Predictors of Clinical Outcomes of Pharmacomechanical Catheter-Directed Thrombolysis for Acute Iliofemoral Deep Vein Thrombosis: Analysis of a Multicenter Randomized Trial

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ABSTRACT

Purpose: To identify the baseline patient characteristics that predict who will benefit from pharmacomechanical catheter-directed thrombolysis (PCDT) of acute iliofemoral deep vein thrombosis (DVT).

Materials and Methods: In the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) multicenter randomized trial, 381 patients with acute iliofemoral DVT underwent PCDT and anticoagulation or anticoagulation alone. The correlations between baseline factors and venous clinical outcomes were evaluated over 24 months using post hoc regression analyses. Interaction terms were examined to evaluate for differential effects by treatment arm.

Results: Patients with clinically severe DVT (higher baseline Villalta score) experienced greater effects of PCDT in improving 24-month venous outcomes, including moderate or severe postthrombotic syndrome (PTS) (odds ratios [ORs] and 95% confidence intervals [CIs] per unit increase in the baseline Villalta scores were as follows: for PCDT, OR, 1.08 [95% CI, 1.01–1.15]; for control, OR, 1.20 [95% CI, 1.12–1.29]; $P_{interaction}$ = .03), PTS severity (between-arm differences in the Villalta [$P_{interaction}$ = .004] and Venous Clinical Severity Scale [VCSS] [$P_{interaction}$ = .002)] scores), and quality of life (between-arm difference in the Venous Insufficiency Epidemiological and Economic Study Quality of Life score; $P_{interaction}$ = .025). Patients with previous DVT had greater effects of PCDT on 24-month PTS severity than those in patients without previous DVT (mean [95% CI] between-arm difference in the Villalta score, 4.2 [1.56–6.84] vs 0.9 [–0.44 to 2.26], $P_{interaction}$ = .03; mean [95% CI] between-arm difference in the VCSS score, 2.6 [0.94–4.21] vs 0.3 [–0.58 to 1.14], $P_{interaction}$ = .02). The effects of PCDT on some but not all outcomes were greater in patients presenting with left-sided DVT (Villalta PTS severity, $P_{interaction}$ = .04; venous ulcer, $P_{interaction}$ = .0499) or a noncompressible popliteal vein (PTS, $P_{interaction}$ = .02). The effects of PCDT did not vary by sex, race, ethnicity, body mass index, symptom duration, hypertension, diabetes, or hypercholesterolemia.

Conclusions: In patients with acute iliofemoral DVT, greater presenting clinical severity (higher baseline Villalta score) and a history of previous DVT predict enhanced benefits from PCDT.

ABBREVIATIONS

ATTRACT = Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis, BMI = body mass index, CDT = catheter-directed thrombolysis, CI = confidence interval, DVT = deep vein thrombosis, OR = odds ratio, PCDT = pharmacomechanical catheter-directed thrombolysis, PTS = postthrombotic syndrome, QOL = quality of life, VCSS = Venous Clinical Severity Scale, VEINES-QOL = Venous Insufficiency Epidemiological and Economic Study Quality of Life, VEINES-Sym = Venous Insufficiency Epidemiological and Economic Study Symptoms

Patients with acute iliofemoral deep vein thrombosis (DVT) frequently develop postthrombotic syndrome (PTS) (1). Catheter-directed thrombolysis (CDT) (image-guided intrathrombus fibrinolytic drug administration) and pharmacomechanical CDT (PCDT) (includes mechanical thrombectomy devices) have been used to treat iliofemoral

Figures E1–E15 and Appendices A and B can be found by accessing the online version of this article on www.jvir.org and selecting the Supplemental Material tab.

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RESEARCH HIGHLIGHTS

- A post hoc analysis of the iliofemoral deep vein thrombosis subgroup of the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) multicenter randomized trial was performed to identify baseline predictors of the treatment effect of pharmacomechanical catheter-directed thrombolysis (PCDT) on the primary and secondary venous outcomes over 24 months.
- Patients with higher baseline Villalta scores experienced greater effects of PCDT in reducing postthrombotic syndrome (PTS) severity, reducing the occurrence of moderate or severe PTS, and improving venous quality of life over 24 months.
- Patients with previous deep vein thrombosis also had greater effects of PCDT in reducing 24-month PTS severity.

DVT for many years (2). In the iliofemoral DVT subgroup of the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial, PCDT led to thrombus reduction and restoration of venous patency in most of the treated patients but did not reduce the occurrence of PTS over 24 months (3). PCDT did improve important secondary outcomes; however, the mean size of these benefits and the associated improvements in health-related quality of life (QOL) were modest (4). Because the trial also observed increased major bleeding in patients undergoing PCDT, it is likely that PCDT is an optimal first-line treatment for some, but not all, patients with iliofemoral DVT (5).

Published reports (3–5) from the ATTRACT trial have evaluated the correlations of a limited number of prespecified baseline factors with PCDT treatment effects, with a central focus on the study's primary outcome (cumulative occurrence of PTS over 24 months). However, additional data elements were collected at study entry to characterize the study population, including demographic factors, comorbidities, and characteristics of the index DVT. The key secondary outcomes that appeared to be favorably influenced by PCDT included the severity of PTS, occurrence of moderate or severe PTS, and venous disease–specific QOL (3–5). This study describes a post hoc exploratory analysis aimed at identifying additional baseline predictors of PCDT treatment effect on 24-month outcomes in patients with acute iliofemoral DVT.

MATERIALS AND METHODS

Study Design, Patients, and Treatments

This study is a post hoc analysis of the iliofemoral DVT subgroup of the ATTRACT trial, a phase III, multicenter, open-label, assessor-blinded, randomized controlled trial. All patients provided written informed consent. The study was approved by the institutional review boards of all clinical centers (**Appendix A**, available online on the article's Supplemental Material page at *www.jvir.org*). The population, methods, and main outcomes of the ATTRACT trial and its iliofemoral DVT subgroup have been previously described (3–5). Briefly, patients with acute symptomatic proximal DVT were randomly assigned to undergo or not undergo PCDT for initial DVT treatment at 56 U.S. clinical centers. Randomization was stratified by clinical center and on the basis of whether there was involvement of the iliac or common femoral vein (iliofemoral DVT) or not (femoral-popliteal DVT) at baseline. All study patients were to undergo anticoagulant therapy and wear elastic compression stockings (BSN Medical, Luxembourg, Luxembourg); in addition, patients in the PCDT arm underwent PCDT at a median of 1 day after randomization. PCDT involved intrathrombus delivery of a recombinant tissue plasminogen activator (alteplase, Activase; Genentech, South San Francisco, California) by board-certified physicians using 1 of several methods, after which they used catheter aspiration, mechanical thrombectomy, balloon maceration, and/or stent placement to restore venous patency (5).

STUDY DETAILS

Study Type: Randomized controlled trial

Study Phase: III

Level of Evidence: 2 (SIR-B)

This analysis included 381 ATTRACT patients with acute iliofemoral DVT who actually received their study-assigned treatment within 7 days (per-protocol study population) (**Fig 1**).

Baseline Characteristics

Previous publications (3–5) have summarized subgroup analyses for 11 categorically expressed baseline factors that were prespecified in the study's statistical analysis plan. This post hoc analysis considered a more detailed set of potential PCDT effect predictors collected at baseline, including demographic characteristics (sex, continuous age, race, and Hispanic/Latino ethnicity), medical history (hypertension, diabetes, hypercholesterolemia, previous DVT, and continuous body mass index [BMI]), and index DVT features (right or left leg, provoked or unprovoked, popliteal vein compressibility, continuous DVT symptom duration, and continuous Villalta clinical severity scores). For some factors, categories that did not constitute at least 10% of the population were combined with an adjacent category for analysis (**Appendix B**, available online at *www.jvir.org*). The distributions of baseline factors were well balanced between the 2 treatment groups (**Table**).

Clinical Outcomes

Patient outcomes were assessed at 6, 12, 18, and 24 months after randomization by blinded clinician examiners. PTS was evaluated with the Villalta scale, in which 4 patient-reported

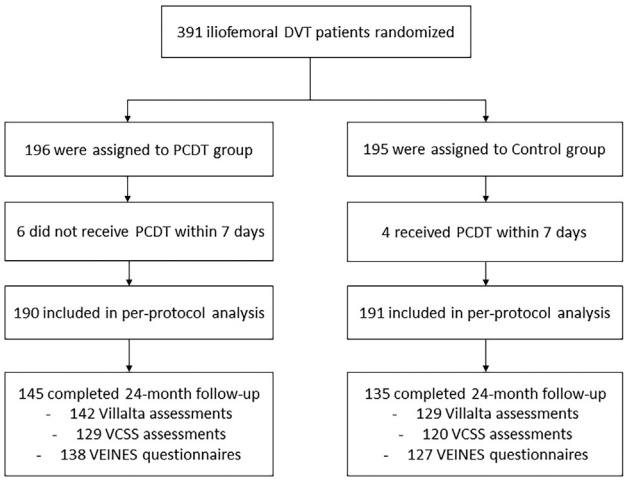

Figure 1. Patient flow (Consolidated Standards of Reporting Trials) diagram. Patient flow and outcome data in the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis trial (per-protocol analysis population). DVT = deep vein thrombosis; PCDT = pharmacomechanical catheter-directed thrombolysis; VCSS = Venous Clinical Severity Scale; VEINES = Venous Insufficiency Epidemiological and Economic Study.

symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and 6 clinician-observed signs (edema, skin induration, hyperpigmentation, venous ectasia, redness, and pain on calf compression) were scored 0–3 and summed together (6). PTS was also assessed using the modified Venous Clinical Severity Scale (VCSS), in which 9 items (8 signs and 1 symptom) were scored 0–3 and summed together (7).

Categorical clinical outcomes in this analysis were the cumulative occurrence over 24 months of the following: (*a*) any PTS (a Villalta score of ≥5 or an ulcer), (*b*) moderate or severe PTS (a Villalta score of ≥10 or an ulcer), (*c*) severe PTS (a Villalta score of ≥15 or an ulcer), and (*d*) venous ulcer. Continuous clinical outcomes included the PTS severity at 24 months as measured by the Villalta score (range, 0–33) and modified VCSS score (range, 0–27); for both the scales, higher scores indicated more severe PTS (6,7). The patient-reported venous disease–specific QOL at 24 months was assessed using the Venous Insufficiency Epidemiological and Economic Study (VEINES) Survey (baseline-adjusted VEINES-QOL and VEINES-Sym subscores, reflecting venous QOL and venous symptoms, respectively) (4,8).

Statistical Analysis

Descriptive statistics were used to summarize the baseline patient characteristics. Continuous data were summarized using mean (standard deviation) and median (interquartile range). Categorical variables were summarized as proportions. The Kruskal-Wallis, chi-square, and Fisher exact tests (when appropriate) were performed to evaluate the associations of baseline variables with treatment response outcomes. Logistic regression was used to assess the associations between independent variables and 4 binary outcomes (PTS, moderate or severe PTS, severe PTS, and venous ulcer). Linear regression models were used to identify the associations between baseline variables and 4 continuous outcomes at 24 months: (*a*) Villalta, (*b*) VCSS, (*c*) VEINES-QOL, and (*d*) VEINES-Sym scores. Each model examined the interaction term between the treatment assignment and the baseline variables to assess whether there was a differential treatment effect for each level of the baseline variables. The odds ratios (ORs) and their 95% confidence intervals (CIs) were reported for logistic regression models. Model estimates, standard errors, and mean differences were reported for linear regression models. To visualize the associations between treatment assignment and 4 continuous baseline variables of interest (Villalta score, DVT symptom duration, patient age, and BMI), plots depicting the predicted probabilities of PTS and moderate or severe PTS as a function of the continuous baseline variables, with 95% CIs, were created for each treatment group on the basis of the logistic regression model. Plots were also created to depict the mean scores at 24 months on the continuous outcome measures, with 95% CIs, as a function of the same 4 continuous baseline variables of interest.

A 2-sided P value of <.05 was considered statistically significant for these exploratory analyses. Analyses were conducted in SAS version 9.4 (SAS, Cary, North Carolina).

RESULTS

Demographic Factors

Patient sex, race (White vs non-White), and ethnicity (Hispanic/Latino vs not) were not associated with the differential effects of PCDT on binary (**Fig 2a, b**; **Fig E1**, available online at *www.jvir.org*) or continuous (**Fig 3a, b**; **Fig E2**, available online at *www.jvir.org*) outcomes. Younger patients undergoing PCDT had nominally lower odds of developing moderate or severe PTS over 24 months; however, this finding was not statistically significant (OR [95% CI] per 5-year increase in age, PCDT, 1.20 [1.05–1.40]; control, 1.03 [0.91–1.15]; $P_{\text{interaction}} = .08$). The predicted probability plots from this model (**Fig 4a–d**; **Figs E3–E6**, available online at *www.jvir.org*) suggest that PCDT may be more likely to reduce moderate or severe PTS than the control treatment in younger patients up to approximately 60 years of age (**Fig 4c**).

Medical History and Comorbidities

Patients with previous DVT experienced a greater effect of PCDT on 24-month PTS severity than patients with no previous DVT (mean [95% CI] PCDT-control difference in the Villalta score, 4.2 [1.56–6.84] points vs 0.9 [−0.44 to 2.26] points; $P_{\text{interaction}} = .03$ [**Fig 3a**]; and VCSS score, 2.6 [0.94–4.21] points vs 0.3 [−0.58 to 1.14] points, $P_{\text{interaction}} = .02$ [**Fig 3b**]). The effects of PCDT on binary outcomes (**Fig 2a, b**) and QOL (**Fig E2**, available online at *www.jvir.org*) were nominally greater in patients with previous DVT than in those with no previous DVT; however, these findings were not statistically significant.

Table. Distribution of Baseline Variables

Factor	Overall (N = 381)	PCDT arm (N = 190)	Control arm (N = 191)	*P* value
Age (y)	51.0 (39.0–62.0)	51.0 (38.0–62.0)	52.0 (42.0–61.0)	.65*
Sex				.72†
Male	203 (53.3%)	103 (54.2%)	100 (52.4%)	
Female	178 (46.7%)	87 (45.8%)	91 (47.6%)	
Race				.28†
White	296 (77.7%)	152 (80.0%)	144 (75.4%)	
Other	85 (22.3%)	38 (20.0%)	47 (24.6%)	
Ethnicity				.34†
Not Hispanic or Latino	352 (92.4%)	178 (93.7%)	174 (91.1%)	
Hispanic or Latino	29 (7.6%)	12 (6.3%)	17 (8.9%)	
BMI (kg/m^2)	30.8 (27.0–36.7)	30.9 (27.6–36.9)	30.8 (25.5–36.4)	.26*
Index leg				.78†
Left	244 (64.0%)	123 (64.7%)	121 (63.4%)	
Right	137 (36.0%)	67 (35.3%)	70 (36.6%)	
Previous DVT				.64†
No	295 (77.4%)	149 (78.4%)	146 (76.4%)	
Yes	86 (22.6%)	41 (21.6%)	45 (23.6%)	
Provoked DVT				.42†
No	319 (83.7%)	162 (85.3%)	157 (82.2%)	
Yes	62 (16.3%)	28 (14.7%)	34 (17.8%)	
Hypertension				.23†
No	226 (59.3%)	107 (56.3%)	119 (62.3%)	
Yes	155 (40.7%)	83 (43.7%)	72 (37.7%)	
Diabetes				.41†
No	311 (81.6%)	152 (80.0%)	159 (83.2%)	
Yes	70 (18.4%)	38 (20.0%)	32 (16.8%)	
High cholesterol				.55†
No	270 (70.9%)	132 (69.5%)	138 (72.3%)	
Yes	111 (29.1%)	58 (30.5%)	53 (27.7%)	
PV compressible				.89†
No	273 (80.1%)	135 (80.4%)	138 (79.8%)	
Yes	68 (19.9%)	33 (19.6%)	35 (20.2%)	
Total Villalta score	10.0 (6.0–14.0)	10.0 (7.0–14.0)	9.6 (6.0–14.0)	.23*
Symptom duration (d)	6.0 (3.0–9.0)	6.0 (3.0–9.0)	6.0 (3.0–9.0)	.42*

BMI = body mass index; DVT = deep vein thrombosis; PCDT = pharmacomechanical catheter-directed thrombolysis; PV = popliteal vein.
*Kruskal-Wallis test.
†Pearson chi-square test.

The impact of baseline continuous variables on the effects of PCDT on continuous outcomes is presented in **Figure 5a–c** and **Figures E7–E15** (available online at *www.jvir.org*). Continuous BMI was not a statistically significant predictor of the effect of PCDT treatment in the overall model (moderate or severe PTS, OR [95% CI] per 5-unit increase in BMI, PCDT, 1.14 [0.90–1.44]; control, 1.31 [1.08–1.59]; $P_{interaction} = .36$). The predicted probability plots from this model depicted a gradual divergence of the PCDT and control curves for moderate or severe PTS as the BMI increased (**Fig 4d**). The effect of PCDT appeared prominent in patients with a very high BMI (moderate or severe PTS in patients with a BMI of >40 kg/m^2; OR, 0.23 [0.07–0.75]); however, the 95% CIs overlapped with those for patients with a BMI of <40 kg/m^2 (OR, 0.71 [0.41–1.21]), perhaps reflecting the fact that these estimates are based on very small numbers of patients who had a BMI of that magnitude. BMI did not have significant effects on between-arm differences in the Villalta, VCSS, and VEINES-QOL scores (**Figs E13–E15**, available online at *www.jvir.org*). Pooled across treatment arms, patients with an elevated BMI did have increased odds of developing moderate or severe PTS ($P = .006$).

A history of hypertension, diabetes, or hypercholesterolemia did not show a differential effect by treatment arm on clinical outcomes (**Figs 2a, b**; **3a, b**; **Figs E1**, **E2**, available online at *www.jvir.org*).

Characteristics of a Presenting DVT Episode

A patient's presenting DVT clinical severity was a key predictor of the effects of PCDT on 24-month clinical outcomes in this analysis of patients with iliofemoral DVT. Adjusted for treatment assignment, as the baseline Villalta score increased, the occurrence of PTS increased ($P < .0001$

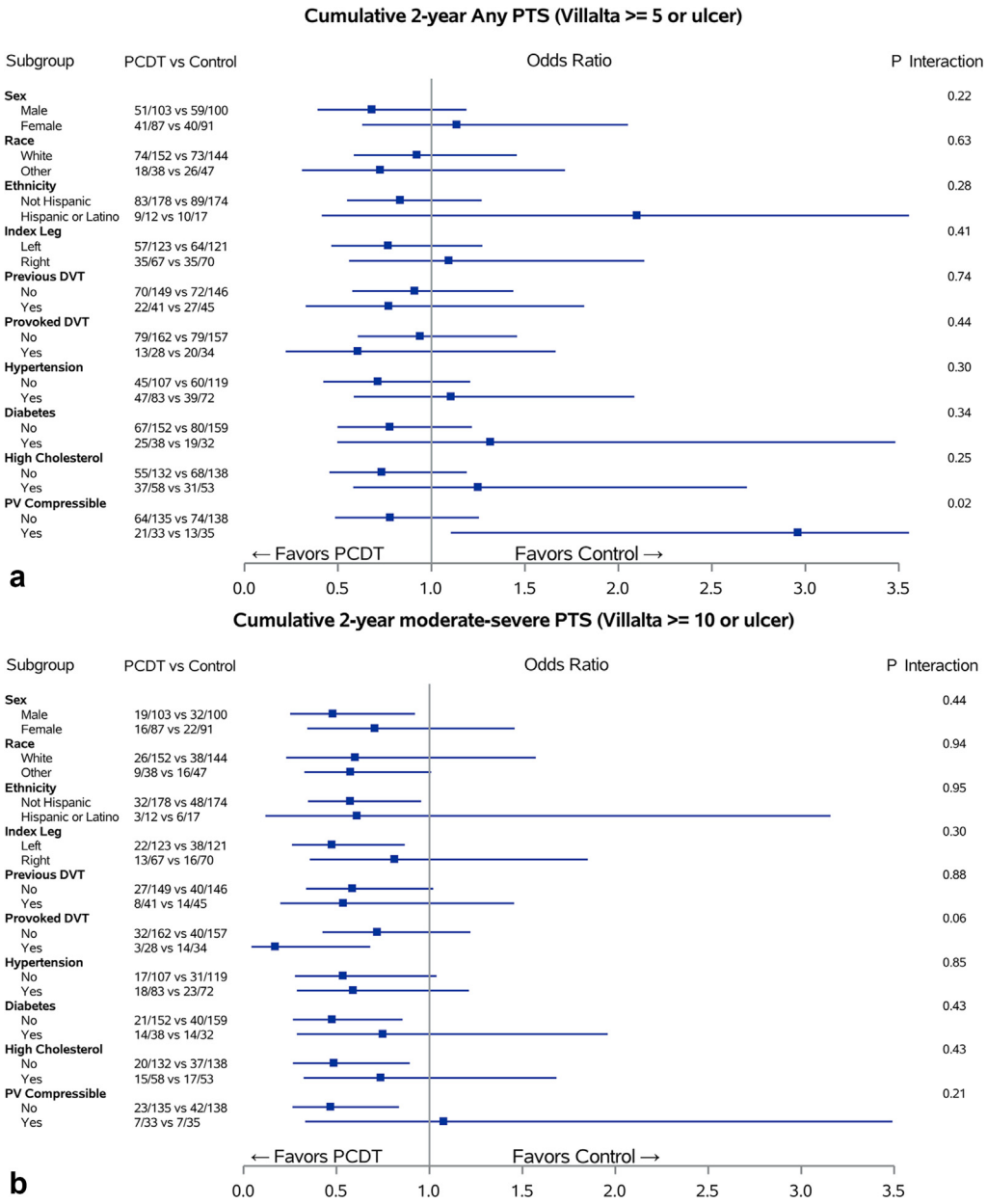

Figure 2. Baseline predictors of the effect of pharmacomechanical catheter-directed thrombolysis (PCDT) on 24-month binary venous outcomes. Forest plots of odds ratios for the 24-month cumulative occurrences of **(a)** postthrombotic syndrome (PTS) and **(b)** moderate or severe PTS in the subgroups of the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis trial patients with acute iliofemoral deep vein thrombosis (DVT) for each level of baseline factors. The horizontal lines represented 95% confidence intervals. PV = popliteal vein.

in the logistic interaction model). The use of PCDT was associated with lower odds of moderate or severe PTS in patients with higher baseline Villalta scores (OR [95% CI] per unit increase in the baseline Villalta score, PCDT, 1.08 [1.01–1.15]; control, 1.20 [1.12–1.29]; $P_{\text{interaction}} = .03$). This effect was also nominally apparent for PTS but was not statistical significant (OR [95% CI] per unit increase in the baseline Villalta score, PCDT, 1.06 [1.01–1.13]; control, 1.14 [1.07–1.21]; $P_{\text{interaction}} = .11$). The predicted probability plots from the models suggest that relative to control, PCDT is most likely to reduce moderate or severe PTS in patients with a baseline Villalta score that exceeds 10 (Fig 4a).

As the baseline Villalta score increased, the benefits of PCDT on PTS severity and venous QOL also increased. For patients with a baseline Villalta score of >10, the mean 24-month Villalta ($P_{\text{interaction}} = .004$) (Fig 5a) and VCSS ($P_{\text{interaction}} = .002$) (Fig 5b) scores were lower in the PCDT arm than in the control arm, and the mean VEINES-QOL ($P_{\text{interaction}} = .025$) (Fig 5c) and VEINES-Sym ($P_{\text{interaction}} = .02$) scores were higher for PCDT arm than for controls, with 95% CIs that did not overlap.

The duration of DVT symptoms did not predict the effects of PCDT on the 24-month occurrences of PTS (OR [95% CI] per additional day of symptoms, PCDT, 1.04

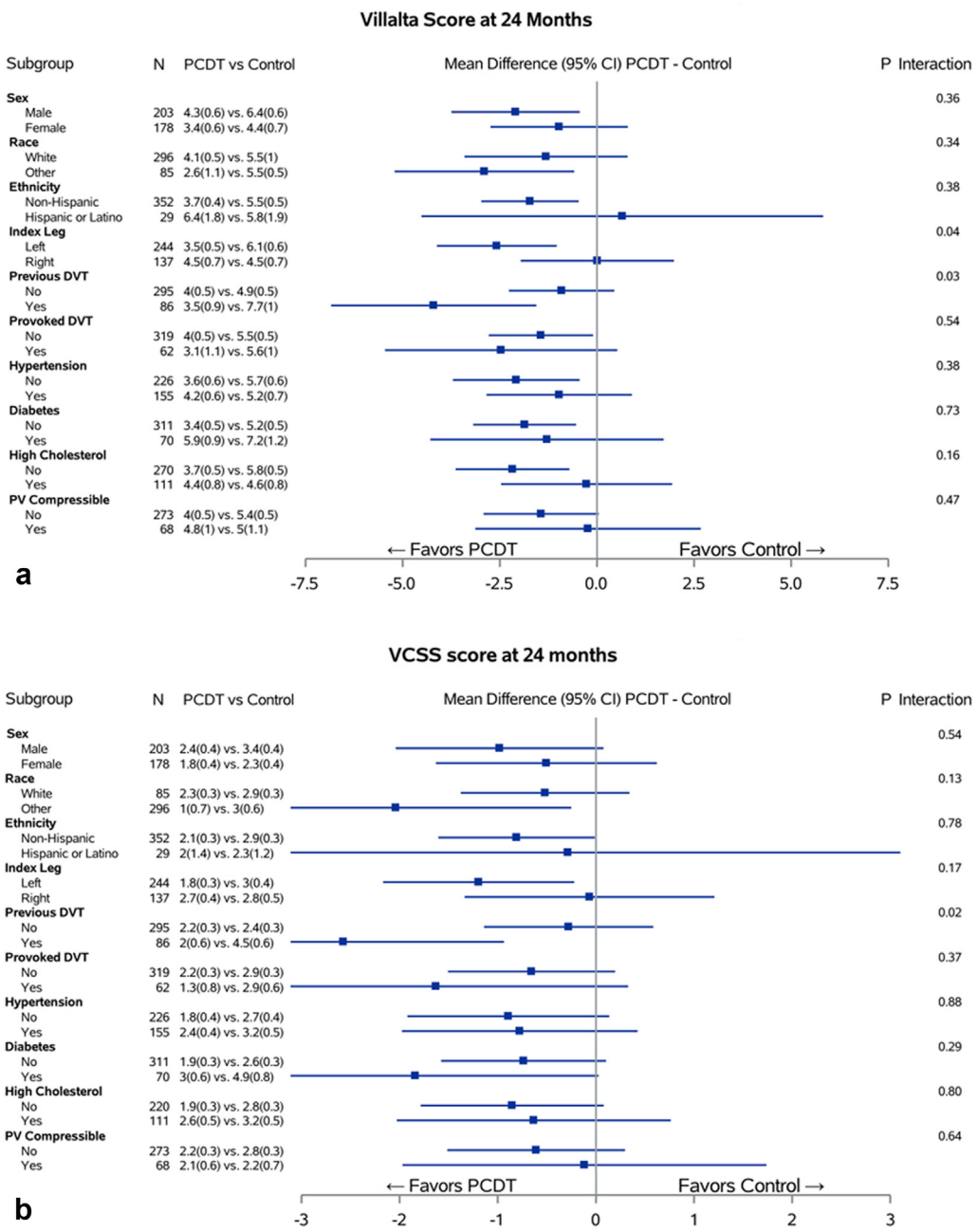

Figure 3. Baseline predictors of the effect of pharmacomechanical catheter-directed thrombolysis (PCDT) on 24-month continuous venous outcomes. Associations of binary baseline factors with 24-month **(a)** Villalta and **(b)** Venous Clinical Severity Scale (VCSS) scores in the subgroups of Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis patients with acute iliofemoral deep vein thrombosis (DVT) for each level of baseline factors. The horizontal lines represented 95% confidence intervals (CIs). PV = popliteal vein.

[0.96–1.11]; control, 1.00 [0.94–1.06]; $P_{\text{interaction}} = .46$), moderate or severe PTS ($P_{\text{interaction}} = .52$), or between-arm differences in the 24-month Villalta or VCSS scores. Although gradual divergence of PCDT and control curves for VEINES-QOL and VEINES-Sym was apparent as symptom duration increased, the 95% CIs around these curves overlapped at all symptom durations (**Figs E7–E9**, available online at *www.jvir.org*).

For all outcomes assessed over 24 months, PCDT was nominally more effective in patients with left leg DVT than in those with right leg DVT; however, the differences only reached statistical significance for PTS severity (mean [95% CI] PCDT-control difference in Villalta score, left DVT, 2.60 [1.04–4.12] points; right DVT, 0.01 [−1.96 to 1.98] points; $P_{\text{interaction}} = .04$) (**Fig 3a**) and venous ulcer (left leg, PCDT, 2.4% vs control, 7.4%; right leg, PCDT, 9.0% vs control, 4.3%; $P_{\text{interaction}} = .049$) (**Fig E1**, available online at *www.jvir.org*). Similarly, patients with a noncompressible popliteal vein appeared to have nominally more favorable outcomes with PCDT than

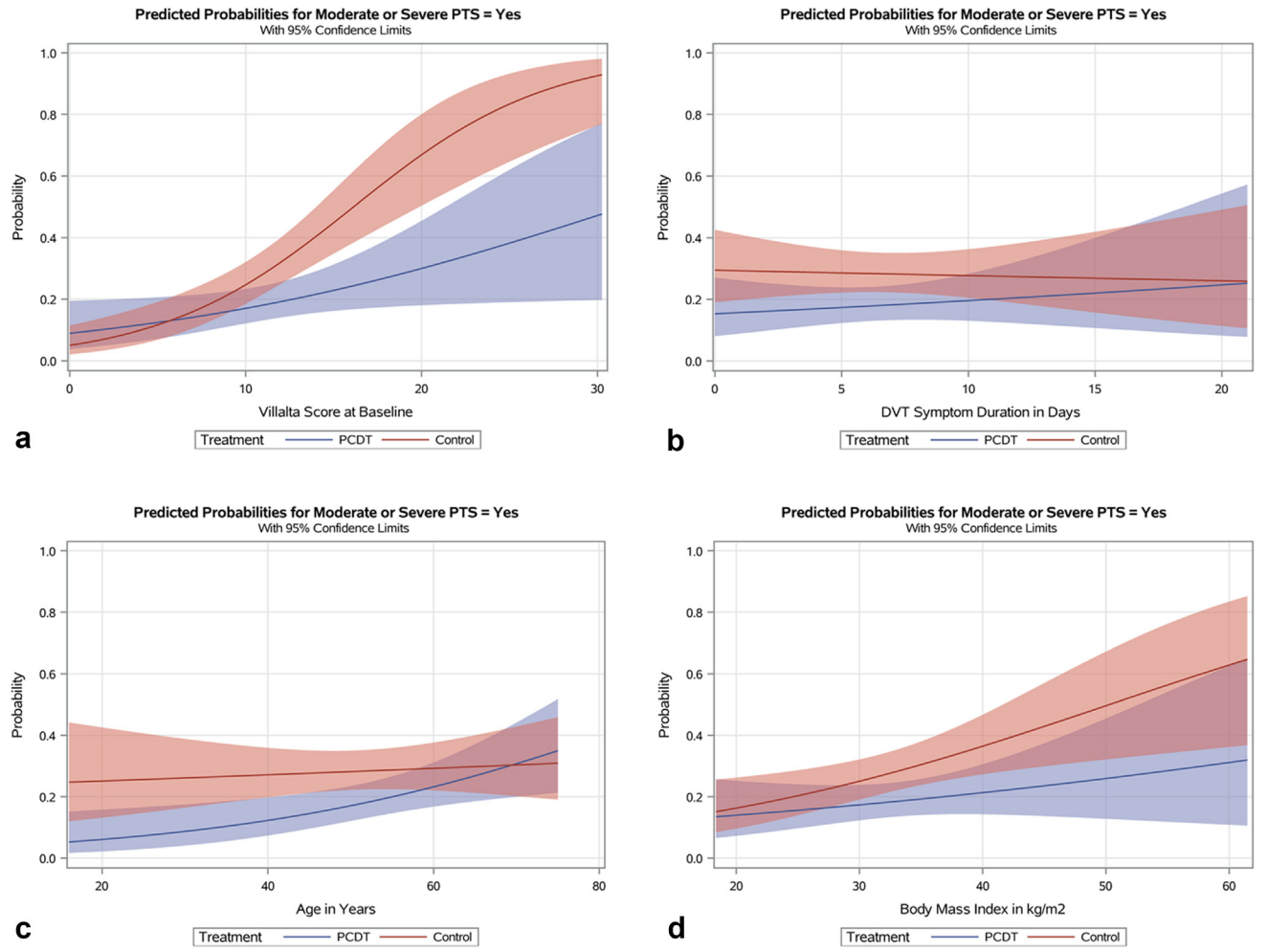

Figure 4. Predicted probabilities of venous outcomes by continuous baseline factors. The plots depicted the predicted probabilities of moderate or severe postthrombotic syndrome (PTS) in patients with increasing **(a)** baseline Villalta score, **(b)** symptom duration, **(c)** patient age, and **(d)** body mass index. The light red and blue bands represented the 95% confidence intervals around the estimates for each respective treatment arm; the dark red/purple bands represented the areas of overlap between the 95% confidence intervals for the 2 treatment arms. DVT = deep vein thrombosis; PCDT = pharmacomechanical catheter-directed thrombolysis.

patients with a compressible popliteal vein; however, significance was only observed for PTS (compressible, PCDT, 64% vs control, 37%; noncompressible, PCDT, 47% vs control, 54%; $P_{\text{interaction}} = .02$) (**Figs 2a,b**; **3a,b**). The presence of provoking risk factors at the time of the index DVT did not show a differential effect by treatment arm on clinical outcomes (**Figs 2a, b**; **3a, b**).

DISCUSSION

This analysis of the ATTRACT trial found the following: (*a*) in patients with acute iliofemoral DVT, higher presenting clinical severity (baseline Villalta score) predicts greater benefits of PCDT (vs anticoagulation alone) on PTS severity, moderate or severe PTS, and venous QOL over 24 months; (b) a history of previous DVT predicts greater PCDT effects in reducing 24-month PTS severity; (c) patients with left-sided DVT or a noncompressible popliteal vein at baseline may experience stronger PCDT effects on some 24-month outcomes; however, these findings were not compelling in magnitude or consistency; and (d) PCDT treatment effects did not differ on the basis of sex, race, Hispanic/Latino ethnicity, continuous BMI, continuous symptom duration (within trial parameters), hypertension, diabetes, hypercholesterolemia, or provoked DVT.

Although some societal guidelines now suggest the use of CDT/PCDT for selected patients with acute iliofemoral DVT, evidence linking discernible baseline patient characteristics to the treatment effects of endovascular therapies has not been available to guide such decisions (9,10).

In the randomized Catheter-Directed Venous Thrombolysis trial (11,12), baseline factors, including symptom duration (≤21 days), thrombus extent, and side of DVT, did not influence thrombolysis grade, residual thrombus score, patency, or PTS. Late patency was more frequent in women; however, PTS was similar for men and women. Left leg

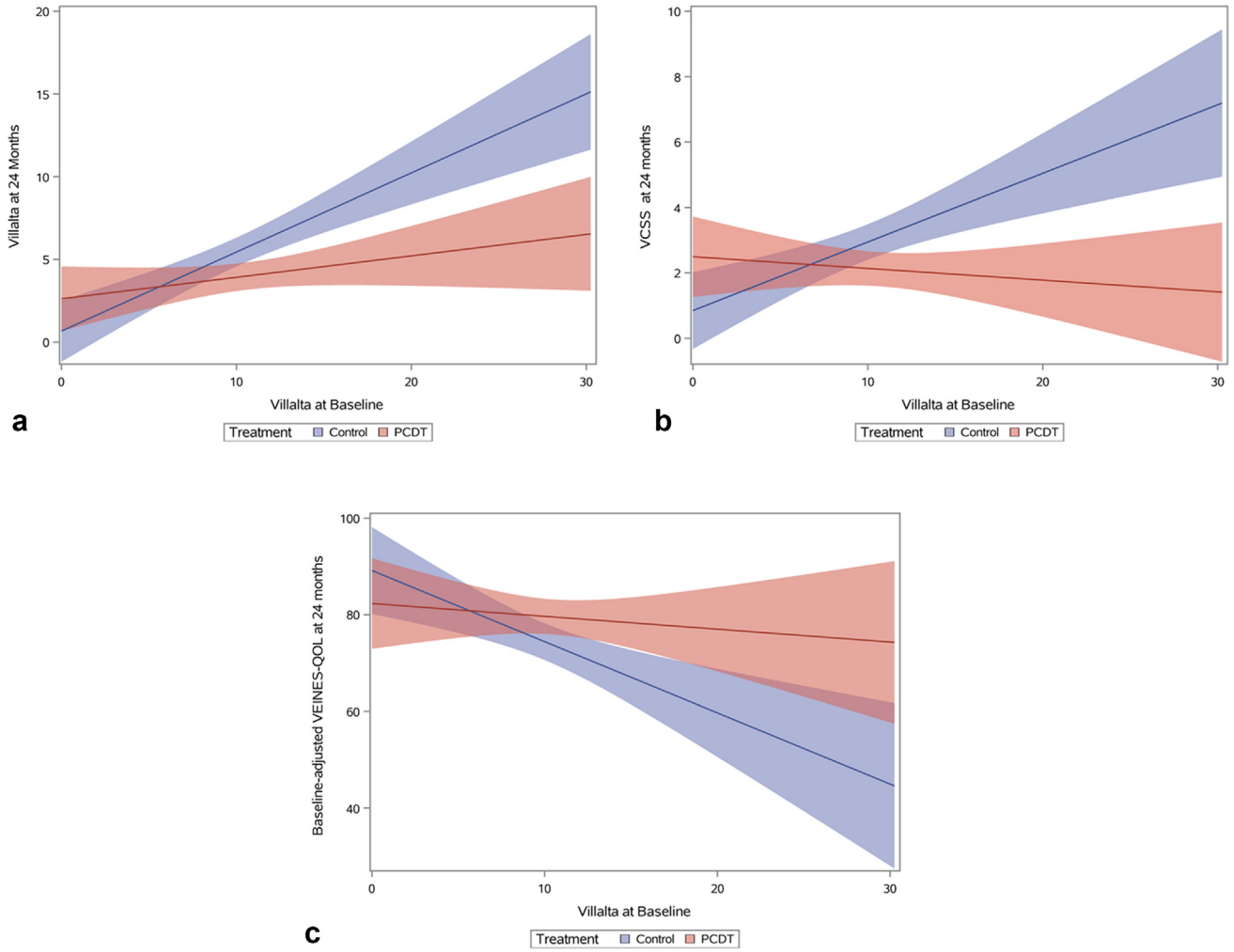

Figure 5. Association of continuous baseline factors with 24-month venous outcomes. The plots depicted the predicted mean scores for the **(a)** Villalta, **(b)** Venous Clinical Severity Scale (VCSS), and **(c)** baseline-adjusted Venous Insufficiency Epidemiological and Economic Study Quality of Life (VEINES-QOL) scores at 24 months as a function of increasing continuous baseline Villalta score. The light red and blue bands represented the 95% confidence intervals around the estimates for each respective treatment arm; the dark red/purple bands represented the areas of overlap between the 95% confidence intervals for the 2 treatment arms. PCDT = pharmacomechanical catheter-directed thrombolysis.

DVT predicted lower 24-month Villalta scores than those predicted by right leg DVT; however, PTS occurrence was similar in both legs. The randomized Ultrasound-Accelerated Catheter-Directed Thrombolysis versus Anticoagulation for the Prevention of Post-thrombotic Syndrome trial (13), which studied ultrasound-assisted CDT for acute iliofemoral DVT, was unable to identify baseline modifiers of the treatment effects of the intervention.

A prespecified subgroup analysis of the ATTRACT trial found PCDT to lead to a higher PTS occurrence over 2 years in patients with proximal DVT aged ≥65 years than that in younger patients ($P_{interaction}$ = .04); the age of ≥65 years also predicted major bleeding (P < .0001) (5,14). In the trial's iliofemoral DVT subgroup, PCDT reduced the occurrence of moderate or severe PTS over 2 years in patients aged <65 years (PCDT, 16% vs control, 30%) compared with that in patients aged ≥65 years (PCDT, 28% vs control, 19%) ($P_{interaction}$ = .04) (3). Hence, it has been noted that it is important to factor in patient age when making PCDT treatment decisions. This conclusion is supported to some extent here by the predicted probability plots, which suggest that moderate or severe PTS is less frequent in PCDT-treated patients aged up to approximately 65 years. However, viewed as a continuous variable, age was not a statistically significant predictor of PCDT effect in this study, perhaps partly because of the limited number of very young patients in the analysis.

In this analysis, a history of previous DVT predicted a stronger effect of PCDT on PTS severity. In theory, this finding could be explained by a greater ability of anticoagulation alone to permit restoration of a normal venous system in the limbs with only acute thrombus (no previous event) and/or a greater likelihood that patients with previous DVT had chronic venous abnormalities (compression and residual thrombus) that were addressed via adjunctive endovascular therapy during PCDT. Similarly, patients with

a compressible popliteal vein may respond well to anticoagulation alone, and the treatment of iliac vein compression in patients with left leg DVT could account for the finding of greater PCDT benefit in some analyses.

Randomized trials of CDT/PCDT have limited enrollment to patients with symptom duration of ≤14 to 21 days. In a venogram analysis of ATTRACT patients undergoing PCDT, patients randomized within 7 days of symptom onset had a higher rate of complete lysis (35% vs 23%; $P_{interaction} = .04$) and nominally greater thrombus removal (88% vs 82%; $P = .06$) than patients randomized 7–14 days after symptom onset (15). However, complete lysis did not lead to reduced PTS and the effect of PCDT on PTS prevention did not differ between these 2 groups. The current study, which analyzed symptom duration as a continuous variable, also does not suggest a major effect on clinical outcomes that would argue for expedited conduct of PCDT.

The current analysis identified greater presenting DVT severity (higher baseline Villalta score) as a key predictor of enhanced PCDT effect in improving 24-month venous outcomes. Patients with a baseline Villalta score of >10 experienced very high rates of moderate or severe PTS. In these patients, PCDT reduces the probability of developing moderate or severe PTS by over one-third, with the projected effect increasing as the baseline clinical severity increases. These effects were also visualized in consistently larger differences between the PCDT and control arms in PTS severity scores and QOL in patients with severe clinical presentations.

The Villalta scale was originally developed as a tool to identify and quantify PTS and is endorsed for this purpose by the International Society on Thrombosis and Hemostasis (6). In the ATTRACT trial, the Villalta scale was also used to grade the clinical severity of DVT in the acute phase. The correlations identified in this analysis suggest that using the Villalta scale at the time of DVT diagnosis may help in stratifying a patient's risk of developing clinically important PTS and in predicting the effects of more aggressive treatment.

The current analysis has several limitations. In the ATTRACT trial, the benefits of PCDT on PTS severity and venous QOL were mainly apparent in the iliofemoral DVT subgroup. Stratification of randomization by baseline thrombus extent enhanced the study's ability to evaluate PCDT treatment effects within each anatomic subgroup. For these reasons, the current analysis was limited to the iliofemoral subgroup; however, this reduced the sample size and statistical power. The study was not able to analyze genetic determinants or other biomarkers that may predict PCDT effects. Because this study was intended as an exploratory analysis that would transparently present the observed outcomes against the baseline factors, subgrouping of continuous scale data by arbitrarily selected threshold cutpoints was not performed, and a P value threshold of .05 was used for statistical significance. The predicted probability plots should be interpreted with care because for any variable, the number of patients at each point on the spectrum varied, precluding robust statistical comparisons. For these reasons, prospective confirmation of these findings in additional studies would be desirable.

In conclusion, in patients with acute iliofemoral DVT, PCDT is more effective in improving 24-month venous outcome in patients with more severe baseline clinical presentation or a history of previous DVT. Left-sided DVT and a noncompressible popliteal vein may also connote a greater likelihood to benefit from PCDT; however, these apparent relationships are less conclusive because they were only observed for some of the evaluated outcomes. The findings of this analysis may help to inform the design of future studies evaluating new or existing thrombus removal strategies.

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APPENDIX. ACUTE VENOUS THROMBOSIS: THROMBUS REMOVAL WITH ADJUNCTIVE CATHETER-DIRECTED THROMBOLYSIS STUDY LEADERSHIP AND INVESTIGATORS

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APPENDIX B. DEFINITIONS FOR SELECTED BASELINE FACTORS

Race and Hispanic/Latino ethnicity were self-reported by the participants and transcribed on the case report forms by the site coordinators. Body mass index was derived via measurement of participants' height and weight at the time of enrollment.

Previous medical conditions (hypertension, diabetes, hypercholesterolemia, and previous deep vein thrombosis [DVT]) were determined by the site investigators and research coordinators from the medical history and medical record review at the time of participant enrollment and entered on the case report forms. The laboratory/imaging testing criteria were not used to verify the presence of these conditions. For purposes of this analysis, patients with any type of past DVT (ipsilateral or contralateral, proximal or distal, identified by medical history or by imaging, and with or without accompanying pulmonary embolism) were considered to have previous DVT. Because patients with symptomatic ipsilateral DVT within the previous 2 years were excluded from the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis trial, most cases of previous DVT occurred in the contralateral limb.

Provoked DVT was considered to represent DVT that occurred in association with a major reversible risk factor, including major surgery, plaster cast immobilization, childbirth, or hospitalization for acute medical illness within the preceding 6 weeks.

ANALYSIS CATEGORIES

To enable meaningful analysis, for some baseline factors, categories with few patients were combined with adjacent categories. For race, the American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and not reported or refused categories were combined into 1 "Other" analytic group. In addition, patients who did not report Hispanic/Latino ethnicity were combined with the not Hispanic/Latino category.

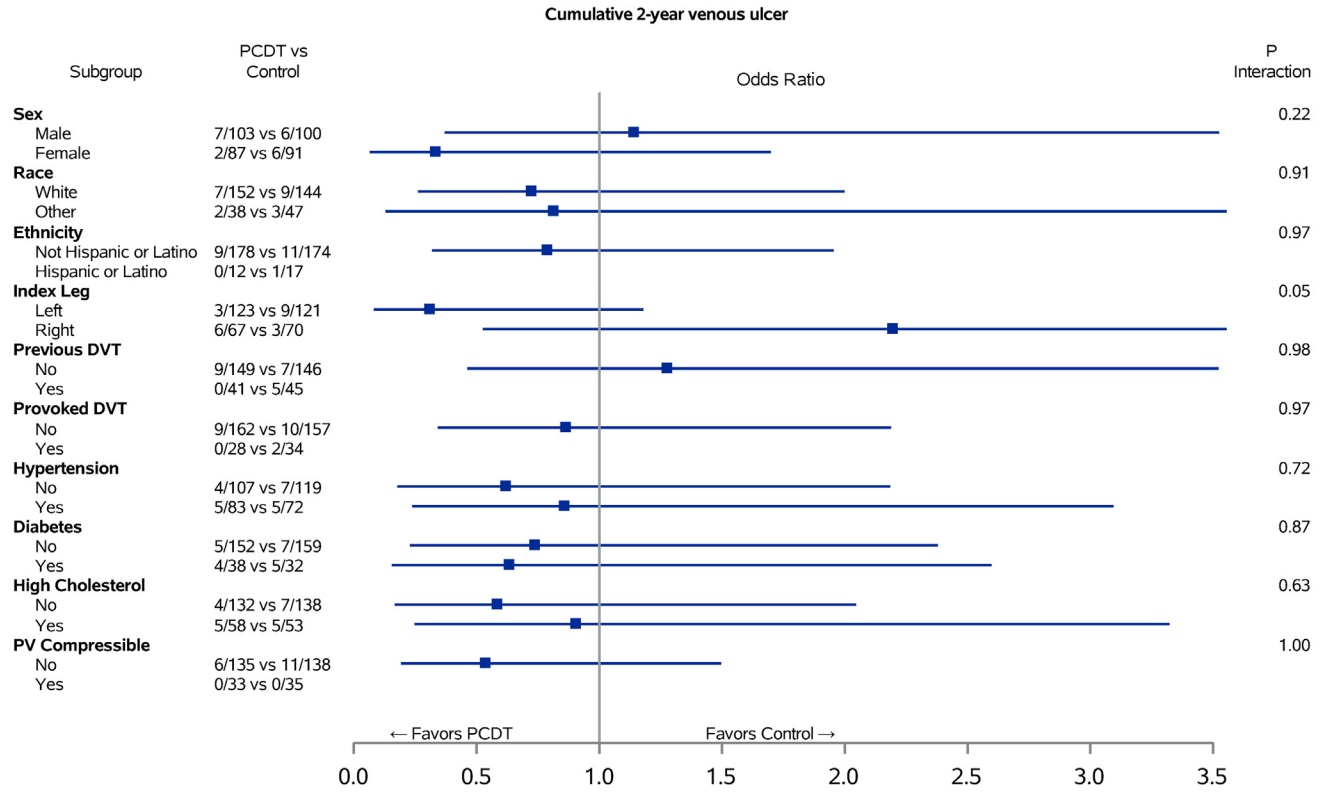

Fig E1. Baseline predictors of PCDT effect on 24-month occurrence of venous ulcer. Forest plots of odds ratios for the 24-month cumulative occurrences of venous ulcer in subgroups of ATTRACT patients with acute iliofemoral DVT for each level of baseline factors. The horizontal lines represent 95% confidence intervals (CIs).

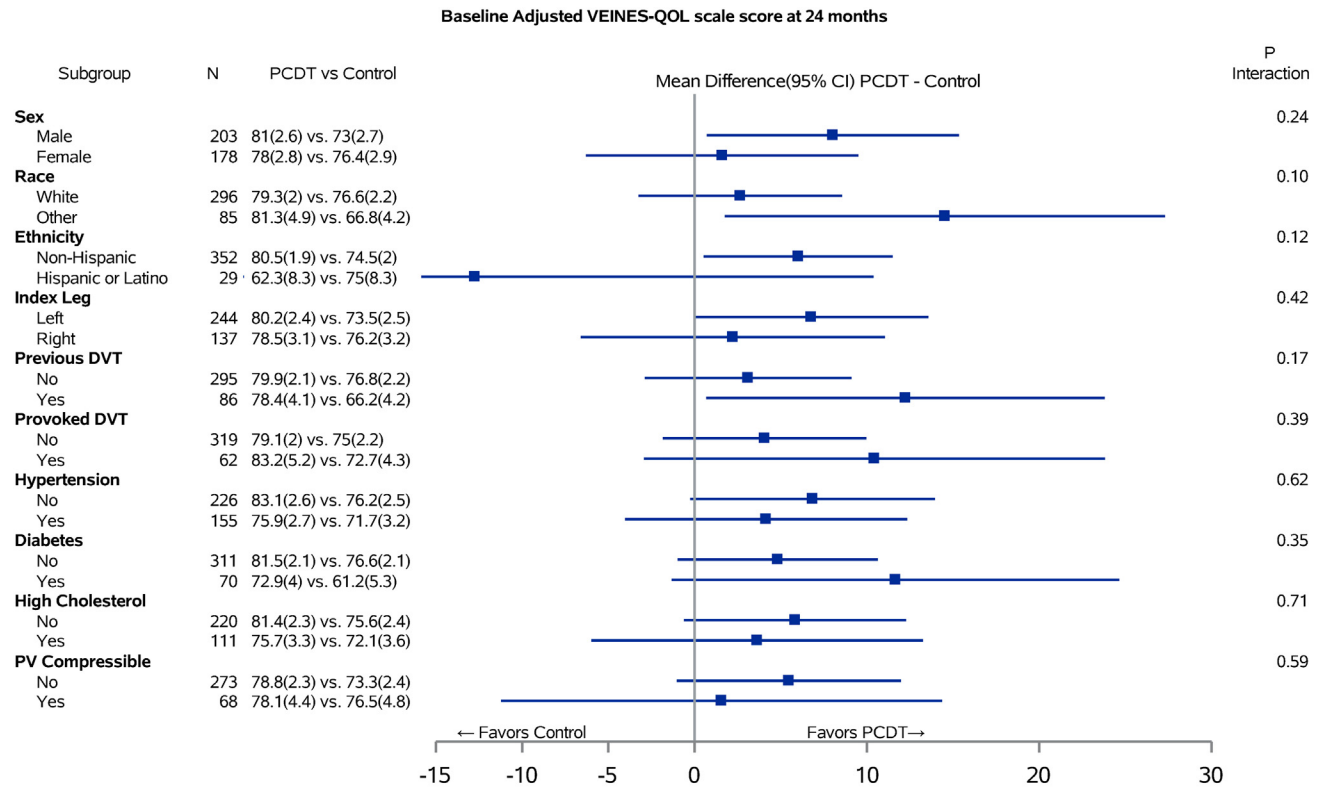

Fig E2. Baseline predictors of PCDT effect on 24-month venous disease-specific QOL. Associations of binary baseline factors with 24-month VEINES-QOL scores in subgroups of ATTRACT patients with acute iliofemoral DVT for each level of baseline factors. The horizontal lines represent 95% confidence intervals (CIs).

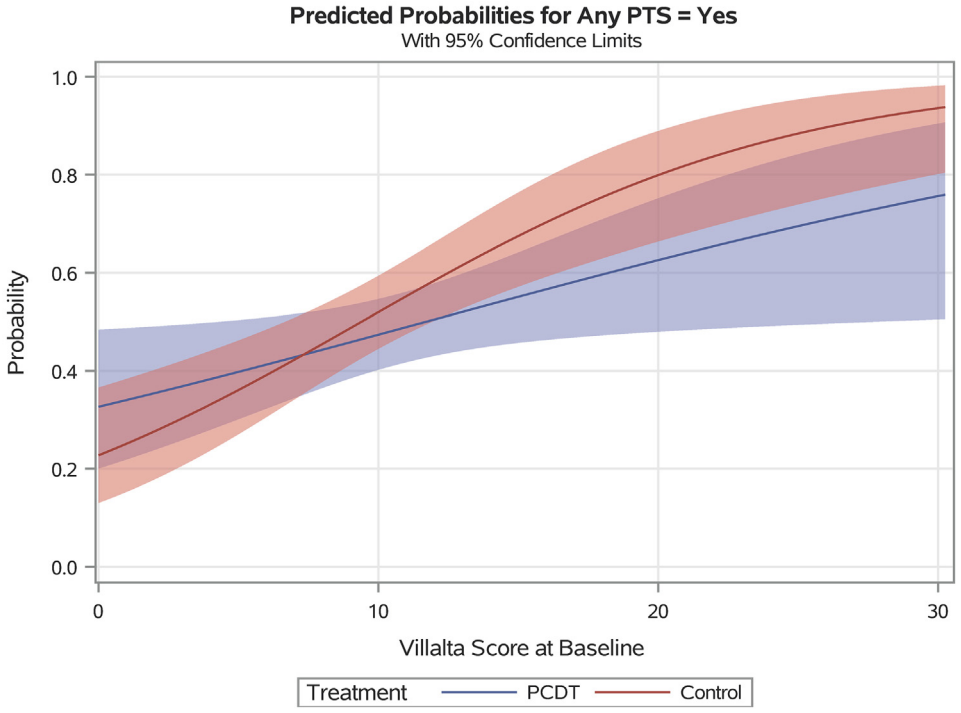

Fig E3. Plot depicts the predicted probabilities of postthrombotic syndrome (PTS) in patients with increasing baseline Villalta score.

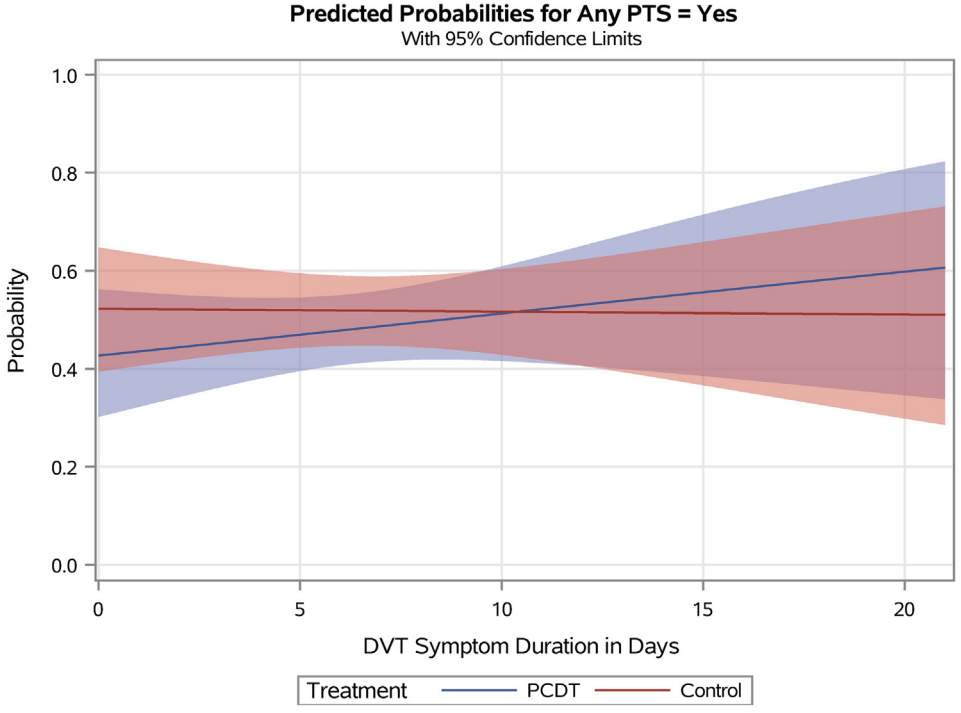

Fig E4. Plot depicts the predicted probabilities of postthrombotic syndrome (PTS) in patients with increasing symptom duration of the index deep vein thrombosis episode.

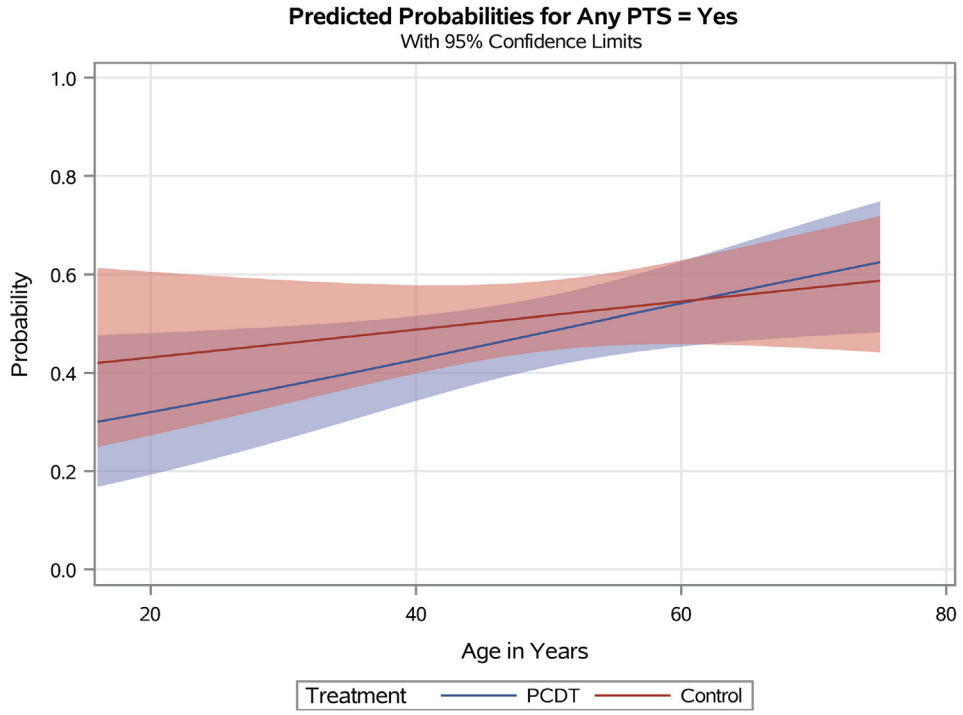

Fig E5. Plot depicts the predicted probabilities of postthrombotic syndrome (PTS) in patients with increasing age at baseline.

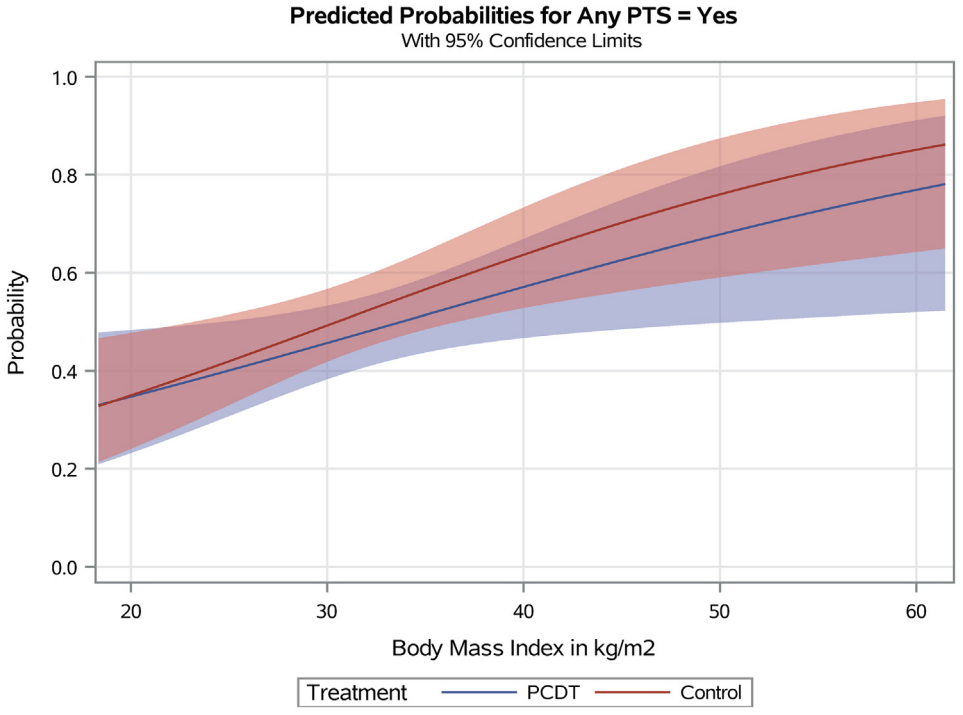

Fig E6. Plot depicts the predicted probabilities of postthrombotic syndrome (PTS) in patients with increasing baseline body-mass index.

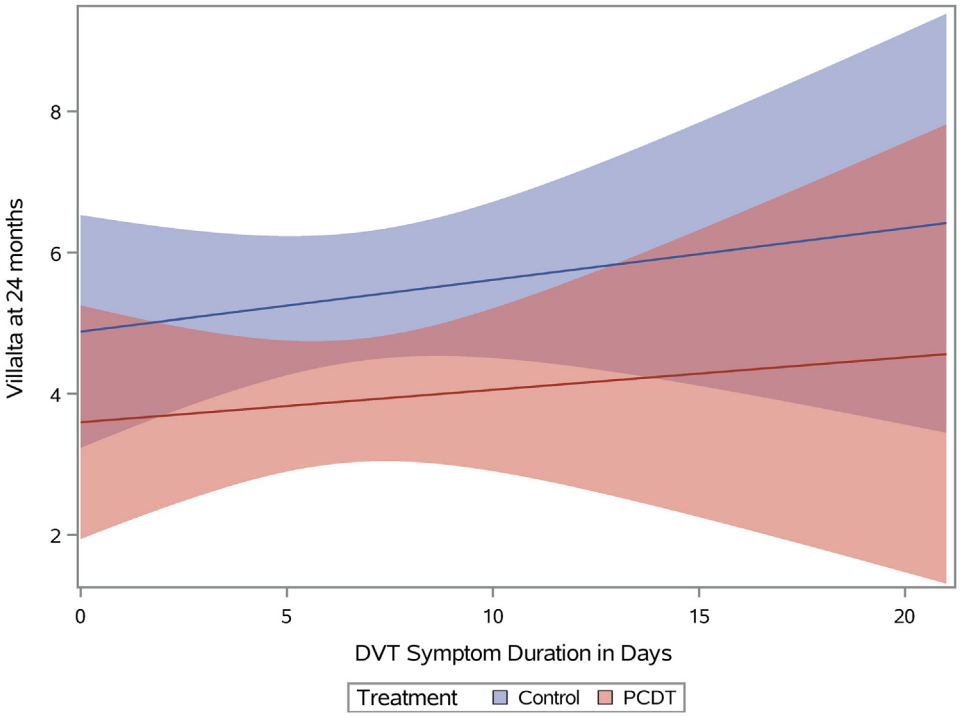

Fig E7. Plot depicts the mean 24-month Villalta scale scores as a function of increasing symptom duration for the index deep vein thrombosis episode.

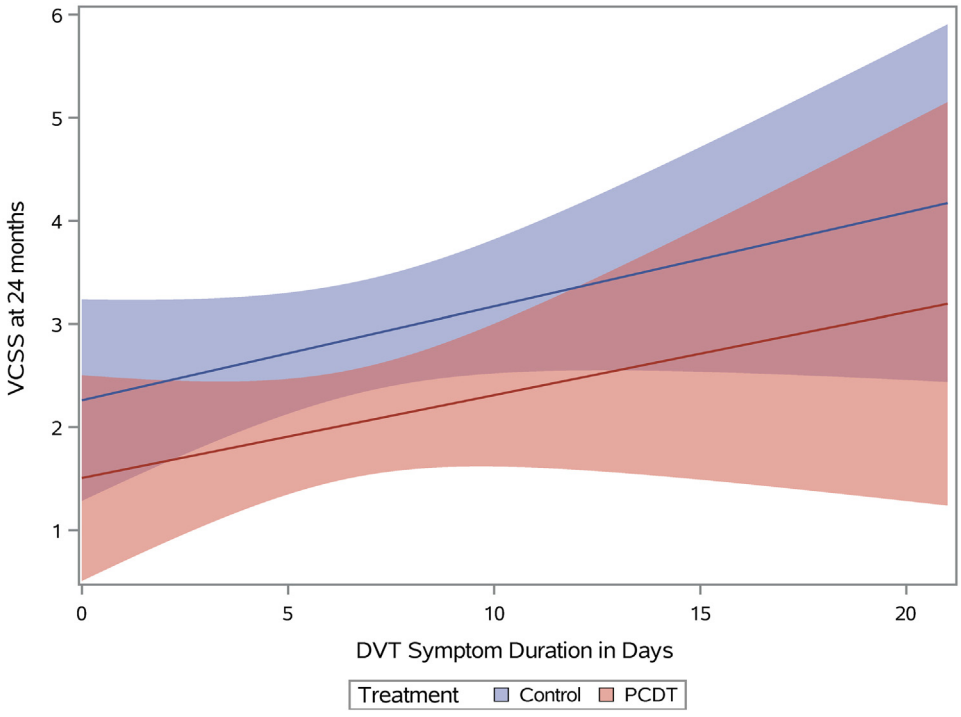

Fig E8. Plot depicts the mean 24-month Venous Clinical Severity Scale scores as a function of increasing symptom duration for the index deep vein thrombosis episode.

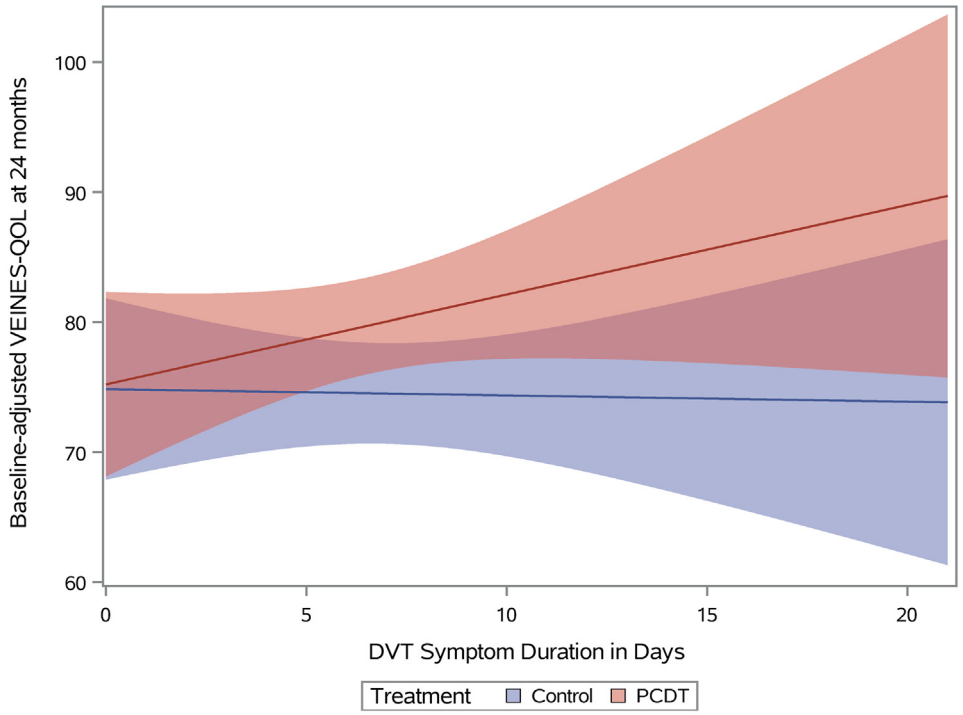

Fig E9. Plot depicts the mean scores on the VEINES-QOL venous disease-specific quality of life scale at 24 months as a function of increasing symptom duration for the index deep vein thrombosis episode.

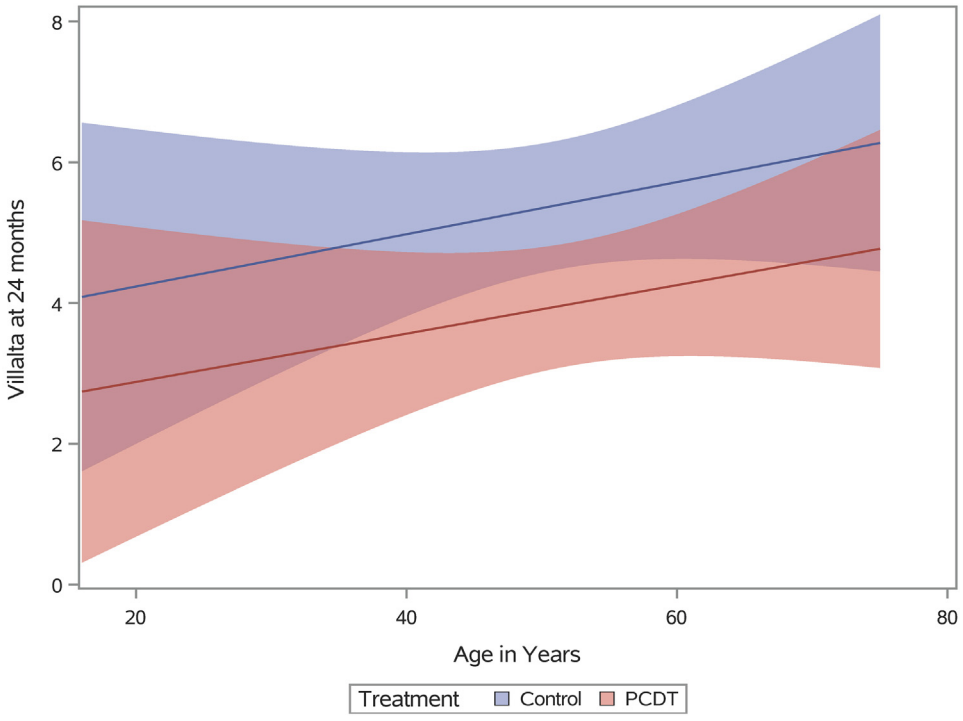

Fig E10. Plot depicts the mean 24-month Villalta scale scores as a function of increasing patient age at baseline.

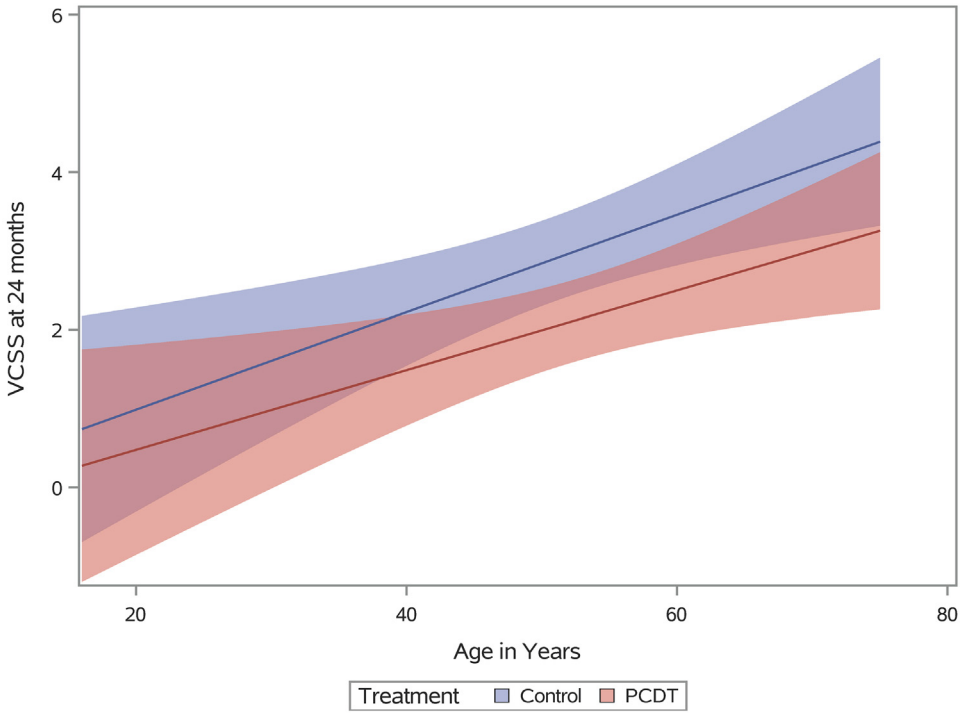

Fig E11. Plot depicts the mean 24-month Venous Clinical Severity Scale scores as a function of increasing patient age at baseline.

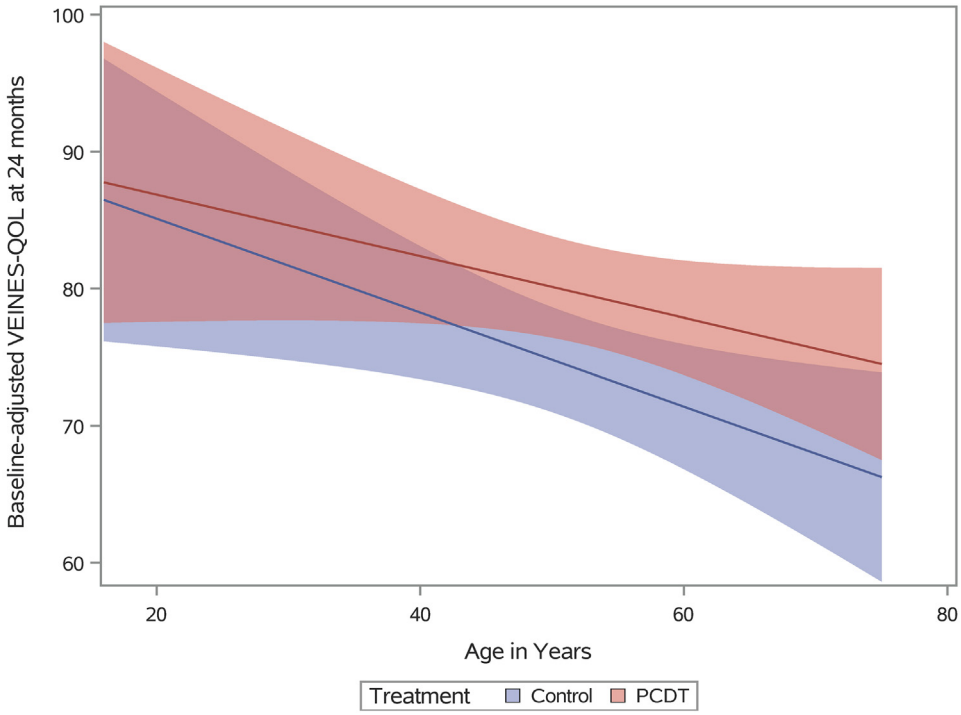

Fig E12. Plot depicts the mean scores on the VEINES-QOL venous disease-specific quality of life scale at 24 months as a function of increasing patient age at baseline.

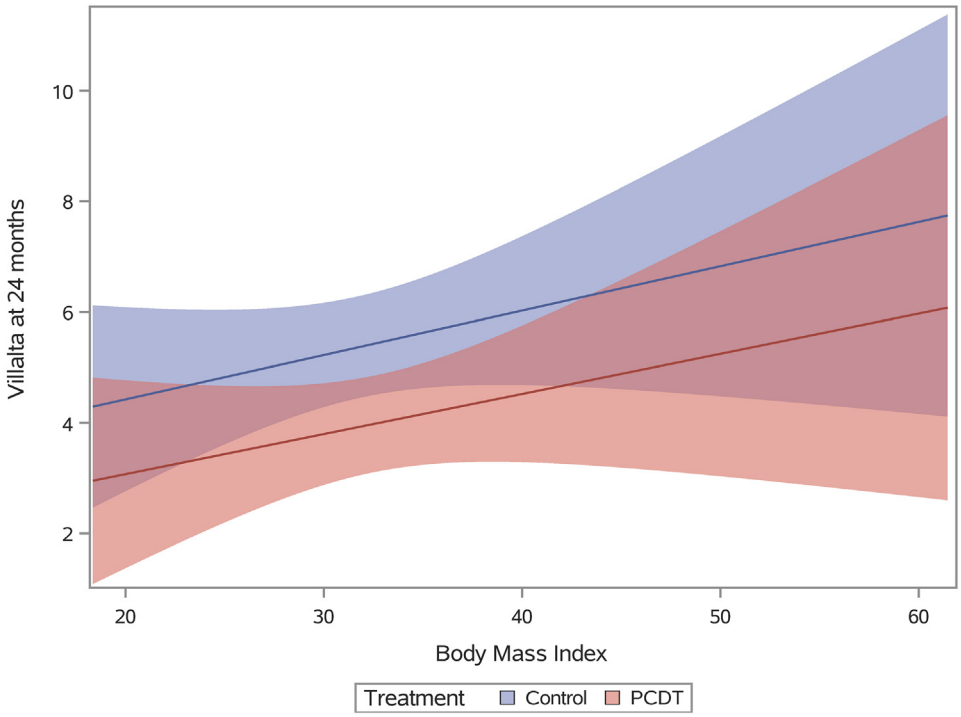

Fig E13. Plot depicts the mean 24-month Villalta scale scores as a function of increasing body-mass index at baseline.

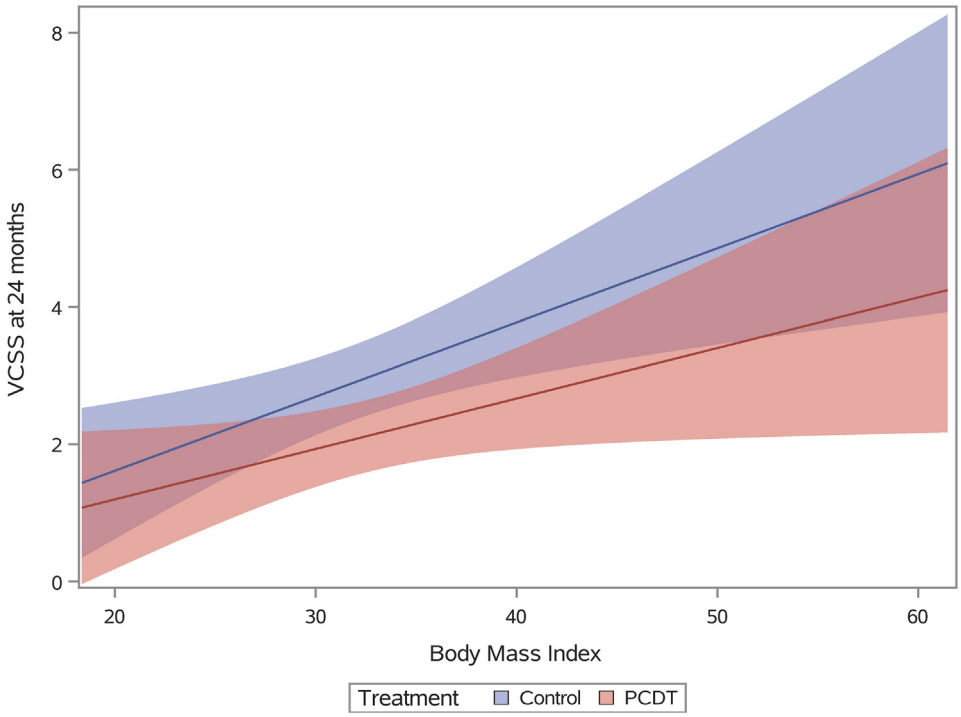

Fig E14. Plot depicts the mean 24-month Venous Clinical Severity Scale scores as a function of increasing body-mass index at baseline.

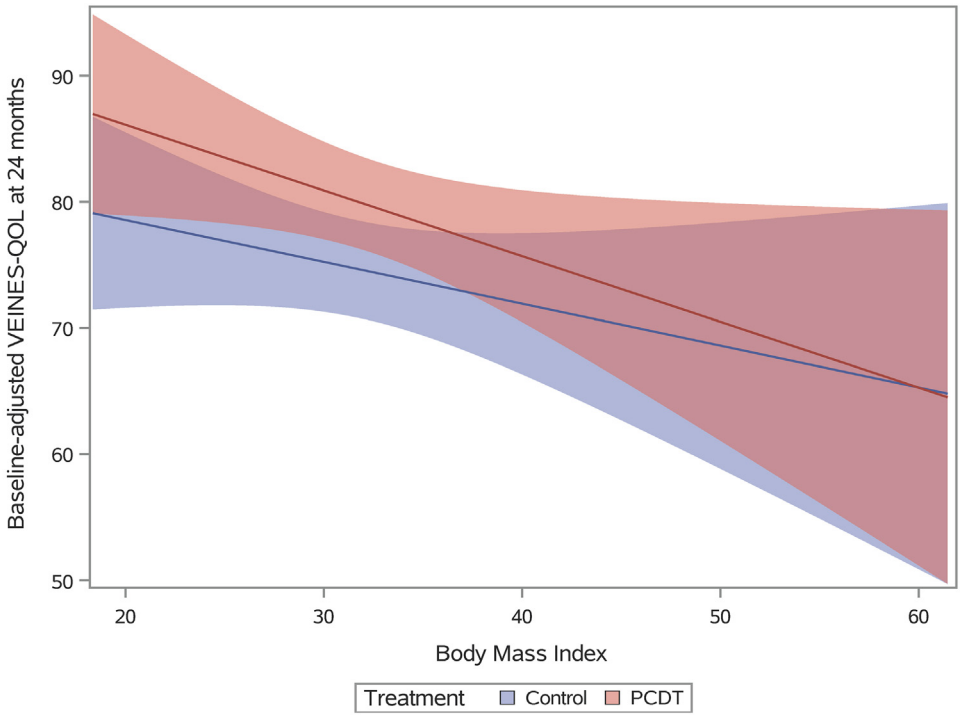

Fig E15. Plot depicts the mean scores on the VEINES-QOL venous disease-specific quality of life scale at 24 months as a function of increasing body-mass index at baseline.