT patients with immediate-post-PCDT scores of 0 were found to have lower (better) Villalta scores at 24 months than those with immediate-post-PCDT scores of 1-5 ( $p=0.02$ ) and  $> 6$  ( $p=0.005$ ). Lower (worse), yet non-significant, VEINES-QOL scores were observed with increasing post-PCDT thrombus score categories ( $p=0.08$ ) (**Figure 3**). PTS developed in 44% of iliofemoral DVT patients with complete thrombolysis, in 49% of patients with minor residual thrombus, and in 48% of patients with substantial residual thrombus. Moderate-or-severe PTS developed in 8% of iliofemoral patients with complete thrombolysis and in 19% of patients with either minor or substantial residual thrombus (**Figure 4**). Patients with less immediate post-PCDT residual thrombus trended towards improved symptom status at 1 month, as shown by less pain ( $p=0.04$ ), lower Villalta scores ( $p=0.02$ ), and better venous disease-specific QOL ( $p=0.02$ ) (**Table 5**).

## Discussion

In ATTRACT, PCDT facilitated substantial thrombus removal and venous flow restoration.

However, in the overall proximal DVT population, the immediate-post-PCDT thrombus volume did not correlate with subsequent clinical outcomes or valvular reflux. In the iliofemoral DVT subgroup alone, a lower volume of immediate-post-PCDT residual thrombus was not associated with less frequent PTS but was associated with reduced 24-month PTS severity and probably also with better 1-month symptom status and venous QOL over 1 month and 24 months.

### Immediate Anatomic Results in the ATTRACT Trial

The current analyses demonstrate that PCDT in ATTRACT provided immediate anatomic results that were comparable to previous studies that reported independent core laboratory assessment of venograms. In an early urokinase CDT registry, Grade I (< 50%), Grade II (50-99%), or Grade III (100%) lysis was seen in 13%, 52%, and 34% of patients, respectively, equating to residual thrombus of at least 9% (weighted mean) of the vein volume as represented on the scale (19). In the CAVENT randomized trial, the venograms showed a mean residual thrombus of 9% of the vein volume (1.3 points on 14-point scale) to be present after CDT (20). In ATTRACT, residual thrombus occupied 11% of the vein volume post-PCDT (2.7 points on 24-point scale) (5).

Based largely on operator-reported findings, current SIR guidelines report about 92% of CDT-treated patients to have > 50% thrombus removal or restoration of iliofemoral venous patency; the guidelines propose performance thresholds of 80% on these parameters (21). In ATTRACT, 96% of PCDT-treated patients were reported to have  $\geq$  50% thrombus removal, and 99% had iliofemoral venous patency at procedure end. Hence, the immediate post-procedure results in ATTRACT exceeded SIR performance thresholds and the pooled results from past studies.



## Residual Thrombus and Clinical Outcome

*Overall Proximal DVT Study Population:* In the study's PCDT Arm, we did not identify strong relationships between immediate-post-PCDT residual thrombus volume and clinical outcomes. Specifically, (1) PCDT Arm patients who developed PTS over 2 years did not have more end-of-procedure thrombus than PCDT Arm patients who did not develop PTS; (2) even in patients with complete lysis (post-PCDT thrombus score of 0), 46% developed PTS and 13% developed moderate-or-severe PTS; and (3) although point estimates of the amount of post-PCDT residual thrombus appeared higher for patients who later developed valvular reflux, this relationship did not reach statistical significance. These findings are similar to those of the CAVENT Trial. In that study (3,4,20), the immediate-post-PCDT residual thrombus score in the CDT Arm did not correlate with development of PTS or with the continuous Villalta score over 24 months either.

*Iliofemoral DVT and Femoral-Popliteal DVT:* In patients with DVT limited to the femoral and popliteal veins, significant correlations were not observed between the immediate-post-PCDT residual thrombus score and early or late clinical outcomes. In contrast, in patients with iliofemoral DVT, a lower volume of immediate-post-PCDT residual thrombus correlated with reduced PTS severity over 2 years, and moderate-or-severe PTS developed in only 8% of iliofemoral DVT patients who had complete lysis. Associations with less severe leg pain, lower Villalta score, and better venous QOL at 1 month follow-up and with better venous disease-specific QOL at 24 months were highly suggestive but did not reach statistical significance.

## Re-Assessing the Open Vein Hypothesis

Although the open vein hypothesis is supported by a substantial body of published literature (22-29), this study's findings leave open the possibility that it may not be valid, or that it requires

substantial modification. Clearly, the pathophysiology of PTS remains poorly understood. Given that PCDT provided robust thrombus removal and venous patency restoration in this study, why did it fail to demonstrate a much larger effect upon long-term clinical outcomes?

In contrast with most previous studies, strengths of ATTRACT include its size, randomized design, performance of PCDT by a large number of credentialed physician operators, standardized assessor-blinded outcome assessment using validated instruments, venogram assessment by physician operators and independent readers, and overall methodological rigor.

On the other hand, in ATTRACT, operator assessments of venous flow were not independently adjudicated. The operators did not routinely utilize intravascular ultrasound (IVUS), which may be more sensitive than venography for evaluating residual thrombus and stenosis (30). However, during this study, IVUS was not an established element of standard practice for acute DVT therapy, and we are not aware of any well-validated IVUS scoring systems for venous thrombus. It has been speculated that PCDT outcomes could have been improved by more frequent, or less frequent, stent placement (31). Although venographically occult disease could have been missed in some patients, the small volume of post-PCDT residual iliofemoral thrombus and the near-universal iliofemoral venous patency restoration do not support the notion that a “failure to stent” influenced the study’s outcome or that additional intervention would have justified the risks.

Was PCDT in ATTRACT simply performed too late to prevent irreversible venous injury and PTS? In this analysis, patients randomized within 7 days after symptom onset may have had slightly greater thrombus removal and had a higher likelihood of complete lysis than patients randomized  $\geq 7$  days. But as reported previously, symptom duration  $< 7$  days did not influence the effect of PCDT upon the occurrence of PTS or moderate-or-severe PTS (5,7,8).

It is possible that differences between CDT and PCDT are relevant to long-term patient outcome. Among the CAVENT, CAVA, and ATTRACT Trials, only CAVENT observed an effect on PTS prevention (3). Unlike PCDT in ATTRACT, CDT in CAVENT did reduce valvular reflux (32). Visualization of the venous system in these studies was limited to axial veins above the sheath entry site. It remains possible that the safety/efficiency advantages of PCDT (relative to CDT) are offset by less complete restoration of inflow from axial (below-knee popliteal) or non-axial (tibial, profunda femoral) veins due to the reduced rt-PA exposure, or that the mechanical action of thrombectomy devices causes macroscopic or microscopic injury to the vein wall or valves.

Another potential explanation for the ineffectiveness of PCDT in preventing PTS is that the initial technical result was undermined by new thrombus deposition (perhaps with accompanying inflammation) over time. This is supported by the observed lack of correlation in this study between immediate thrombus removal and ultrasound findings at 1 and 12 months. Despite the high degree of thrombus removal by PCDT, approximately 20% of common femoral, 50% of femoral, and 60% of popliteal veins were incompletely compressible at 1 month (10). Similarly, in the urokinase CDT registry, the 1-year primary patency rate was just 60% (19). In CAVENT, at 6 months, only 66% of CDT-treated patients had patent veins and just 29% were free of residual thrombus and valvular reflux (20,32). Neither CAVENT nor ATTRACT saw a correlation between the status of the immediate-post-thrombolysis venogram and 2-year PTS in the thrombolysis-treated patients. However, both studies identified significant relationships between the subsequent status of the deep veins and PTS in the overall study. In CAVENT, 6-month and 24-month iliofemoral venous patency did correlate with PTS (20,32). In ATTRACT, ultrasound non-compressibility of the CFV at 1 month correlated with more PTS and moderate-or-severe PTS, and worse venous disease-specific QOL over 24 months ( $p < 0.01$ ) (10).

Hence, subclinical thrombus formation during the early weeks after CDT/PCDT may be more frequent than previously appreciated, and may undermine the long-term results of therapy. Additional study of the optimal anti-thrombotic strategy after CDT/PCDT is therefore warranted.

*Additional Limitations:* This analysis involved substantial multiple statistical testing. The study's sample size limited the analyses of subgroups and, in particular, the 1-year ultrasound outcome evaluation. Our analysis was limited to the PCDT Arm of the trial, with data skewing heavily towards very low post-PCDT thrombus scores. Hence, the applicability of our findings to non-PCDT-treated patients (who might have more extensive residual thrombus) is unknown.

### Conclusion

PCDT in ATTRACT was highly effective in removing venous thrombus and in restoring flow in patients with acute proximal DVT. However, the occurrence of PTS over 2 years did not parallel the degree of initial thrombus clearance. In patients with iliofemoral DVT, reduced immediate-post-PCDT thrombus burden appeared to correlate with reduced 2-year PTS severity, with better 1-month symptom status, and with better QOL. Future study of the open vein hypothesis should focus on iliofemoral DVT, with particular attention to how patency can be maintained over time. Other mechanisms of PTS pathogenesis also warrant investigation to reduce the burden of PTS.

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## Figure Captions

### Figure 1 - Patient Flow (CONSORT) Diagram

Patient flow and outcomes data capture in the PCDT Arm of the ATTRACT Trial (per-protocol analysis population).

### Figure 2 – Subgroup Analysis of Thrombus Removal with Pharmacomechanical Thrombolysis

Forest plots of odds ratios for the occurrence of complete thrombus removal (A) and the median percent thrombus removed (B) among subgroups of PCDT recipients. The horizontal lines represent 95% confidence intervals (CIs).

### Figure 3 - Association of Post-PCDT Residual Thrombus and 24 Month Clinical Outcomes

Analysis of covariance (ANCOVA) for association of post-PCDT residual thrombus (modified Marder score) with baseline-adjusted 24-month Villalta, VCSS, and VEINES-QOL scores in the following groups of PCDT recipients: (A) overall proximal DVT population; (B) iliofemoral DVT subgroup; and (C) femoral-popliteal DVT subgroup.

### Figure 4 - Proportion with Any and Moderate-or-Severe PTS by Post-PCDT Thrombus Score

Bar graphs depicting the occurrence of any PTS and moderate-or-severe PTS in patients who had complete thrombolysis (post-PCDT total thrombus score 0), mild residual thrombus (post-PCDT total thrombus score between 0 and 6), and substantial residual thrombus (post-PCDT total thrombus score > 6). Differences between the groups were evaluated using chi square tests. Pairwise comparisons were examined using a Tukey post-hoc adjustment if the overall F test was significant.

**Table 1. Baseline characteristics for participants who received initial PCDT\***

	PCDT Arm of ATTRACT Trial		
	Overall (N=317)	IF*** (N=200)	FP*** (N=117)
Age (years), <i>median (range)</i>	51.0 (16.0, 75.0)	51.0 (16.0, 75.0)	52.0 (16.0, 75.0)
Male, <i>n (%)</i>	192/317 (61%)	111/200 (56%)	81/117 (69%)
White, <i>n (%)</i>	251/317 (79%)	189/200 (80%)	92/117 (79%)
Hispanic or Latino, <i>n (%)</i>	15/317 (5%)	13/200 (7%)	2/117 (2%)
BMI (kg/m <sup>2</sup> ), <i>median (range)</i>	30.9 (18.4, 59.6)	30.9 (18.4, 57.6)	30.7 (19.9, 59.6)
eGFR (ml/min), <i>median (range)</i>	78.0 (39.0, 182.0)	80.0 (48.0, 182.0)	75.4 (39.0, 135.0)
DVT Left Leg, <i>n (%)</i>	199/317 (63%)	122/200 (61%)	77/117 (66%)
Any Previous DVT, <i>n (%)</i>	70/317 (22%)	52/200 (26%)	18/117 (15%)
Any Previous Ipsilateral DVT, <i>n (%)</i>	4/317 (1%)	4/200 (2%)	0/117 (0%)
Non-compressible CFV, <i>n (%)**</i>	175/300 (59%)	147/186 (79%)	28/114 (25%)
Non-compressible FV, <i>n (%)**</i>	279/300 (93%)	168/186 (90%)	111/114 (98%)
Non-compressible PV, <i>n (%)**</i>	260/300 (87%)	154/186 (80%)	106/114(96%)

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, IF = Iliofemoral, FP = Isolated Femoral Popliteal, SD=Standard Deviation

\*Per protocol dataset. 10 patients underwent venography but did not undergo PCDT – because this study is focused on mechanistic questions, they were excluded from this analysis.

\*\*Data is from pre-randomization baseline ultrasounds

\*\*\* For these analyses, patients were categorized in the IF and FP subgroups based on thrombus extent on the pre-PCDT venogram, irrespective of the findings on the baseline ultrasound.

**Table 2. Effect of PCDT upon Thrombus Volume and Venous Patency**

Thrombus Scores*	Independent Core Lab Assessment of Venograms**								
	All			IF			FP		
	Pre-lysis (N=317)	Post-lysis (N=317)	P-value	Pre-lysis (N=200)	Post-lysis (N=200)	P-value	Pre-lysis (N=117)	Post-lysis (N=117)	p-value
Iliac, <i>mean (SD)</i>	1.6 (2.4)	0.3 (1.0)	-	2.6 (2.6)	0.5 (1.2)	-	0.0 (0.0)	0.0 (0.0)	-
CFV, <i>mean (SD)</i>	1.7 (1.7)	0.4 (0.8)	-	2.8 (1.2)	0.6 (1.0)	-	0.0 (0.0)	0.0 (0.0)	-
Iliac and CFV subscore, <i>mean (SD)</i>	3.3 (3.7)	0.7 (1.6)	<0.001	5.4 (3.2)	1.1 (1.9)	<0.001	0.0 (0.0)	0.0 (0.0)	0.99
Femoral, <i>mean (SD)</i>	6.0 (3.6)	1.3 (2.2)	-	6.2 (3.8)	1.5 (2.4)	-	5.7 (3.2)	1.1 (1.8)	-
Popliteal, <i>mean (SD)</i>	2.2 (1.8)	0.7 (1.1)	-	1.8 (1.8)	0.6 (1.0)	-	2.8 (1.5)	0.9 (1.2)	-
Femoral and Popliteal subscore, <i>mean (SD)</i>	8.1 (4.8)	2.0 (2.9)	<0.001	7.9 (5.2)	2.0 (3.1)	<0.001	8.5 (4.0)	1.9 (2.5)	<0.001
Total Thrombus Score, <i>mean (SD)</i>	11.3 (5.7)	2.7(3.6)	<0.001	13.2 (5.9)	3.1 (4.1)	<0.001	8.5 (4.0)	1.9 (2.5)	<0.001
<b>End-of-Procedure Operator Assessment of Venograms</b>									
Anterograde flow in iliac and CFV, <i>n (%)</i>	313/317 (99%)			196/200 (98%)			117/117 (100%)		
Anterograde flow in FV and PV, <i>n (%)</i>	281/317 (89%)			177/200 (89%)			104/117 (89%)		
Estimate of clot lysis, proximal veins, <i>n (%)</i>									
>90%	234/317 (74%)			144/200 (72%)			90/117 (77%)		
75-90%	46/317 (15%)			29/200 (15%)			17/117 (15%)		
50-75%	23/317 (7%)			16/200 (8%)			7/117 (6%)		
< 50%	14/317 (4%)			11/200 (6%)			3/117 (3%)		

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, IF = Iliofemoral, FP = Isolated Femoral Popliteal

\*Marder scores (range 0 [no thrombus] to 24 [complete thrombosis])

\*\*15 patients initially stratified in the FP group based on pre-randomization ultrasound but were found to have thrombus in the iliofemoral segment, so they were considered to belong to the IF group in this analysis

**Table 3. Immediate Thrombus Removal and Venous Patency by Thrombolytic Technique Used**

Thrombus Scores*	Independent Core Lab Assessment of Venograms								
	Technique A Trellis (N=50)		p-value	Technique B Angiojet (N=75)		p-value	Technique C Infusion-First (N=192)		p-value
	Pre-lysis	Post-lysis		Pre-lysis	Post-lysis		Pre-lysis	Post-lysis	
Iliac, <i>mean (SD)</i>	2.5 (2.7)	0.5 (1.2)	-	1.7 (2.4)	0.3 (0.9)	-	1.3 (2.3)	0.3 (0.9)	-
CFV, <i>mean (SD)</i>	2.4 (1.6)	0.6 (0.8)	-	1.7 (1.7)	0.4 (0.9)	-	1.6 (1.7)	0.4 (1.0)	-
Iliac and CFV subscore, <i>mean (SD)</i>	4.9 (3.7)	1.1 (1.7)	<0.001	3.3 (3.5)	0.6 (1.6)	<0.001	2.9 (3.6)	0.6 (1.6)	<0.001
Femoral, <i>mean (SD)</i>	4.9 (3.9)	1.0 (1.9)	-	3.8 (3.3)	0.7 (1.6)	-	7.1 (3.1)	1.7 (2.3)	-
Popliteal, <i>mean (SD)</i>	1.3 (1.8)	0.3 (0.8)	-	1.4 (1.6)	0.4 (0.9)	-	2.7 (1.6)	0.9 (1.2)	-
Femoral and Popliteal subscore, <i>mean (SD)</i>	6.1 (5.1)	1.2 (2.4)	<0.001	5.1 (4.3)	1.1 (2.2)	<0.001	9.7 (4.1)	2.5 (3.1)	<0.001
Total Thrombus score, <i>mean (SD)</i>	10.8 (6.7)	2.3 (2.9)	<0.001	8.4 (4.5)	1.7 (2.8)	<0.001	12.6 (5.5)	3.1 (4.0)	<0.001
End-of-Procedure Operator Assessment of Venograms									
Anterograde flow in both the iliac and CFV vein, <i>n (%)</i>	47/50 (94%)		-	75/75 (100%)		-	191/192 (99%)		-
Anterograde flow in both the FV and PV, <i>n (%)</i>	46/50 (92%)		-	71/75 (95%)		-	164/192 (85%)		-
Estimate of clot lysis in all proximal veins, <i>n (%)</i>			-			-			-
>90%	40/50 (80%)			56/75 (75%)			138/192 (72%)		
75-90%	4/50 (8%)			9/75 (12%)			33/192 (17%)		
50-75%	4/50 (8%)			6/75 (8%)			13/192 (7%)		
< 50%	2/50 (4%)			4/75 (5%)			8/192 (4%)		

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

\*Marder scores



**Table 4. Association between Immediate-Post-PCDT Residual Thrombus and Ultrasound Outcomes**

		Immediate-Post-PCDT Thrombus* Scores				
		N	Mean (SD)	N	Mean (SD)	p-value^
<b>Total Thrombus Score</b>	<b><u>1 Month</u></b>	<b>Yes</b>		<b>No</b>		
	CFV compressible	225	2.4 (3.4)	58	3.2 (4.0)	0.23
	FV/PV compressible	99	2.0 (2.8)	187	2.9 (3.8)	0.06
	<b><u>12 Months</u></b>					
	CFV compressible	54	1.9 (2.6)	8	1.6 (1.4)	0.73
	FV/PV compressible	28	1.7 (2.9)	34	2.1 (2.0)	0.54
	Any reflux	50	1.7 (2.2)	9	3.1 (3.9)	0.14
	Deep vein reflux	49	1.8 (2.2)	10	2.8 (3.8)	0.24
	Superficial vein reflux	26	1.9 (2.1)	31	1.9 (2.9)	0.98
<b>IF Sub-Score</b>	<b><u>1 Month</u></b>					
	CFV compressible	225	0.5 (1.5)	58	1.1 (1.5)	0.15
	FV/PV compressible	99	0.8 (1.7)	187	0.6 (1.5)	0.34
	<b><u>12 Months</u></b>					
	CFV compressible	54	0.4 (1.3)	8	0.5 (0.5)	0.62
	FV/PV compressible	28	0.9 (1.7)	34	0.1(0.3)	0.07
	Any reflux	50	0.4 (1.0)	9	1.0 (2.4)	0.21
	Deep vein reflux	49	0.4 (1.0)	10	0.9 (2.3)	0.27
	Superficial vein reflux	26	0.3 (1.0)	31	0.6 (1.5)	0.44
<b>FP Sub-Score</b>	<b><u>1 Month</u></b>					
	CFV compressible	225	1.9 (2.7)	58	2.2 (3.1)	0.54
	FV/PV compressible	99	1.3 (2.2)	187	2.3 (2.9)	0.006
	<b><u>12 Months</u></b>					
	CFV compressible	54	1.5 (2.0)	8	1.3 (1.4)	0.84
	FV/PV compressible	28	0.9 (1.6)	34	2.0 (2.0)	0.03
	Any reflux	50	1.4 (1.9)	9	2.2 (2.1)	0.28
	Deep vein reflux	49	1.5 (1.9)	10	2.0 (2.1)	0.44
	Superficial vein reflux	26	1.6 (2.1)	31	1.4 (1.9)	0.65

\*Marder scores

^p-values are adjusted for the baseline CFV and FV/PV compressibility for 1 and 12 months.

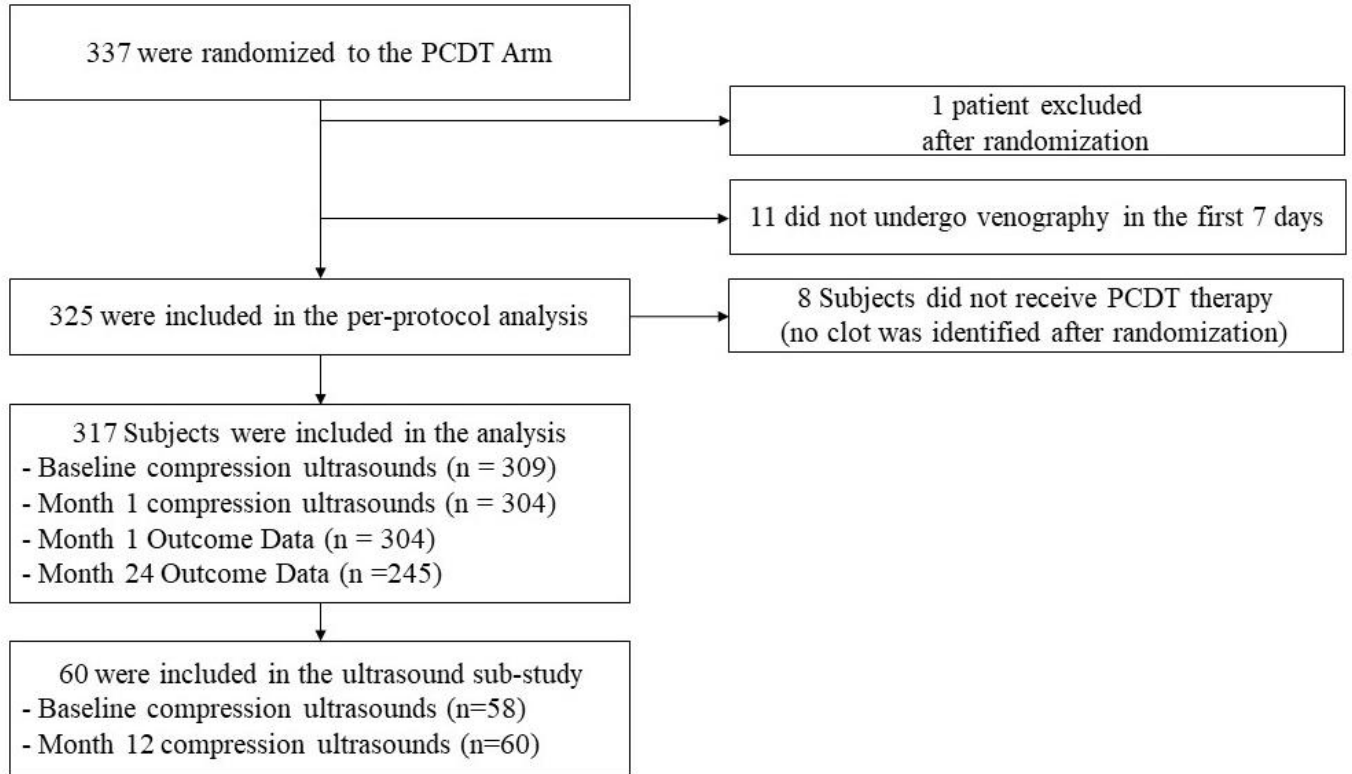
CFV=Common Femoral Vein, FV=Femoral Vein, PCDT=Pharmacomechanical Catheter-Directed Thrombolysis, PV=Popliteal Vein, SD=Standard Deviation, IF = Iliofemoral, FP = Isolated Femoral Popliteal, PTS=post-thrombotic syndrome

**Table 5. One-Month Clinical Outcomes by Total Thrombus Score Categories (0, 1 to 5, 6+)**

<b>1 Month Outcome</b>	<b>Total Thrombus Score</b>	<b>All Patients</b>	<b>p-value</b>	<b>IFDVT</b>	<b>p-value<sup>^</sup></b>	<b>FPDVT</b>	<b>p-value</b>
Leg Pain, Likert Scale, <i>Adjusted mean, Std Err</i>	<b>0</b>	2.1 (0.1)	0.23	1.7 (0.2)	0.04	2.5 (0.2)	0.42
	<b>1 to 5</b>	2.1 (0.1)		2.1 (0.1)		2.2 (0.2)	
	<b>6+</b>	2.5 (0.2)		2.4 (0.2)		2.7 (0.5)	
Villalta score, <i>Adjusted mean, Std Err</i>	<b>0</b>	4.3 (0.4)	0.21	3.1 (0.5)	0.02	5.7 (0.8)	0.45
	<b>1 to 5</b>	4.4 (0.3)		4.1 (0.4)		4.8 (0.6)	
	<b>6+</b>	5.6 (0.7)		5.4 (0.7)		6.6 (1.6)	
VEINES-QOL, <i>Adjusted mean, Std Err</i>	<b>0</b>	66.1 (2.3)	0.11	71.1 (2.8)	0.02	59.6 (3.8)	0.11
	<b>1 to 5</b>	65.8 (1.7)		63.9 (2.0)		68.5 (2.9)	
	<b>6+</b>	58.3 (3.4)		58.5 (3.7)		57.6 (7.7)	

<sup>^</sup> Leg Pain Severity (0 vs 6+, p=0.01), Villalta scores (0 vs 6+, p=0.007), and VEINES QOL (0 vs 6+, p=0.007; 0 vs 1 to 5, p=0.04)

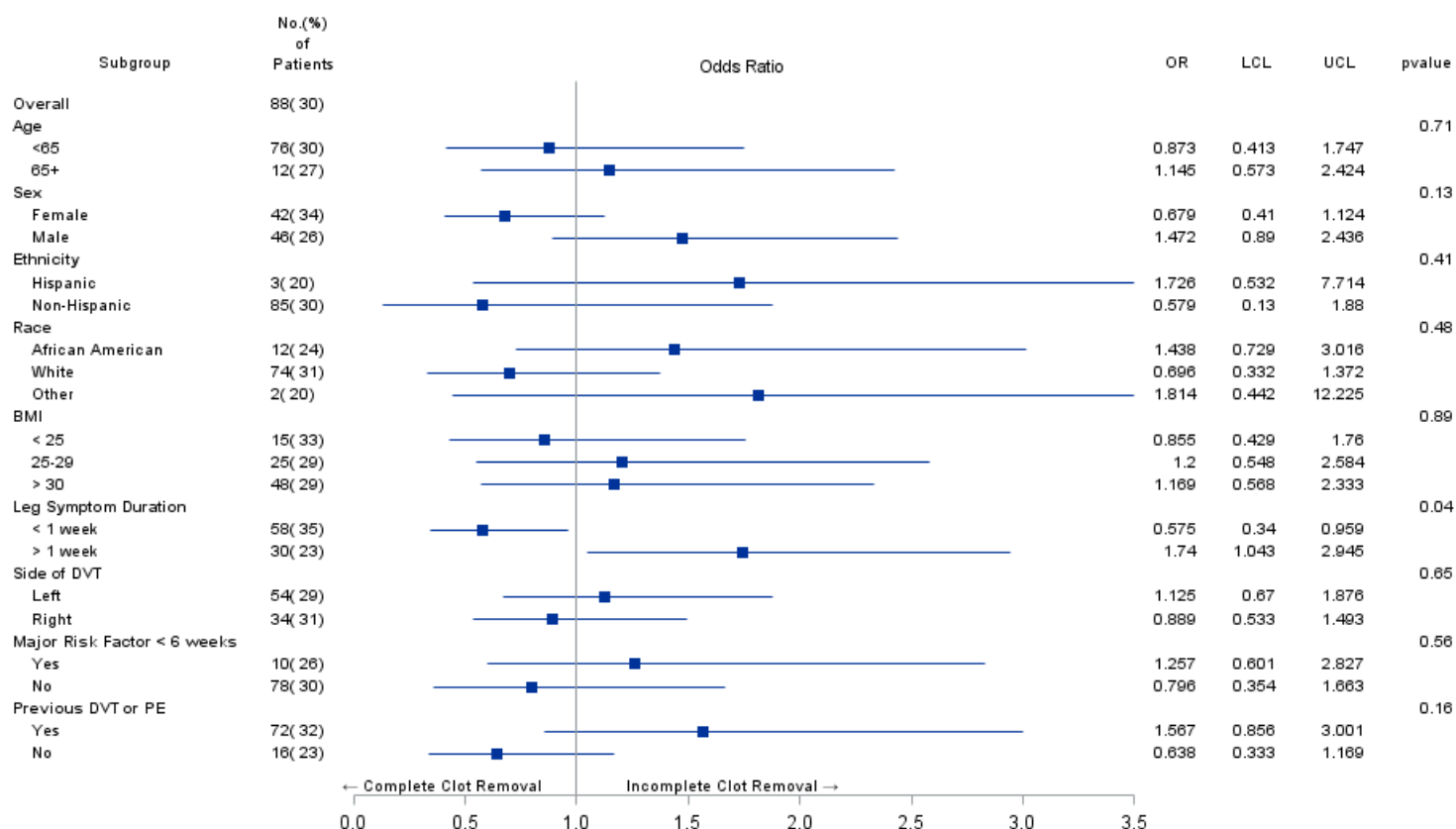
**Figure 1. Patient Flow (CONSORT) Diagram**



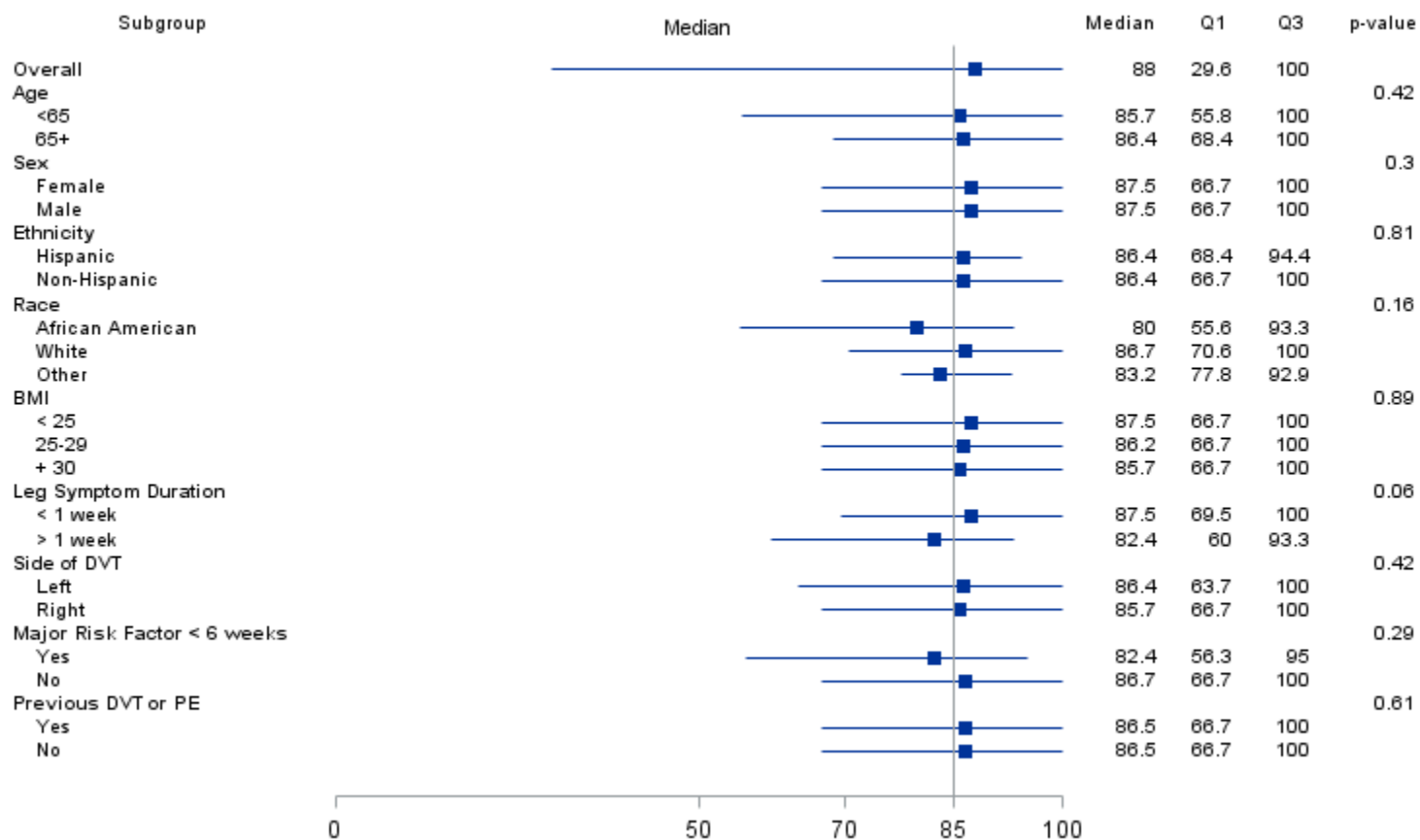
**Figure 2. Subgroup Analysis of Thrombus Removal with Pharmacomechanical Thrombolysis**

A. Proportion with Complete Thrombus Removal by Subgroup

B. Percentage of Thrombus Removed by Subgroup

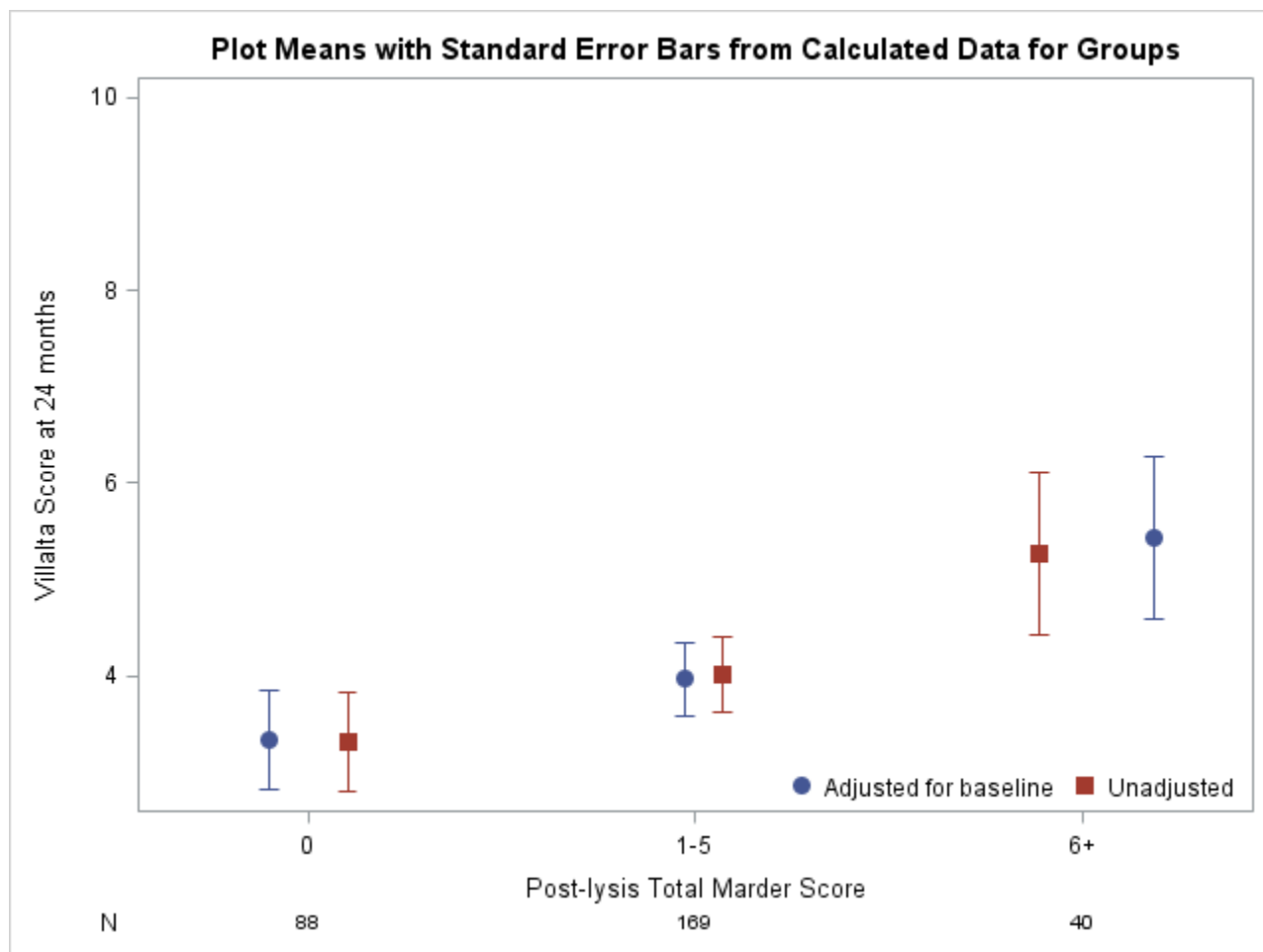


Forest Plots of Percent Clot Removal within Subgroups



**Figure 3. Association of Post-PCDT Residual Thrombus and 24 Month Clinical Outcomes**

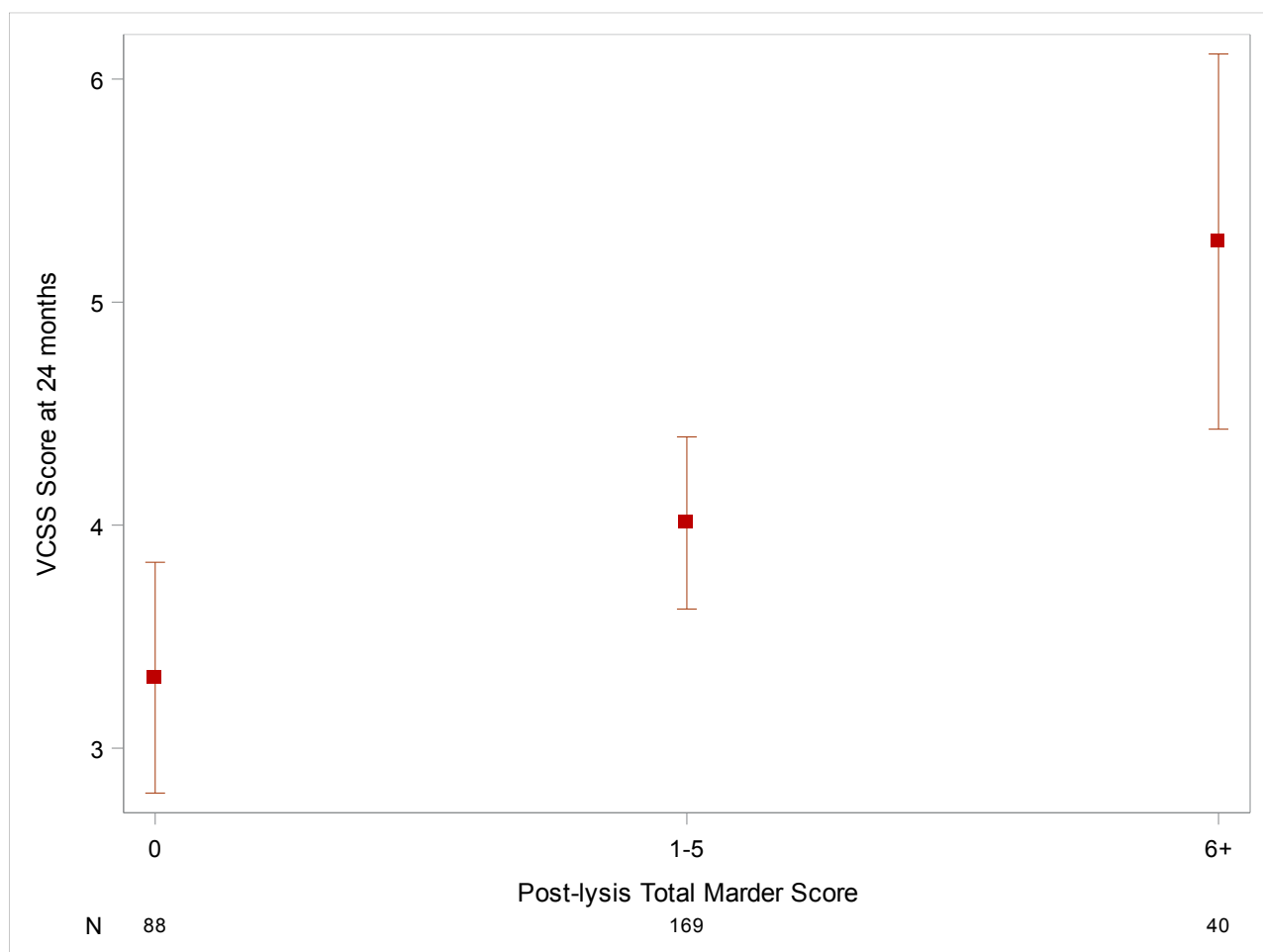
A. All Proximal DVT Patients: Post-PCDT total thrombus score versus 24 month Villalta, VCSS, VEINES-QOL



*Unadjusted p-value = 0.1382*

*Adjusted p-value = 0.1035*

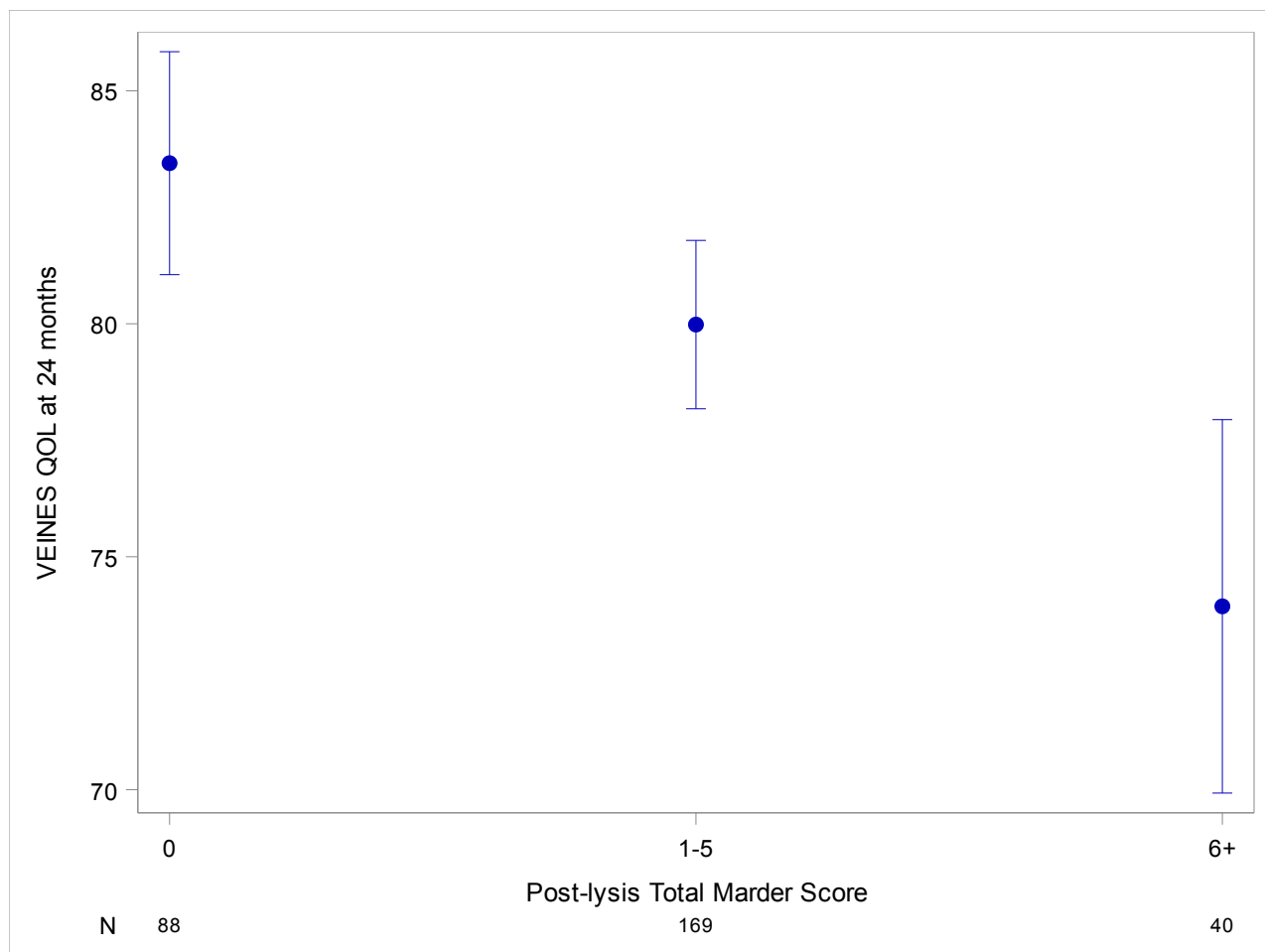
## All Proximal DVT



*Unadjusted p-value = 0.2186*

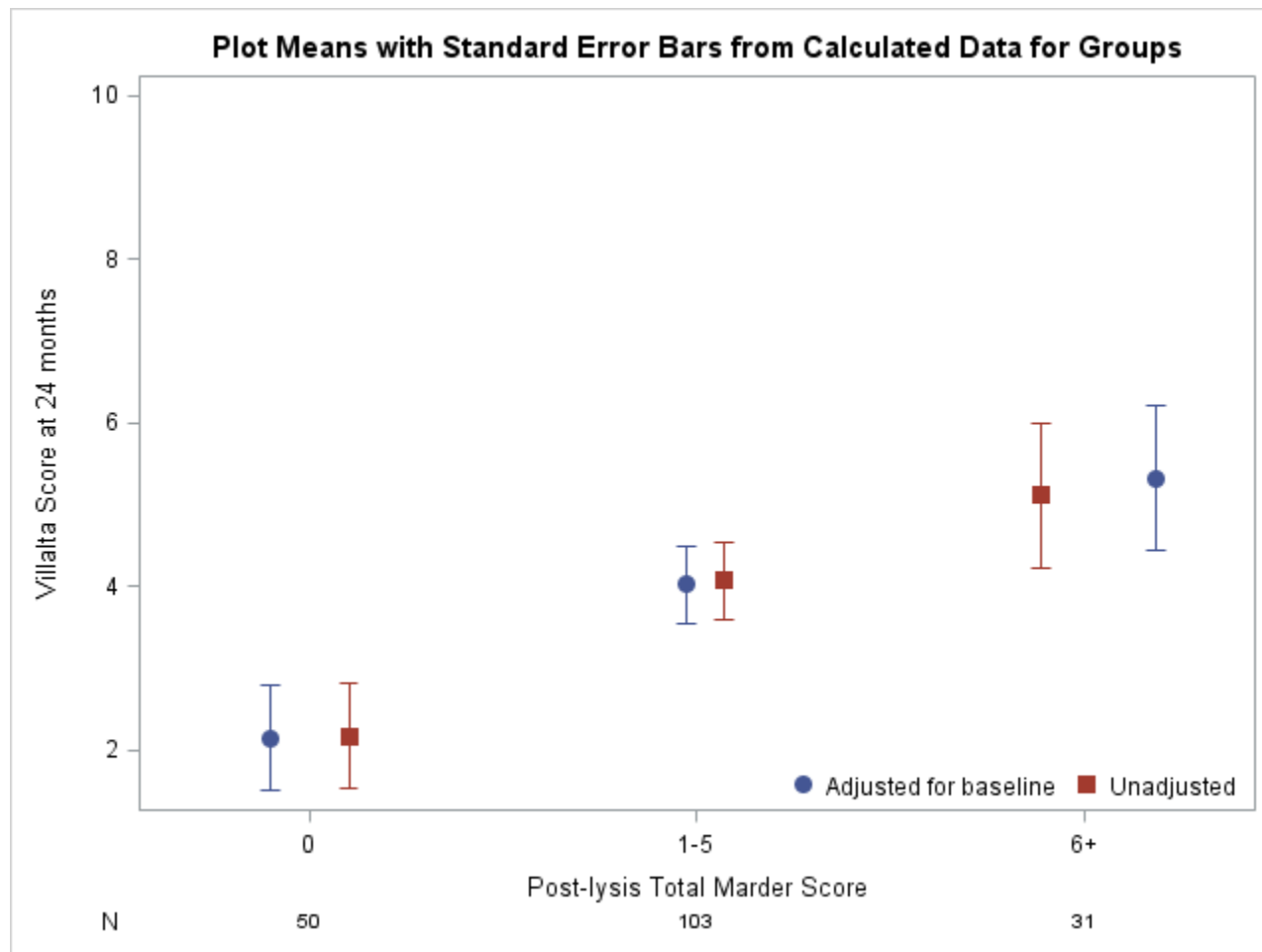


## All Proximal DVT



*Adjusted p-value = 0.1203*

B. Iliofemoral DVT Patients: Post-PCDT total Marder score versus 24 month Villalta, VCSS, VEINES-QOL

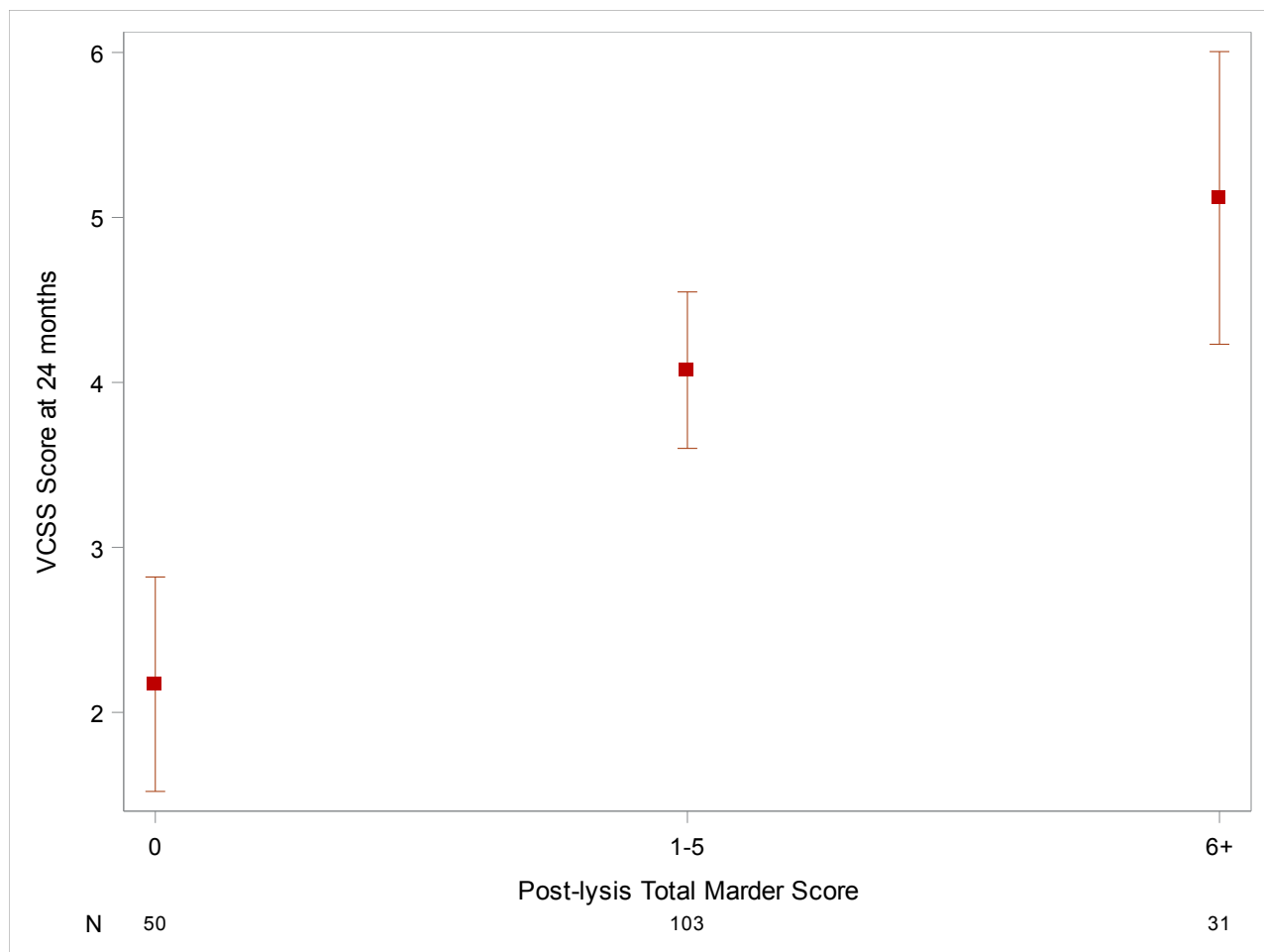


*Unadjusted p-value = 0.0146*

*Adjusted p-value = 0.0098*

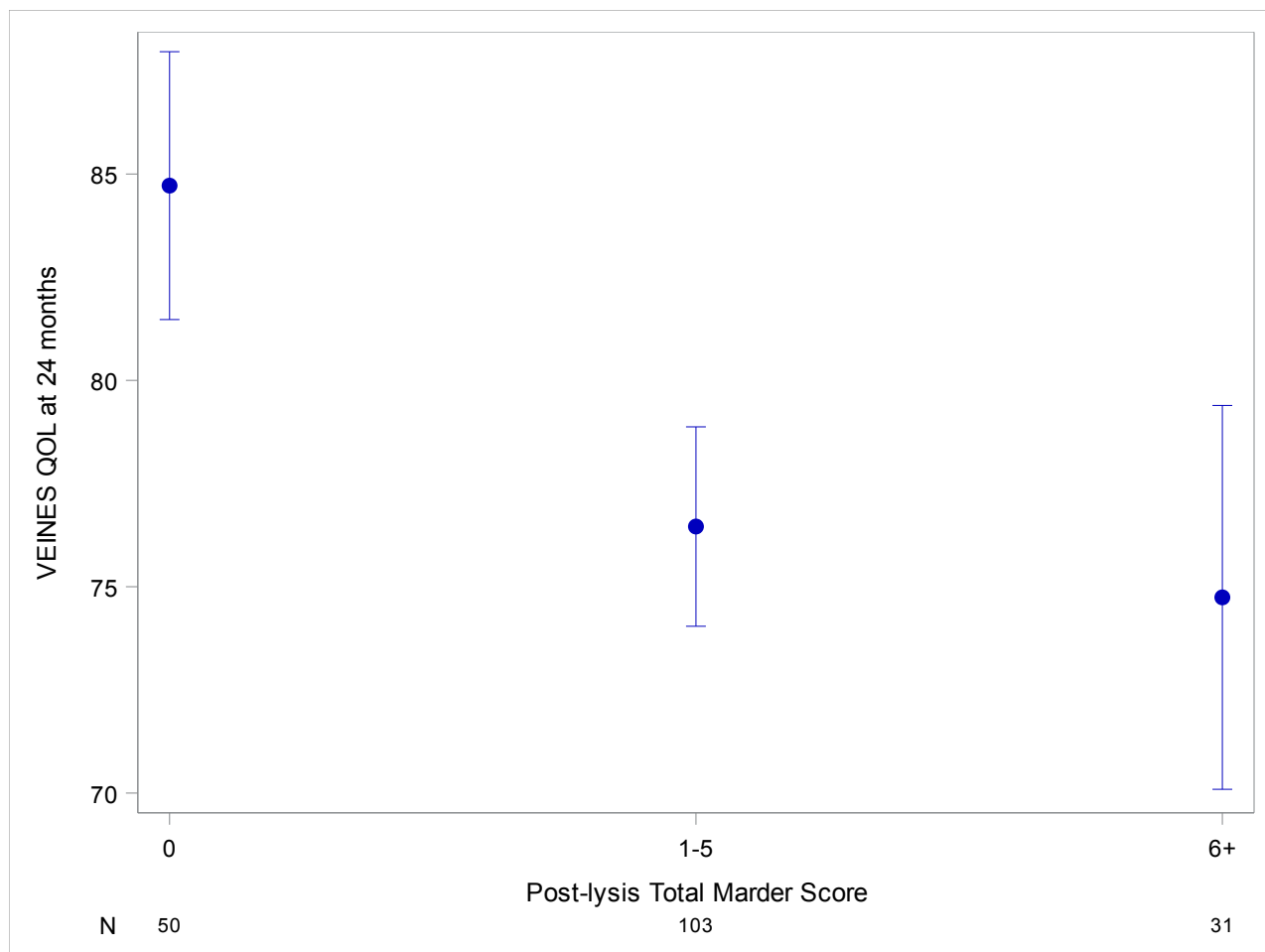
*Adjusted, 0 vs 6+,  $p=0.0046$*

## Iliofemoral DVT



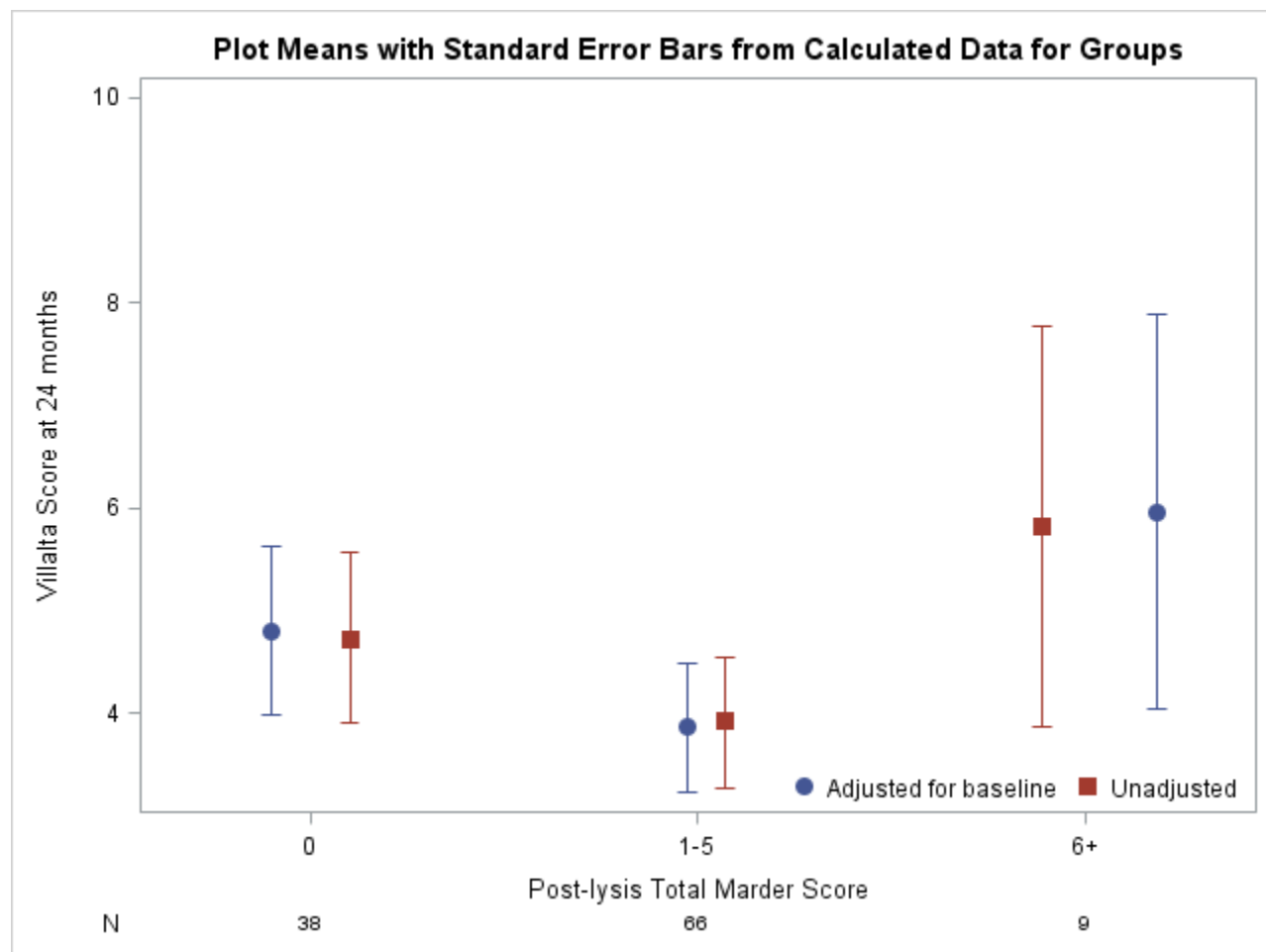
*Unadjusted p-value = 0.1233*

## Iliofemoral DVT



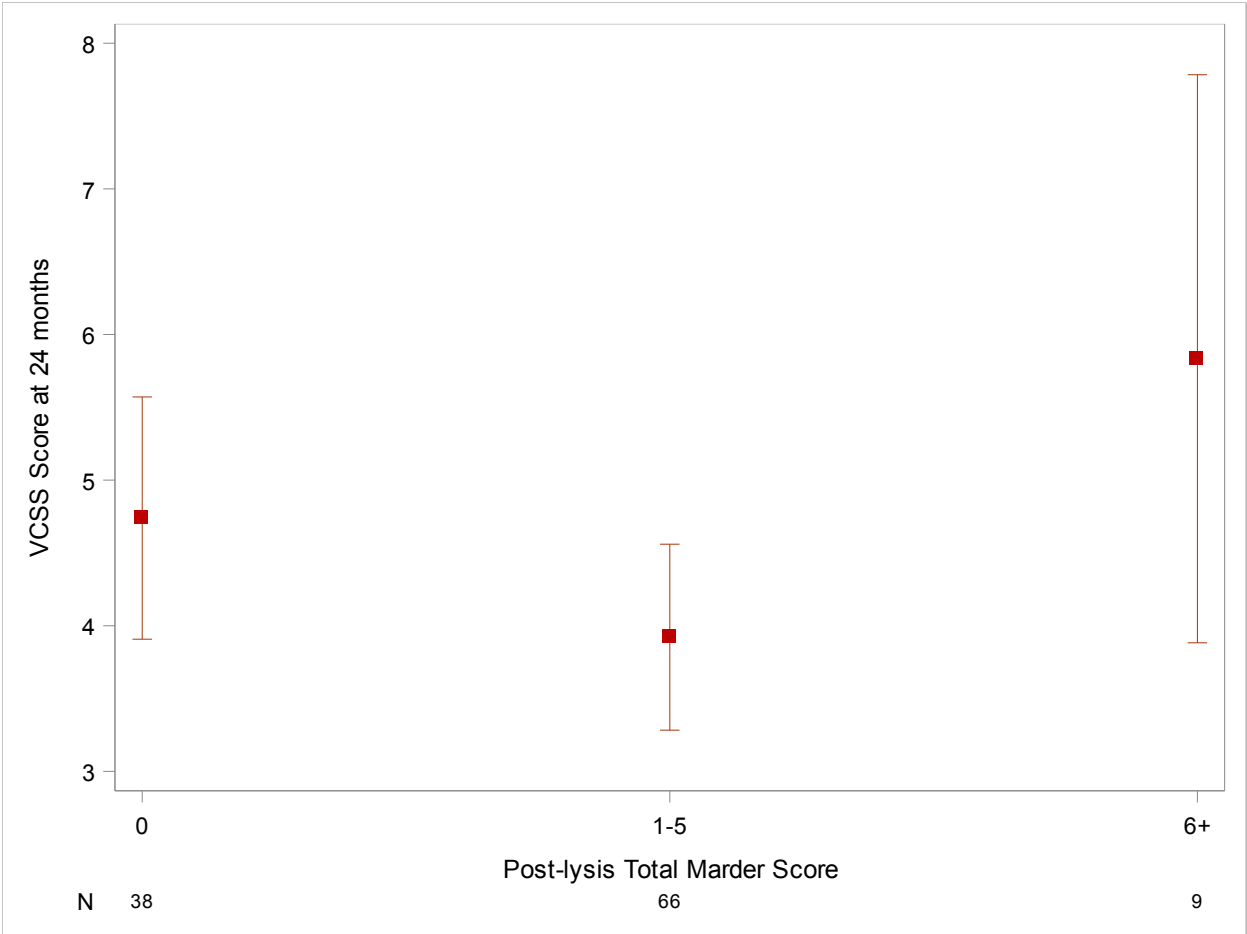
*Adjusted p-value = 0.0849*

C. Femoral-Popliteal DVT Patients: Post-PCDT total Marder score versus 24 month Villalta, VCSS, VEINES-QOL



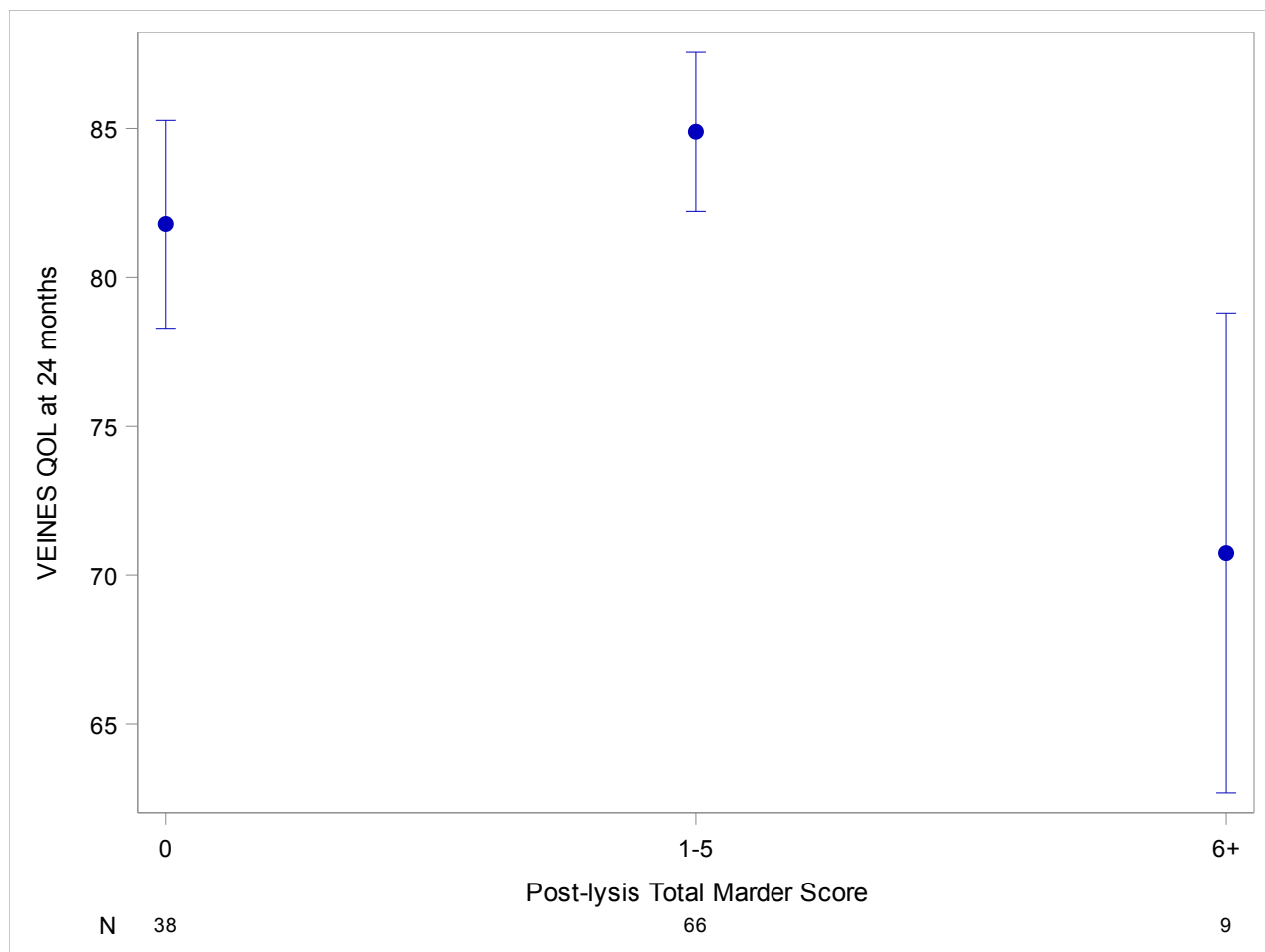
*Unadjusted p-value = 0.5386*

*Adjusted p-value = 0.4496*



*Unadjusted p-value = 0.8561*

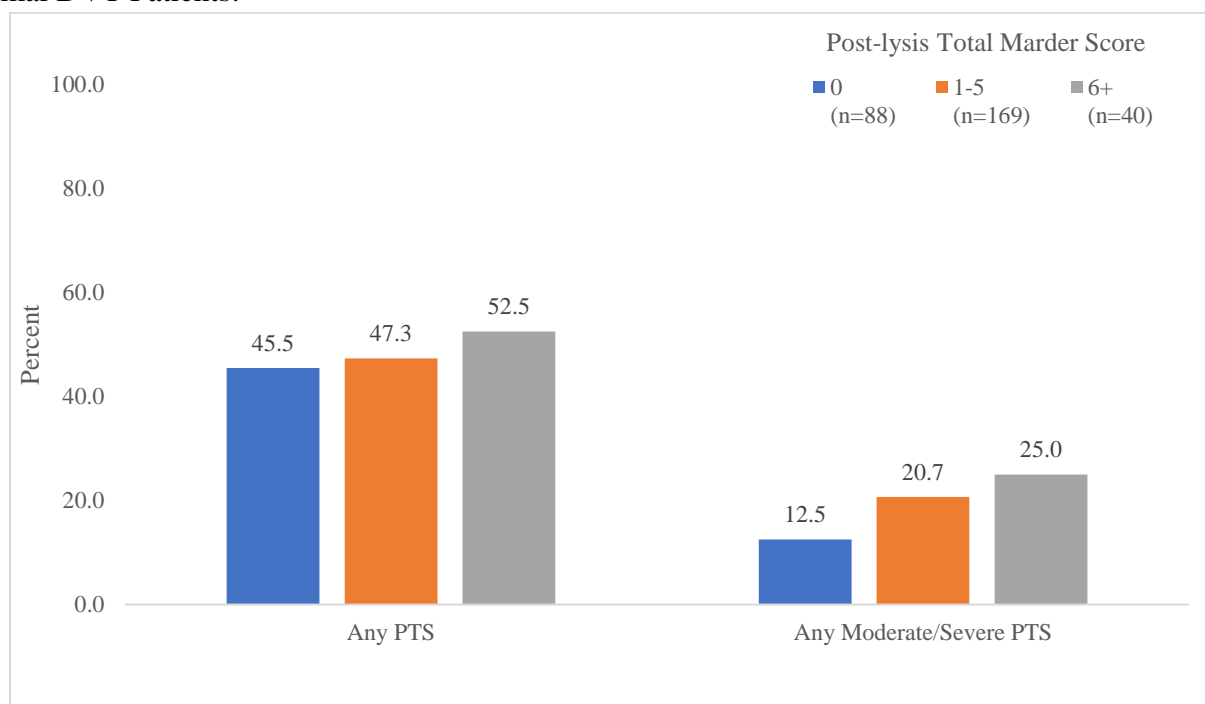
## Femoral-Popliteal DVT



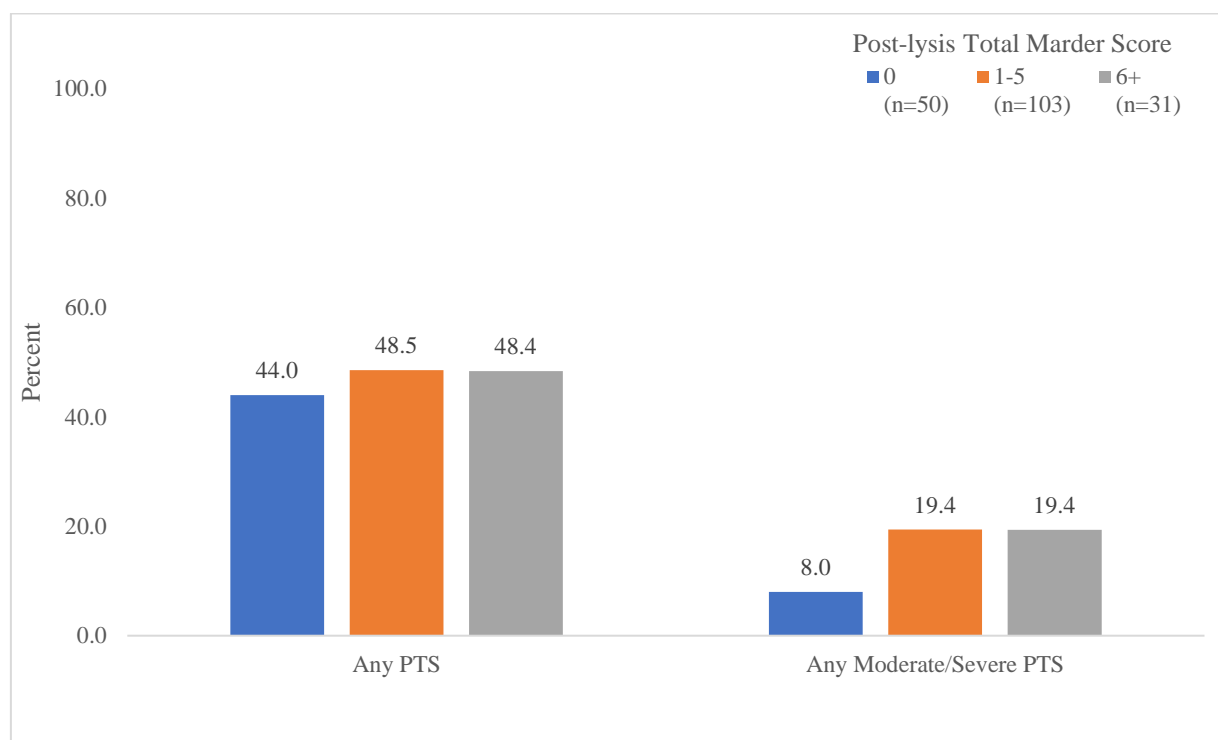
*Adjusted p-value = 0.2386*

**Figure 4. Proportion with Any and Moderate-or-Severe PTS by Post-PCDT Total Thrombus score**

**A. All Proximal DVT Patients:**

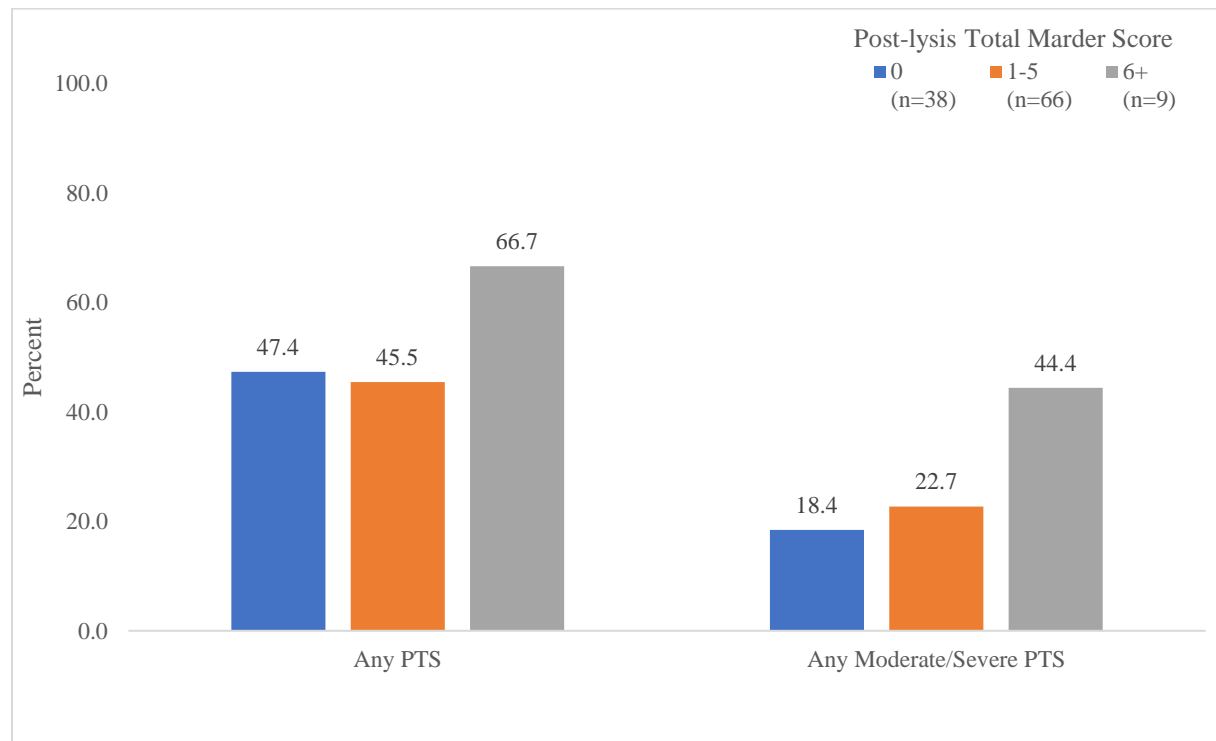


**B. Iliofemoral DVT Patients:**





C. Femoral-Popliteal DVT Patients:





**Table E2. Effect of immediate post-PCDT femoral-popliteal venous patency on 24 month clinical outcomes in patients with an open iliofemoral (IF) venous segment\***

<b>Outcomes</b>	<b>Operator-assessed post PCDT status of femoral-popliteal venous segment</b>		
	<b>Patent (n=281)</b>	<b>Not Patent (n=32)</b>	<b>p-value</b>
<b><u>24 Months</u></b>			
Any PTS, <i>n (%)</i> **	121/281 (46%)	19/32 (60%)	0.17
Moderate-or-Severe PTS, <i>n (%)</i> **	45/281 (17%)	10/32 (31%)	0.06
Villalta score, <i>mean (SD)</i>	3.8 (4.4)	4.9 (4.9)	0.82^
VCSS, <i>mean (SD)</i>	2.0 (2.7)	2.0 (2.3)	0.99
VEINES-QOL, <i>mean (SD)</i>	80.9 (21.2)	79.2 (18.5)	0.89^

\* 4 subjects did not have a patent iliofemoral venous segment post-PCDT, and were not included in the analysis in this table

\*\*Denominator is based on available scores at each time point

^Comparison adjusts for baseline

CFV=Common Femoral Vein, FV=Femoral Vein, PCDT=Pharmacomechanical Catheter-Directed Thrombolysis, PV=Popliteal Vein, SD=Standard Deviation, IF = Iliofemoral, FP = Isolated Femoral Popliteal, PTS=post-thrombotic syndrome