

## ORIGINAL ARTICLE

# New and known predictors of the postthrombotic syndrome: A subanalysis of the ATTRACT trial

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## Abstract

**Introduction:** Postthrombotic syndrome (PTS) remains associated with significant clinical and economic burden. This study aimed to investigate known and novel predictors of the development of PTS in participants of the ATTRACT (Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis) trial.

**Methods:** We used multivariable logistic regression to identify baseline and postbaseline factors that were predictive of the development of PTS during study follow-up, as defined by a Villalta score of 5 or greater or the development of a venous ulcer from 6 to 24 months after enrollment.

**Results:** Among 691 patients in the study cohort (all had proximal deep vein thrombosis [DVT] that extended above the popliteal vein, of which 57% had iliofemoral DVT), 47% developed PTS. Further, we identified that Villalta score at baseline (odds ratio [OR], 1.09 [95% confidence interval [CI], 1.05–1.13] per one-unit increase) and employment status (unemployed due to disability: OR, 3.31 [95% CI, 1.72–6.35] vs. employed more than 35 hours per week) were predictive of PTS. In terms of postbaseline predictors, leg pain severity at day 10 (OR, 1.28 [95% CI, 1.13–1.45] per 1-point increase in a 7-point scale) predicted PTS. Also, patients receiving rivaroxaban on day 10 following randomization had lower rates of PTS (OR, 0.53 [95% CI, 0.33–0.86]) than patients on warfarin.

**Conclusions:** Novel predictors for PTS identified in our study include baseline Villalta score, leg pain severity at 10 days, and unemployed due to disability. Our findings also suggest that the initial choice of anticoagulant to treat DVT may have an impact on the development of PTS.

## KEYWORDS

deep vein thrombosis, postthrombotic syndrome, predictors, prognosis, venous thrombosis

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## Essentials

- The postthrombotic syndrome (PTS) is a common complication of deep vein thrombosis.
- This study used the ATTRACT trial study population to find new predictors for PTS.
- Baseline Villalta score and being unemployed due to disability were found to predict PTS.
- The use of rivaroxaban may protect against development of PTS, compared to use of warfarin.

## 1 | INTRODUCTION

The postthrombotic syndrome (PTS) is defined as a constellation of symptoms and signs following deep vein thrombosis (DVT).<sup>1</sup> The development of PTS has a significant negative impact on quality of life.<sup>2</sup> PTS has also been associated with significant economic burden. In patients diagnosed with DVT, health care costs were significantly higher in patients who developed PTS than in those who did not.<sup>3,4</sup> Given that there are limited ways to treat PTS, identification of risk factors could aid in targeting PTS prevention strategies. Multiple factors have been reported to be predictors of PTS, such as elevated body mass index, older age, male sex, and prior ipsilateral DVT.<sup>5,6</sup> In addition, characteristics and sequelae of the index DVT including more proximal anatomic extent of DVT, development of recurrent ipsilateral DVT, and presence of residual thrombosis on venous ultrasound at follow-up visits appear to be predictive of development of PTS.<sup>6,7</sup>

The ATTRACT (Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis) trial was a large, multicenter, randomized trial of pharmacomechanical catheter-directed thrombolysis (PCDT) plus anticoagulation versus anticoagulation alone (no PCDT) to prevent PTS in patients with acute proximal DVT.<sup>8</sup> In this exploratory analysis of the ATTRACT trial, we aimed to assess whether previously described risk factors for PTS predicted development of PTS and moderate to severe PTS during study follow-up in the ATTRACT trial population, and whether new predictors of PTS could be identified in this population.

## 2 | METHODS

The ATTRACT trial, conducted from 2009 to 2016, recruited patients with acute symptomatic DVT in the femoral, common femoral, or iliac vein at 56 clinical centers in the United States. Patients were excluded if they were younger than 16 years old or older than 75 years old, had symptoms for more than 14 days, were pregnant, had active cancer, or had established PTS prior to enrollment. Additional exclusion criteria can be found in trial's primary publication.<sup>8</sup> The protocol was approved by the ethics committee of each participating center, and written informed consent was obtained from all patients.

Participants were randomized 1:1 to either pharmacomechanical catheter-directed thrombolysis (PCDT) and standard care or standard care alone (no PCDT). All patients received initial and long-term

anticoagulation as recommended by guidelines at the time. Patients were required to receive at least 5 days of low-molecular-weight heparin or unfractionated heparin, with subsequent transition to either warfarin or rivaroxaban as determined by the clinician. Patients also received 30–40 mm Hg elastic compression stockings at the 10-day study visit, with replacement every 6 months.

Participants were assessed at study visits conducted at 10 and 30 days and 6, 12, 18, and 24 months after randomization. The primary outcome was the development of PTS, defined as a Villalta score of 5 or higher or a venous ulcer in the leg with the index DVT documented at any study visit during 6–24 months after randomization. Patients were also considered to have developed PTS if they underwent an unplanned endovascular procedure to treat severe venous symptoms beyond 6 months after randomization, unless a Villalta score within the previous 4 weeks was lower than 5. The occurrence of moderate-to-severe postthrombotic syndrome, defined as a Villalta score of 10 or greater documented at any study visit during 6–24 months after randomization, was assessed as a secondary outcome. The Villalta score is endorsed by the ISTH as the most suitable scale to diagnose and grade the severity of PTS.<sup>9</sup> At the 10-day and 30-day visits, leg pain was assessed using a 7-point Likert pain scale, and the type of anticoagulation used was registered.

For this secondary analysis of the ATTRACT trial, baseline variables and postrandomization variables were analyzed using univariate logistic regression to assess their ability to predict PTS and moderate to severe PTS during 6–24 months after randomization. Regarding missing data, any patient who missed assessments was considered to not have developed PTS. The list of variables, including age, body mass index (BMI), or the choice of anticoagulation, can be found in [Table 2](#).

All variables with a *p* value of less than 0.10 in univariate analysis were included in multivariable analyses to identify independent predictors of PTS. The variables age and BMI were included in all the models, given that they were previously confirmed to predict PTS. The randomized assignment to PCDT versus no PCDT was also included, given the nature of the trial. Finally, we chose to include sex in all models, given that its association with PTS remains uncertain. A multivariable logistic regression model was used to assess the predictors and the probability of developing PTS. Using a backward elimination modeling strategy, the additional predictors that maintained a *p* value of less than 0.05 on the basis of the likelihood ratio test were retained in the final model. All analyses were conducted by using SAS version 9.4 (SAS Institute). An alpha score of 0.05 or below was considered to be statistically significant.

**TABLE 1** Baseline and postrandomization characteristics

| Characteristic  | Total (N = 691) |
|---|-----------------|
| Age (years), mean (SD)  | 51 (13)         |
| Male sex, n (%)   | 426 (62)        |
| Race  |                 |
| White   | 541 (78)        |
| American Indian/Alaska Native   | 4 (1)           |
| Asian   | 5 (1)           |
| Black   | 123 (24)        |
| Not reported or refused   | 18 (22)         |
| Body mass index (kg/m <sup>2</sup> ), mean (SD)                         | 32 (7.6)        |
| Employment status, n (%)  |                 |
| Employed ≥35 h/week   | 324 (47)        |
| Employed <35 h/week   | 67 (10)         |
| Homemaker/housewife   | 15 (2)          |
| Unemployed due to disability  | 75 (11)         |
| Retired or unemployed due to other reasons                              | 208 (30)        |
| Unknown   | 2 (<1)          |
| Chronic kidney disease, n (%)   | 60 (9)          |
| Extent of DVT, n (%)  |                 |
| Iliofemoral DVT   | 391 (57)        |
| Femoropopliteal DVT   | 300 (43)        |
| Provoking factors for DVT, n (%)  |                 |
| Major surgery   | 61 (9)          |
| Hospitalization   | 64 (9)          |
| Plaster cast immobilization   | 17 (2)          |
| Previous DVT in index leg, n (%)  | 19 (3)          |
| Treatment allocation, n (%)   |                 |
| PCDT  | 336 (49)        |
| No PCDT   | 355 (51)        |
| Villalta score at baseline (range, 0–33), mean (SD)                     | 9.7 (5.4)       |
| Villalta score at baseline, Symptoms component (range, 0–15), mean (SD) | 5.5 (3.6)       |
| Villalta score at baseline, Signs component (range, 0–18), mean (SD)    | 4.1 (3.0)       |
| Use of anticoagulants at Day 10 visit, n (%) <sup>a</sup>               |                 |
| Warfarin  | 520 (75)        |
| Low-molecular-weight heparin  | 197 (29)        |
| Rivaroxaban   | 104 (15)        |
| Compression stocking use (any use), n (%)                               |                 |
| Day 30 (n = 55 missing responses)                                       | 497/636 (78)    |
| Month 6 (n = 116 missing responses)                                     | 389/575 (68)    |
| Month 12 (n = 160 missing responses)                                    | 328/531 (62)    |
| Month 18 (n = 223 missing responses)                                    | 275/468 (59)    |
| Month 24 (n = 208 missing responses)                                    | 268/483 (55)    |

Abbreviations: DVT, deep venous thrombosis; PCDT, pharmacomechanical catheter-directed thrombolysis; PE, pulmonary embolism; SD, standard deviation.

<sup>a</sup>Total of percentages are >100%, as some patients were on more than one anticoagulant.

**TABLE 2** Univariate logistic regression models for predictors of PTS

| Characteristic  | Odds ratio estimate (95% CI) | p value   |
|---|------------------------------|-----------|
| Age (per year increment)  | 1.02 (1.01–1.03)             | 0.003     |
| Sex (female vs. male)   | 0.89 (0.65–1.21)             | 0.45      |
| Race  |                              |           |
| White   | Reference                    | Reference |
| American Indian/Alaska Native                                   | 1.10 (0.15–7.84)             | 0.93      |
| Asian   | 0.73 (0.12–4.41)             | 0.73      |
| Black   | 0.95 (0.64–1.40)             | 0.79      |
| BMI (kg/m <sup>2</sup> ) (per unit increment)                   | 1.05 (1.03–1.08)             | <0.0001   |
| Employment status at baseline (vs. employed ≥35 h/week)         |                              |           |
| Employed <35 h/week   | 1.83 (0.90–3.71)             | 0.093     |
| Homemaker   | 1.88 (0.47–7.53)             | 0.37      |
| Unemployed due to disability                                    | 2.09 (1.09–4.01)             | 0.03      |
| Retired or unemployed for other reason                          | 1.08 (0.64–1.84)             | 0.76      |
| Extent of DVT (iliofemoral vs. femoropopliteal)                 | 1.28 (0.95–1.73)             | 0.11      |
| Provoking factors for DVT (yes vs. no)                          |                              |           |
| Major surgery   | 1.00 (0.59–1.70)             | 0.99      |
| Hospitalization   | 1.04 (0.62–1.75)             | 0.87      |
| Plaster cast immobilization                                     | 0.60 (0.22–1.63)             | 0.31      |
| Previous DVT or PE (yes vs. no)                                 | 1.00 (0.40–2.48)             | 0.99      |
| Treatment allocation (PCDT vs. No PCDT)                         | 0.94 (0.70–1.27)             | 0.70      |
| Villalta Score at baseline (per unit increment)                 | 1.10 (1.07–1.14)             | <0.0001   |
| Villalta Score, symptoms component (per unit increment)         | 1.11 (1.07–1.16)             | <0.0001   |
| Villalta Score, signs component (per unit increment)            | 1.16 (1.10–1.23)             | <0.0001   |
| Leg pain at Day 10 (per unit increment on 7-point Likert scale) | 1.39 (1.25–1.55)             | <0.0001   |
| Use of rivaroxaban on Day 10 (vs. warfarin)                     | 0.56 (0.36–0.87)             | 0.009     |
| Use of low-molecular-weight heparin at Day 10 (yes vs. no)      | 1.09 (0.78–1.52)             | 0.63      |
| Compression stockings use (yes vs. no)                          |                              |           |
| Day 30  | 0.58 (0.40–0.85)             | 0.006     |
| Month 6   | 0.93 (0.65–1.32)             | 0.67      |
| Month 12  | 1.02 (0.72–1.45)             | 0.91      |
| Month 18  | 1.04 (0.72–1.50)             | 0.85      |
| Month 24  | 1.38 (0.97–1.99)             | 0.08      |

Abbreviations: DVT, deep venous thrombosis; PCDT, pharmacomechanical catheter-directed therapy; PE, pulmonary embolism; SD, standard deviation.

### 3 | RESULTS

The mean age of the ATTRACT trial population (n = 691) was 51 years and 62% were male. Among study participants, 336 (49%)

were randomized to PCDT and 355 (51%) were randomized to no PCDT. Only 19 (3%) patients had a previous ipsilateral DVT. Additional baseline and postrandomization characteristics are shown in [Table 1](#).

PTS developed during follow-up in 328 of 691 (47%) patients, and moderate to severe PTS developed in 144 of 691 (21%) patients. A substantial proportion of patients reported wearing compression stockings during study follow-up (e.g., 78% at Day 30 and 55% at Month 24).

In the ATTRACT trial, a number of patients missed their study follow-up visits. Of 691 patients, 576 were assessed for PTS at 6 months, 530 at 12 months, 467 at 18 months, and 498 at 24 months. Due to losses to follow-up, 80 patients had no PTS assessments at all between 6 and 24 months. Baseline characteristics between the patients who missed all their PTS assessments versus patients who had at least one assessment were similar, except those who missed all PTS assessments were slightly younger and more likely to be female (data not shown).

### 3.1 | Univariate analyses

[Table 2](#) shows results of univariate analyses. For baseline variables, age (odds ratio [OR], 1.02; 95% confidence interval [CI], 1.01–1.03) and BMI (OR, 1.05; 95% CI, 1.03–1.08) were predictive of PTS development, whereas race, presence of provoking factors, extent of DVT, previous DVT or pulmonary embolism, and treatment allocation did not predict PTS. Regarding the postbaseline variables, the use of rivaroxaban at Day 10 (protective) (OR, 0.56; 95% CI, 0.36–0.87) was predictive of PTS development, as was use of compression stockings at Day 30 (OR, 0.58; 95% CI, 0.40–0.85) but not at other time points.

### 3.2 | Multivariable analyses

In multivariable analyses, baseline variables age (OR, 1.03 per year increase; 95% CI, 1.02–1.04) and BMI (OR, 1.05 per 1 kg/m<sup>2</sup>; 95% CI,

1.02–1.07) remained statistically significant predictors for the development of PTS, and sex (OR, 0.63; 95% CI, 0.44–0.92) for (female vs. male), Villalta score at baseline (OR, 1.09 per unit increment in score; 95% CI, 1.05–1.13), and employment status were also found to independently predict PTS. Regarding postbaseline variables, leg pain severity at Day 10 (OR, 1.28 per unit increment in score; 95% CI, 1.13–1.45) and use of rivaroxaban at Day 10 (OR, 0.53; 95% CI, 0.33–0.86) (protective effect) were independent predictors of PTS. The multivariable model is shown in [Table 3](#).

Results of the univariate and multivariable analyses of predictors of moderate to severe PTS are shown in [Tables S1](#) and [S2](#). Statistically significant independent predictors of the development of moderate to severe PTS included age, sex, BMI, employment status, baseline Villalta score, and leg pain at Day 10. In addition, use of rivaroxaban at Day 10 (vs. coumadin) had a greater impact in protecting from moderate to severe PTS (OR, 0.39; 95% CI, 0.19–0.78).

## 4 | DISCUSSION

In this secondary analysis of the ATTRACT trial, we aimed to confirm known risk factors for PTS as well as identify new factors that predicted development of PTS. We confirmed that age, sex, and BMI were predictors of PTS in the ATTRACT population. We also identified that baseline Villalta score, unemployment due to disability as assessed at baseline, and leg pain severity at 10 days are independent predictors of PTS. Our findings also suggest that the initial choice of anticoagulant to treat DVT may have an impact on the development of PTS. In contrast to some previous studies, we did not find that extent of DVT was predictive of PTS.

The above-noted independent predictors of PTS also predicted development of moderate to severe PTS, and the use of rivaroxaban at Day 10 had a more pronounced protective effect for moderate to severe PTS.

| Characteristic                                  | Odds ratio estimate (95% CI) | p value |
|---|------------------------------|---------|
| Age (per year increment)                        | 1.03 (1.02–1.04)             | <0.0001 |
| Sex (female vs. male)                           | 0.63 (0.44–0.92)             | 0.016   |
| BMI (kg/m <sup>2</sup> ) (per unit increment)   | 1.05 (1.02–1.07)             | 0.0002  |
| Treatment allocation (PCDT vs. control)         | 0.87 (0.61–1.22)             | 0.41    |
| Villalta Score at baseline (per unit increment) | 1.09 (1.05–1.13)             | <0.0001 |
| Leg pain at Day 10 (per unit increment)         | 1.28 (1.13–1.45)             | <0.0001 |
| Use of rivaroxaban on Day 10 (vs. warfarin)     | 0.53 (0.33–0.86)             | 0.0095  |
| Employment status (vs. employed ≥35 h/week)     |                              |         |
| Employed <35 hours per week                     | 1.77 (0.97–3.25)             | 0.064   |
| Homemaker                                       | 3.31 (1.72–6.35)             | 0.0003  |
| Unemployed due to disability                    | 3.87 (1.07–13.99)            | 0.040   |
| Retired or unemployed for other reason          | 0.97 (0.65–1.46)             | 0.89    |

**TABLE 3** Multivariable logistic regression model for predictors of PTS

Abbreviations: DVT, deep venous thrombosis; PCDT, pharmacomechanical catheter-directed therapy; PE, pulmonary embolism; SD, standard deviation.

## 4.1 | Strengths and weaknesses of the study

Our study has several strengths. Patients were prospectively enrolled in the ATTRACT trial, and baseline and follow-up data were carefully collected and documented as part of the trial procedures. In addition, PTS and moderate to severe PTS were assessed using a standardized PTS assessment tool by observers who were kept blinded to the patient's trial allocation group. Both baseline and postbaseline variables were assessed as potential predictors of PTS.

However, interpretation of the results must account for some limitations. The exclusion of patients with active malignancy limits the external validity of our study, as it is estimated that 20%–30% of DVT occurs in patients with active malignancy,<sup>10</sup> and it is unknown whether the risk factors for PTS identified in our study also apply to patients with cancer with DVT. ATTRACT evaluated an invasive fibrinolytic treatment method and like other similar studies, its patient population was on average younger and more male than traditional anticoagulation studies, which might influence the generalizability of this analysis to some degree.<sup>11</sup> Another limitation is that employment status may be a surrogate for underlying mobility, which could be linked to risk of PTS, but the ATTRACT trial did not collect information on degree of mobility per se or whether those employed had a physically active job versus a sedentary job, or the precise type of job. Hence, the interpretation of our finding of employment status as a predictor of PTS must be interpreted with caution. Caution is needed when interpreting associations between postbaseline variables and development of PTS, as these may reflect associations with other factors rather than causal associations. The ATTRACT trial was medium-sized, and this analysis focused on the occurrences of two binary outcomes; evaluation of outcomes that were measured on continuous scales (e.g., PTS severity using continuous scores on the Villalta scale or Venous Clinical Severity Scale, or quality of life scores) may have conferred additional statistical power.

The way missing data were handled also represents a limitation of our study. A nonnegligible number of patients missed PTS assessments at various study visits. Given that these patients were considered not to have developed PTS, this could have underestimated the associations between some predictors and development of PTS. Losses to follow-up can introduce bias if there are differences in likelihood of loss to follow-up that are related to predictor status and the outcome, PTS. Finally, all the statistical analyses are exploratory. Due to the retrospective nature of our secondary analysis, we were limited to examining PTS predictor variables that had already been collected for the ATTRACT trial and could not analyze additional variables of interest.

## 4.2 | Comparison of our results with the literature

Anatomic extent of DVT, and proximal versus distal location of DVT are clearly established in the literature as predictors of PTS.<sup>6</sup> Although the point estimates of the occurrences of PTS and moderate or severe PTS were higher in the patients with iliofemoral DVT

than the patients with femoral-popliteal DVT, the extent of DVT was not a statistically significant independent predictor of PTS in our study, perhaps because all patients in the ATTRACT trial had femoral or iliac DVT.

A history of prior ipsilateral DVT has also been described to strongly predict PTS<sup>6</sup> but was not a predictor of PTS in our study. However, because the ATTRACT trial excluded patients with ipsilateral DVT within the previous 2 years or established postthrombotic syndrome; the number of patients with previous ipsilateral DVT was very small in this analysis.

Our study suggests that rivaroxaban could play a protective role for the development of PTS and moderate to severe PTS when compared to coumadin, reducing the risk by about half. Several retrospective analyses<sup>12–15</sup> along with a recent small ( $n = 84$ ) randomized controlled trial<sup>16</sup> have supported this hypothesis. A recent meta-analysis<sup>17</sup> reported that the OR for the development of PTS when using rivaroxaban when compared to warfarin is around 0.53, similar to our results. The use of warfarin might lead to undertreatment of DVT in the context of subtherapeutic international normalized ratio. Rivaroxaban provides sustained and predictable anticoagulation in the first months after a DVT, which might explain its protective effect. On the other hand, it can be questioned whether a difference in antithrombotic effects (which appear absent or minimal in clinical studies comparing these agents) would be sufficient to explain this large apparent effect upon PTS. To date, recent studies of the association between other direct oral anticoagulants and PTS have not shown a protective effect,<sup>18</sup> raising the possibility that this effect, if confirmed, could be unique to rivaroxaban rather than a class effect. The possibility that this correlation may simply represent a noncausal association, perhaps due to a common effect of an unknown variable upon the choice of therapy and upon PTS, should also be considered.

## 4.3 | Implications of our study

Our study identified several baseline and postbaseline predictors of PTS. This information can be helpful for clinicians and patients during follow-up after acute DVT. Our findings on baseline predictors of PTS could also be helpful to guide acute DVT treatment; for example, the most recent American Society of Hematology anticoagulation guidelines for the management of venous thromboembolism suggest to consider baseline risk of PTS, among other factors, to help guide the decision as to whether or not to use thrombolysis in addition to anticoagulation in selected patients with acute DVT.<sup>19</sup>

## 4.4 | Unanswered questions and future research

While our study indicates that being unemployed might be a significant risk factor for the development of PTS, it remains unclear if this is due to the underlying health status of patients or reflects their mobility status. As it is known that immobility is a risk factor for DVT,<sup>20</sup>

subsequent studies should aim to assess the role of immobility in the development of PTS. We identified that rivaroxaban reduced the risk of PTS compared to warfarin. Further studies should be done to assess the relative associations between the various direct oral anticoagulants in relation to risk of PTS.

How might the results obtained in this study be applied to the care of DVT patients? While the Villalta Scale was developed as a tool to diagnose and grade the severity of chronic PTS, our findings support that when used to grade venous symptoms and signs at the time of acute DVT, it appears to have utility to help predict subsequent development of PTS. Patients who are at increased risk of PTS could be monitored more closely during follow-up to ensure therapeutic anticoagulation. Finally, even if up-front PCDT does not prevent PTS, future trials could assess whether targeting PCDT to patients with proximal DVT at higher baseline risk of developing PTS could be of benefit.

## 5 | CONCLUSION

We confirmed that age, sex, and BMI were predictors of PTS in the ATTRACT population. We identified that baseline Villalta score, leg pain severity at 10 days, and unemployment due to disability are independent predictors of PTS. We also identified an association between the initial choice of anticoagulants to treat DVT and the development of PTS.

### AUTHOR CONTRIBUTIONS

All the authors contributed equally to the research proposal and the interpretation of the data. Chu-Shu Gu completed the statistical analyses. Felix Rinfret and Susan R. Kahn drafted the manuscript, and all authors reviewed and revised the manuscript.

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### RELATIONSHIP DISCLOSURE

Felix Rinfret has no conflicts of interest to disclose. Susan R. Kahn has received grants for venous thrombosis research from the Canadian Institutes of Health Research and the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI), and served as a consultant to Alexion to develop educational materials. Suresh

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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