Comparison of Performance of Two Clinical Scales to Assess the Post-Thrombotic Syndrome: Secondary Analysis of a Multicenter Randomized Trial of Pharmacomechanical Catheter-Directed Thrombolysis for Deep Vein Thrombosis

Angela Young-Ju Lee, MDCM
Division of Experimental Medicine, Faculty of Medicine
McGill University, Montreal
Submitted: April 7, 2020

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Experimental

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Abstract

Introduction

The incidence of post-thrombotic syndrome (PTS) is 20-50% following proximal deep vein thrombosis (DVT), despite anticoagulation treatment. PTS is a chronic condition that is characterized by clinical symptoms and signs. Previously, the International Society on Thrombosis and Haemostasis (ISTH) recommended diagnosing and categorizing PTS severity using the Villalta scale. The Villalta scale is a composite score of 5 symptoms (pain, cramps, heaviness, paresthesia, and pruritus) and six clinical signs (pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, pain on calf compression), each graded out of 3 points. The diagnosis of PTS corresponds to a Villalta score of ≥5 or the presence of an ulcer. The categories of disease severity are mild, moderate and severe. Despite the ISTH's call for standardization, studies continue to use other clinical scales, such as the Venous Clinical Severity Score (VCSS) to assess PTS severity. The VCSS was developed for chronic venous disease, and not specifically PTS; the VCSS has no attributed threshold value to diagnose PTS.

Objective

We determined which of the two measures best captures clinically important PTS and PTS severity by 1) describing the Villalta and the VCSS scores at each assessment time in the entire Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial study population, 2) evaluating the correlation between the Villalta and VCSS during study follow-up, and 3) analyzing the relationship between 3a) Villalta scores and QoL scores and 3b) VCSS and QoL scores in the ATTRACT study population.

Methodology

A secondary analysis of the ATTRACT randomized controlled clinical trial published in the New England Journal Medicine was conducted. Patients between 16 to 75 years old with symptomatic proximal deep vein thrombosis of the femoral, common femoral, or iliac vein were enrolled from 56 clinical centers in the United States. The correlation of the Villalta scale, VCSS score, and QoL score, measured by the Short-Form Health Survey-36 version 2 (SF-36) and/or the Venous Insufficiency Epidemiological and Economic Study-QoL/Symptoms (VEINES-QoL/Sym) questionnaire were examined at the different pre-determined clinical visits from baseline to 24-month follow up. The correlation of random effects was assessed using a multivariate longitudinal model.

Results

The median of the correlations in all follow-up visits between Villalta scale and VEINES-QoL/Sym are -0.68 and -0.71 respectively. Between Villalta scale and SF-36 PCS/MCS, the median of the correlations are -0.51 and -0.31 respectively. The median of the correlations in all follow-up visits between VCSS and VEINES-QoL/Sym are -0.39 and -0.41 respectively. Between VCSS and SF-36 PCS/MCS, the median of the correlations are -0.32 and -0.13 respectively. The correlations between random effects in multivariate longitudinal model have a similar pattern. The impact from covariate adjustment by age, sex and BMI is minor.

Conclusion

The Villalta scale had a strong negative correlation with VEINES-QoL and VEINES-

Sym, a moderate negative correlation with SF-36 PCS, and a weak negative correlation with SF-36 MCS. Conversely, the VCSS had a weak negative correlation with VEINES-QoL, VEINES-Sym and SF-36 PCS, and a very weak negative correlation with SF-36 MCS. For all QoL measurements, the Villalta scale has a significantly higher correlation than does VCSS. Our findings support the use of the Villalta scale to assess PTS and PTS severity in preference to VCSS. The Villalta scale better captures the impact of PTS on patient reported QoL, a key consideration in patients with chronic PTS.

Résumé

Introduction

Malgré l'anticoagulation, l'incidence du syndrome post-thrombotique (STP) est de 20 à 50% suite à une thrombose veineuse profonde (TVP) proximale. Le STP est une maladie chronique caractérisée par des symptômes et des signes cliniques. Auparavant, la Société internationale de thrombose et d'hémostase (ISTH) recommandait le diagnostic et la gradation de la sévérité du STP à l'aide de l'échelle de Villalta. Celle-ci est un score composite qui comprend cinq symptômes (douleur, crampe, lourdeur, paresthésie et prurit) et six signes cliniques (œdème prétibial, induration cutanée, dermite ocre, érythème, varices, douleur à la compression du mollet). Chaque symptôme et signe clinique est évalué à partir d'un score de 0 à 3. Un score Villalta égal ou supérieur à cinq ou la présence d'un ulcère mène au diagnostic du STP. La sévérité de la maladie est repartit en trois grades, soit léger, modéré ou sévère. Bien que l'ISTH recommande l'utilisation de l'échelle de Villalta pour le diagnostic du STP et l'évaluation de sa sévérité, plusieurs études scientifiques et cliniques aient recours aux autres scores cliniques, notamment le Venous Clinical Severity Score (VCSS). Puisque ce dernier a été développé pour les maladies veineuses chroniques, il est non spécifique au syndrome de STP. Le score VCSS n'a donc pas de valeur seuil pour diagnostiquer le STP.

Objectif

Nous avons déterminé laquelle des deux outils, soit l'échelle de Villalta ou le score VCSS, représente mieux la sévérité du STP de façon cliniquement significative: 1) en décrivant les scores Villalta et VCSS à chaque évaluation de suivi de l'entière de la population de l'étude Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed

Thrombolysis (ATTRACT), 2) en évaluant la corrélation entre les scores Villalta et VCSS au cours de l'étude, et 3) en analysant la relation entre 3a) les scores Villalta et de qualité de vie et 3b) les scores VCSS et de qualité de vie dans la population de l'étude ATTRACT.

Méthodologie

Une analyse secondaire de l'essai clinique randomisé et contrôlé ATTRACT a été réalisée. Les patients âgés de 16 à 75 ans atteints d'une TVP proximale symptomatique fémorale, fémorale commune ou iliaque ont été recrutés à partir de 56 centres cliniques aux États-Unis. La corrélation de l'échelle de Villalta, du score VCSS et deux scores de qualité de vie ont été examinés à chaque visite de suivi. Les scores de qualité de vie utilisés dans l'étude sont les suivants : 1) Short-Form Health Survey-36 version 2 (SF-36), qui est composé d'un score physique (PCS) et d'un score mentale (MCS), et 2) Venous Insufficiency Epidemiological and Economic Study-QoL/Symptoms (VEINES-QoL / Sym)]. La corrélation des effets aléatoires a été évaluée à l'aide d'un modèle longitudinal multivarié.

Résultats

La médiane des corrélations de toutes les visites de suivi entre l'échelle de Villalta et le score VEINES-QoL / Sym est de -0,68 et de -0,71, respectivement. La médiane des corrélations entre l'échelle de Villalta et du score SF-36 est de -0,51 et de -0,31, respectivement. La médiane des corrélations de toutes les visites de suivi entre les scores VCSS et VEINES-QoL / Sym est de -0,39 et de -0,41, respectivement. Entre les scores VCSS et SF-36 PCS / MCS, la médiane des corrélations est de -0,32 et de -0,13, respectivement. Les corrélations entre les effets aléatoires

dans un modèle longitudinal multivarié ont démontré un schéma similaire. L'impact de l'ajustement des covariables selon l'âge, le sexe et l'indice de masse corporelle est mineur.

Conclusion

L'échelle de Villalta a démontré une forte corrélation négative avec les scores VEINES-QoL / Sym, une corrélation négative modérée avec le score SF-36 PCS et une faible corrélation négative avec le score SF-36 MCS. Contrairement, le score VCSS a démontré une faible corrélation négative avec les scores VEINES-QoL / Sym et SF-36 PCS et une très faible corrélation négative avec le score SF-36 MCS. Pour toutes les mesures de qualité de vie, l'échelle de Villalta a démontré une corrélation nettement supérieure à celle du VCSS. Nos résultats privilégient l'utilisation de l'échelle de Villalta pour diagnostiquer et évaluer la sévérité du STP plutôt que le score VCSS. L'échelle de Villalta tient mieux en compte de l'impact de STP sur la qualité de vie, ce qui est une considération clé pour les patients avec le STP chronique.

Contribution of Authors

Dr. Angela Lee and Dr. Kahn have both contributed in designing the research project. They have worked in collaboration with Chu-Shu Gu PhD to conduct the statistical analysis. Dr. Angela Lee was solely responsible for writing the outline and the multiple drafts of the thesis. Dr. Kahn, Dr. Blostein and Chu-Shu Gu critically reviewed the thesis.

Acknowledgements

First and foremost, I would like to thank Dr. Susan Kahn, my co-supervisor, for her unconditional support during the course of my graduate studies. Her utmost priority was assuring that I received relevant training, exposure, and experiences through course work, journal reviews, conferences, grant applications and teaching rounds, to maximize my learning. Her guidance and feedback were crucial for my academic, professional and personal growth.

I am grateful to Chu-Shu Gu PhD, senior biostatistician at McMaster University, for his work, guidance and feedback on the statistical analysis. He was fundamental in shaping the project. This thesis could not have been possible without him.

Additionally, I would like to thank Dr. Blostein for supervising my master's thesis and providing constructive feedback. I would also like to acknowledge Dr. Vicky Tagalakis, Dr. Maral Koolian and Dr. Ivan Topisirovic for their involvement as thesis committee members. I would like to thank CanVECTOR for the research start-up award and for a studentship which has helped support my graduate studies and learning.

Lastly, I would like to thank my wonderful parents and siblings that have encouraged me throughout my journey and have travelled hand-in-hand with me through the highs and lows. You have kept me grounded.

Chapter 1 – Literature Review

1. Venous Thromboembolism

Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease associated with major health and economic implications. VTE can affect hospitalized and community dwelling individuals. Accurate diagnosis of VTE is important because treatment with anticoagulants is associated with a risk of bleeding. Elucidation of the cause (i.e. underlying risk factors) for VTE and determining whether the VTE event was provoked or unprovoked are important for further diagnostic workup and treatment.

1.1 Epidemiology

VTE is the third most common cardiovascular disease following myocardial infarction and stroke; the estimated incidence of VTE is 0.5-2 per 1000 person-years; (1-5). The rate of DVT has remained relatively constant over time, however the number PE related hospitalizations have doubled (5-7). In the United States, the estimated annual cost burden of VTE is between $13.5 billion to $27.2 billion (7). The risk of 30 day mortality without treatment in DVT and PE were 3% and 31%, respectively (8). VTE poses a lifelong burden given its high frequency of recurrence; approximately 30% of VTE patients will experience a recurrence within 10 years (9-14).

The incidence of VTE is similar in males and females (5). It has been estimated that VTE will occurs in as high as 25% of hospitalized patients (15). Surgical procedures such as knee or hip replacements are associated with higher risk (16). Recurrence of VTE is 4-13 per 100,000 person-years (17). VTE has immediate health repercussions including death from PE, as well as

long-term complications such as post-thrombotic syndrome (PTS) after DVT and chronic thromboembolic pulmonary hypertension after PE.

1.2 Pathology of Venous Thromboembolism

Virchow's triad has described the pathophysiology of DVT since the mid-19th century. The triad, composed of various elements of endothelial dysfunction/damage, hypercoagulability and venous stasis, predisposes an individual to VTE formation (18).

1.2.1 Abnormalities of the Vessel Wall (Endothelial Dysfunction/Damage)

Endothelial cells produce tissue plasminogen activator and plasminogen activator inhibitor-1. Normally, the cells work harmoniously with nitric oxide, prostacyclin, and cell receptors to create an antithrombotic environment and to localize necessary thrombosis. In the event of endothelial damage or insult, the underlying collagen-rich subendothelial components and tissue factor become exposed. The exposed collagen activates factor XII of the intrinsic pathway. Tissue factor, a transmembrane receptor, found in extravascular tissue can now bind factor VII/VIIa and activate the extrinsic clotting pathway, which amplifies the clotting cascade. Ultimately, both pathways lead to the activation of factor Xa of the common pathway. Then, factor Xa along with co-factor V, cleave prothrombin into thrombin. Consequently, thrombin activates fibrinogen into fibrin. Together the pathways skew the system toward clot formation (18-22).

1.2.2 Hypercoagulability

Hypercoagulability may be due to hereditary or acquired thrombophilic changes. In

inherited hemophilia, factor V Leiden and prothrombin G20210 are frequently prevalent mutations. Factor V Leiden is the result of a mutation at an activated protein C (aPC) cleavage site, which makes it resistant to cleavage and deactivation by aPC (23). Prothrombin G20210 mutation allows for the increased production of prothrombin. Additionally, deficiencies in antithrombin, protein C and protein S and/or plasminogen are also hereditary thrombophilias (23, 24). Furthermore, elevated levels of factor VII, VIII, IX, and von Willebrand factor contribute to hypercoagulability (25, 26). Commonly acquired procoagulant states are cancer, chemotherapy, obesity, oral contraceptive use and hormone replacement therapy, and pregnancy (27-33).

1.2.3 Abnormal Blood Flow (Venous Stasis)

Increased circulatory stasis is a favorable environment for DVT formation. Reduced mobility whether it is in the form of prolonged bed rest, air travel or hospitalization decreases venous blood flow (34, 35). This increases the risk of thrombus formation (36, 37). Likewise, external venous compression by tumors or anatomical variants as seen in May Thurner syndrome also increases stasis of the blood (38). Congestive heart failure, reduced cardiac output and reduced mobility are also linked to increased blood stasis (39, 40). Despite abnormal blood flow increasing the propensity to thrombus formation, prolonged stasis alone is usually insufficient in causing thrombus formation and therefore is often seen in conjunction with other VTE risk factors.

1.3 Demographic and Clinical Risk Factors for Venous Thromboembolism

VTE risk factors can be multifactorial given their complex pathophysiology. As a result, they may influence one or more facets of Virchow's triad; an example of this is malignancy.

Certain types of cancers such as pancreatic, ovarian, brain and leukemias can more than double the risk of DVT (41, 42). Additionally, associated surgeries and complications, immobility, chemotherapy or hormonal effects of the disease can further augment the risk of DVT (42, 43).

Increasing age is one of the most important risk factors for VTE. More than 60% of patients with VTE are greater than 60 years of age (44). Moreover, VTE in children is rare, with 1 event per 100,000 per year, however there is an associated rise in incidence to nearly 1% per year in individuals greater than 75 years of age (3, 45, 46). Other strong predictors of DVT are obesity (BMI $\geq$ 30kg/m^2) and previous history of DVT which increases the risk of thrombosis twofold and fivefold, respectively (15, 27, 42). Elevated VTE risk has also been linked to oral contraceptive use (odds ratio [OR] 2.48), pregnancy and postpartum (relative risk [RR] 4.3), thrombophilia (RR >1-10 depending on the entity), and orthopedic surgery (OR 2 to $\geq$ 10 depending on the surgical procedure) (42, 47-51).

1.4 Clinical Presentation and Diagnosis of Deep Vein Thrombosis

DVT classically manifests as asymmetric limb swelling, with associated erythema, pain and warmth. However, the differential diagnosis for unilateral swelling of the limb is broad and physical examination is not specific for DVT. Therefore, it is important to complement any clinical suspicion of DVT with venous compression ultrasound and biomarkers in order to establish an accurate diagnosis.

1.4.1 Pre-Test Probability

The history, clinical presentation and physical exam can be used to calculate the pre-test probability of DVT, for which the Wells Score is most frequently used (Table 1) (52). The Wells

score consists of nine clinical findings that are assigned points and tallied into a total score. In the two-level Wells score, a score of <2 denotes a 6% probability of DVT, categorizing the presentation as "unlikely" DVT. A score of ≥2 has a 28% probability of DVT, categorically the presentation as "likely" (53). The estimated sensitivity and specificity of the Wells score is 77–98% and 38–58% respectively (54). In "unlikely" DVT individuals, the Wells score has a high negative predictive value, a good indicator to exclude DVT. However, the Wells score should not be used as a standalone diagnostic tool, but rather a guide for further investigation and treatment. Thrombosis Canada, in accordance with the National Institute for Health and Care Excellence guidelines, recommends D-dimer testing in "unlikely" pre-test probability stratified patients, and a proximal venous compression ultrasound in pre-test probability stratified "likely" patients (54, 55).

Table 1: The Wells Score for Predicting Pre-test Probability of Deep Vein Thrombosis

Clinical Findings	Points
Paralysis, paresis or recent orthopedic casting of lower extremity	1
Bedridden >3 days recently or major surgery within past 12 weeks	1
Localized tenderness of the deep veins	1
Swelling of entire leg	1
Calf swelling 3 cm greater than other leg (measured 10 cm below the tibial tuberosity)	1
Pitting edema greater in the symptomatic leg	1
Non-varicose collateral superficial veins	1
Active cancer or cancer treated within 6 months	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT (Baker's cyst, cellulitis, muscle damage, superficial vein thrombosis, post-thrombotic syndrome, inguinal lymphadenopathy, extrinsic venous compression)	-2

1.4.2 Biomarkers of Deep Vein Thrombosis

D-dimer is a fibrin degradation product found in the blood plasma following thrombus formation as a result of the fibrinolytic response. D-dimer has high sensitivity, but low

specificity for DVT, 75–100% and 26–83%, respectively (54). It is an acute phase reactant that is elevated in, but not limited to, malignancy, inflammation, infection, pregnancy and trauma (56-58). In the event of an "unlikely" DVT pre-test probability and a negative D-dimer, DVT can be ruled out (55, 59, 60). However, if the patient has a positive D-dimer, or has a "likely" pre-test probability of a DVT, then a compression ultrasound should be conducted in a timely manner (54, 55).

1.4.3 Imaging Modalities

Given its accessibility, cost-effectiveness and non-invasive nature, compression ultrasound is the first-line imaging modality for proximal DVT diagnosis. In the absence of full venous compressibility, a DVT is diagnosed. In conjunction with color flow Doppler, the specificity for proximal DVT is 94.2% and sensitivity 90% (61). Other imaging modalities are conventional contrast venography, computed tomography venography, and magnetic resonance venography (62). However, these methods may not be readily available or safe to use in patients with renal insufficiency or contrast allergies (63).

1.5 Treatment of Deep Vein Thrombosis with Anticoagulation

Recent evidence has consistently supported the use of non-vitamin K antagonist direct oral anticoagulants (DOAC) in the acute and extended treatment of DVT. The efficacy and safety of DOAC such as factor Xa inhibitors (i.e. apixaban, rivaroxaban, edoxaban) and oral direct thrombin inhibitors (i.e. dabigatran) has been demonstrated through randomized control trials and meta-analysis (64-69). Compared with standard older therapy defined as unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) followed by warfarin, there was no

significant difference in rates of recurrent VTE, recurrent DVT, recurrent PE, acute coronary syndrome, stroke, major bleeds, intracranial hemorrhage, cardiovascular death, or all-cause death (69). The American College of Chest Physicians (ACCP), Thrombosis Canada and the European Society of Cardiology guidelines recommend the use of DOAC in the treatment of DVT (55, 70, 71). However, LMWH is the preferred DVT therapy in patients with active malignancy or pregnancy (55, 72). The use of UFH is now limited to individuals with severe kidney failure (eGFR<30 ml/min/1.72 m^2) and/or high risk of bleeding who may need rapid reversal of anticoagulation (73). Warfarin may be preferred in cases where DOAC are contraindicated (i.e. a patient with severe renal dysfunction) or too expensive.

1.6 Complications of Deep Vein Thrombosis

Complications of DVT range from acute thrombus extension, acute PE, death, DVT recurrence, chronic thromboembolic pulmonary hypertension, and PTS (74). In addition to anticoagulation which helps resolve DVT and prevent complications, inferior vena cava filters can be effectively used in patients with proximal DVT or PE who cannot receive anticoagulation. However, there is an associated increased risk of recurrent DVT (12). The use of elastic compression stockings (ECS) and thrombolysis in the prevention of PTS will be discussed in section 2.6.

2. Post-Thrombotic Syndrome

PTS is a complication that may occur $\geq$ 6 months following the initial DVT, despite anticoagulation treatment (75). PTS is a chronic condition that is characterized by clinical symptoms and signs such as fatigue, pain, swelling, hyperpigmentation and heaviness in the

affected limb (Table 2) (76, 77). In more severe cases, patients can present with intractable edema and ulceration of the affected limb (75). The manifestations of PTS wax and wane over time (78). PTS is a syndrome because its clinical presentation varies from patient to patient. Furthermore, pre-existing venous insufficiency, recurrent DVT and other non-specific lower extremity complaints secondary to congestive heart failure present in a similar manner, or may appear concurrently with PTS (79, 80).

Table 2: Clinical Features of Post-Thrombotic Syndrome

Symptoms*	**Sign**
Heaviness	Edema
Fatigue	Peri-malleolar telangiectasiae
Pain	Venous ectasia, varicose veins
Swelling	Hyperpigmentation
Itching	Redness
Cramps	Dependant cyanosis
Paresthesia	Lipodermatosclerosis
Bursting pain when walking (venous claudication)	Healed or open ulcer

**Symptom pattern: Worse with activity, standing, walking; better with rest, recumbency, leg elevation*

2.1 Epidemiology

The incidence of post-thrombotic syndrome (PTS) is 20-50% following DVT despite anticoagulation treatment (78, 81). Recent trials such as the Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis (CaVenT) trial, the Compression Stockings to Prevent the Post-Thrombotic Syndrome (SOX) trial and the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial, have supported previous findings with 2-year PTS incidence ranging from 47% to 55.6% (82-84). Most cases of PTS develop within the first two years after DVT (78, 85). However, some studies have demonstrated an increase in incidence over the 5 years after DVT (86, 87). Meanwhile, one

study has shown a gradual increase in severity of PTS, but no increase in overall incidence beyond 1 year (88). Five to 10% of individuals will develop severe PTS after DVT (89-91). The incidence of venous ulceration after 2 to 5 years follow-up is 1% to 2%, and increases up to 10% at 10 years follow-up (89, 91-93).

2.2 Societal Burden of Disease

PTS confers an importance economic and morbidity burden to society. MacDougall *et al.* estimated the mean annualized total healthcare costs to be 32% higher in DVT patients with PTS than their counterparts without PTS. This difference in annualized total healthcare costs equated to $11,667 valued in 2004 US dollars (94). Similarly, the Canadian VETO study also demonstrated that the direct medical cost and total costs of patients with PTS were 35% to 45% greater than those without PTS (95). After hip replacement surgery, a strong risk factor for DVT, the annual cost of treatment per patient was estimated at $839 US for mild-to-moderate PTS and $3817 US for severe PTS. Moreover, PTS accounts for 74% to 81% of the total cost of treating DVT (96). A study in the US estimated that the direct annual cost of PTS is $\geq$ $200 million US dollars (97). Through numerous studies, Kahn *et al.* have demonstrated that PTS is associated with a significantly worse quality of life (QoL) compared to DVT patients without PTS, patients with other forms of chronic venous disease, and patients with osteoarthritis or chronic lung disease (92, 98-100).

Secondary costs attributable to PTS include the treatment of venous ulcers. Venous ulcers are the most costly consequence of PTS (101). The average total medical cost for treating venous stasis ulcers is $10,000 US per patient (102). Furthermore, venous ulcers are associated with increased absenteeism and adverse financial outcomes (103). In the US, approximately 2 million

workdays are lost on an annual basis as a result of venous ulcers. Though PTS is accountable for only a portion of venous ulcers, the associated burden of ulceration adds to the significant health and economic burden of PTS (95).

2.3 Pathophysiology of Post-Thrombotic Syndrome

The pathophysiology of PTS is not well understood. The primary pathophysiological disturbance in patients with PTS is sustained venous hypertension. Valvular reflux and persistent venous obstruction contribute to maintained venous hypertension (104). Consequently, elevated venous pressures compromise venous return, reduces perfusion of the calf muscle, and increases anomalous microvasculature which increases tissue permeability (76). Cellular players are leukocytes, platelet endothelial cell adhesion molecule, CCR7 expressing cells, intercellular adhesion molecule 1, interleukin 10 and matrix metalloproteases. These cellular components contribute to inflammation, vascular permeability and/or vein wall fibrosis which are believed to be necessary in the development of PTS (105-109).

2.4 Risk Factors for Post-Thrombotic Syndrome

Modifiable and non-modifiable risk factors have been linked to an increased risk of PTS. Notably, recurrent ipsilateral DVT and proximal location of the initial DVT are the strongest predisposing factors for PTS with 6-10 and 2-4 fold increased risk, respectively (90, 93, 110). Residual thrombus also increases the risk of PTS (111). Poor quality of anticoagulation is another risk factor associated with increased risk of PTS (85). Subtherapeutic international normalized ratio (INR) results in the initial 3 months while treating with vitamin K antagonists can increase the risk of PTS by a factor of 2-3 (91, 112). However, duration of anticoagulation is

not correlated to PTS risk nor is the nature of the initial DVT (i.e. provoked vs. unprovoked) (92, 104, 113). Systematic reviews and meta-analyses have been conducted to examine the association between thrombophilia, markers of fibrinolysis, endothelial dysfunction and PTS, however, no significant associations were found (113, 114). Older age, obesity, male and female sex, elevated D-dimer levels, and persistent venous symptoms 1 month after the initial DVT have been inconsistently reported to increase the risk of PTS (78, 89, 91, 93, 110, 115).

2.5 Treatment of Post-Thrombotic Syndrome

Conservative treatment of PTS consists of compression stockings and exercise training. Both are aimed at reducing the severity of PTS symptoms and signs and improving the QoL of patients. Compression stockings are the mainstay of treatment for established PTS. Compression stockings should be worn on a daily basis throughout the day until bedtime. A small study of 31 participants showed an improvement of PTS severity scores with daily use of stockings, particularly in those with moderate to severe PTS (30). Likewise, intermittent compression devices (i.e. pneumatic compression sleeves) are effective in moderate to severe PTS. They reduce PTS severity while increasing QoL (48, 116). In 2011, a small two center Canadian randomized controlled trial examined the effect of a 6-month intensive exercise training on PTS severity and QoL of patients. Exercise training focused on improving overall fitness, leg strength and leg flexibility. Patients who received the exercise intervention had improved QoL and reduced PTS severity (117). However, a subsequent study assessing compression therapy alone versus compression therapy in adjunct with exercise training and lymphatic drainage in improving PTS did not show a statistical significant difference between the two groups (118).

Evidence pertaining to the role of surgical or interventional radiological treatment in PTS is limited. Invasive procedures such as vein dilation and stent placement, venous bypass grafting, endophlebectomy with reconstruction, and valve reconstruction have been considered in moderate to severe forms of PTS that are refractory to other treatments. Improved ulcer healing rate and overall clinical improvement have been reported. However, complications relating to the interventions may occur and large studies with sound methodologies are required (116).

2.6 Prevention of Post-Thrombotic Syndrome

Prevention of PTS is largely dependent on the prevention of first and recurrent DVT and the prevention of the development of PTS after an initial DVT event. The effectiveness of thromboprophylaxis with anticoagulation and compression stockings to prevent a first DVT has been well documented. Thromboprophylaxis in high risk populations such as hospitalized medical and surgical patients is crucial in preventing DVT, given their $\geq$ 8 fold increase risk of VTE (119). Thromboprophylaxis reduces the risk of DVT by 50% to 60% (120). Even patients with asymptomatic DVT are 60% more likely to develop PTS than their counterparts without DVT (120, 121).

The evidence surrounding ECS as a means of preventing PTS is conflicting. Smaller studies have demonstrated that the use of 30-40 mmHg knee-high ECS for at least 2 years following proximal DVT effectively prevents PTS (110, 122). However, a more recent multicenter, large randomized controlled trial showed that there was no benefit of ECS worn for 2 years after DVT on PTS occurrence or severity, DVT recurrence and QoL compared to the placebo stocking arm (84). Based on the current evidence, the ACCP guidelines and experts do not suggest routine use of ECS for the prevention of PTS (70, 123).

Thrombolysis at the time of acute DVT has also been studied as a means to prevent PTS. The rationale behind thrombolysis is that by delivering thrombolytic agent to the clot, one would restore acutely patency of the vessel and reduce clot burden. Ultimately, this would reduce the risk of PTS (124, 125). Previously, studies demonstrated that catheter-directed thrombolysis was associated with near complete thrombus lysis, improved venous patency, and reduction of PTS, at the cost of more bleeding complications (126). However, in 2017, the multicenter ATTRACT trial demonstrated that pharmacomechanical catheter-directed thrombolysis (PCDT) plus anticoagulation did not lower the risk of PTS compared to anticoagulation alone, and led to a higher risk of major bleeding (82).

2.7 Diagnosis of Post-Thrombotic Syndrome and Clinical Scales

There is no objective gold standard biomarker test or imaging test to diagnose PTS. Thus, PTS is a clinical diagnosis. Diagnosis is based on the presence of clinical symptoms and signs that occur at least 3-6 months after an initial DVT. Diagnosis of PTS is deferred until then because the acute phase of DVT and its associated pain and swelling can last up to several months (127).

Several PTS classification and severity scales have been developed, assessed and used in the literature, including the Villalta scale (discussed at the end of this section), the Brandjes score and the Ginsberg measure (122, 128, 129). Additionally, clinical scales developed for chronic venous insufficiency such as the Clinical, Etiologic, Anatomic, and Pathophysiologic (CEAP) classifications and the Venous Clinical Severity Score (VCSS) have also been used to evaluate PTS (130, 131).

2.7.1 Brandjes score

The Brandjes score was designed to assess the effect of compression stockings in patients with symptomatic proximal DVT (Table 3) (122). The diagnosis of mild-moderate PTS consists of a score of 3 and must include one objective criterion. A score of ≥ 4 corresponds to severe PTS. All criteria are assigned 1 point except venous ulcer, which is assigned 4 points. The Brandjes score does not differentiate between patients with healed ulcers versus non-healing ulcers. Therefore, a patient who has had a venous ulcer following a DVT, regardless of whether it has healed or not, will always be categorized as having severe PTS.

Table 3: Brandjes Score

Subjective Criteria		**Objective Criteria**	
Symptoms	Score	Signs	Score
Spontaneous pain in calf	1	Calf circumference increased by 1cm	1
Spontaneous pain in thigh	1	Ankle circumference increased by 1 cm	1
Calf pain on standing/walking	1	Pigmentation	1
Thigh pain on standing/walking	1	Venectasia	1
Edema of foot/calf	1	Newly formed varicosis	1
Heaviness of foot/calf	1	Phlebitis	1
Spontaneous pain and pain on walking/standing	1	Venous ulcer	4
Impairment of daily activities	1		

2.7.1 Ginsberg Measure

The Ginsberg measure defines PTS by persistent swelling and leg pain of a chronic nature every day for at least 1 month. The pain and swelling is characterized by relief with rest and elevation and aggravation by prolonged standing; it must occur at least 6 months after DVT (129). The Ginsberg measure does not categorize severity of PTS. When compared to the Villalta scale, the Ginsberg measure identifies more severe disease with worse QoL (132).

2.7.3 CEAP Classification

The CEAP classification consists of a descriptive categorization of chronic venous disease by clinical signs, etiology, anatomic distribution and pathophysiology. The CEAP clinical classification divides the level of clinical severity into 8 classes; it does not have a threshold value corresponding to the absence or presence of PTS (Table 4) (130). This classification system has limited ability to asses change over time (133).

Table 4: CEAP Clinical Classification

Class	Signs
C_0	No visible or palpable sign of venous diseases
C_1	Telangiectasias or reticular veins
C_2	Varicose vein; distinguished from reticular veins by a diameter of 3mm or more
C_3	Edema
C_{4a}	Pigmentation or eczema
C_{4b}	Lipodermatosclerosis or atrophic blanche
C_5	Healed venous ulcer
C_6	Active venous ulcer

2.7.4 Venous Clinical Severity Score

The VCSS draws clinical elements from the CEAP classification and also contains additional criteria such as pain and use of compressive therapy (Table 5). The VCSS provides a numerical score that allows for presence and severity of chronic venous disease. The levels of severity and their corresponding points are as follows: absence of disease $\leq$ 3 points, mild to moderate disease 4-7 points, and severe disease $\geq$ 8 points (134). The VCSS does not have a cut-off value to diagnose PTS; rather, it has been used to measure severity of PTS (131). Another limitation is that only one patient symptom (pain) is assessed.

Table 5: VCSS

Descriptor	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
Pain or other discomfort (ie, aching, heaviness, fatigue, soreness, burning) Presumes venous origin	None	Occasional pain or other discomfort (ie, not restricting regular daily activities)	Daily pain or other discomfort (ie, interfering with but not preventing regular daily activities)	Daily pain or discomfort (ie, limits most regular daily activities)
Varicose vein "Varicose" veins must be ≥3 mm in diameter to qualify in the standing position.	None	Few: scattered (ie, isolated branch varicosities or clusters) Also includes corona phlebectatica (ankle flare)	Confined to calf or thigh	Involves calf and thigh
Venous edema Presumes venous origin	None	Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin pigmentation Presumes venous origin Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Inflammation More than just recent pigmentation (ie, erythema, cellulitis, venous eczema, dermatitis)	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Induration Presumes venous origin of secondary skin and subcutaneous changes (ie, chronic edema with fibrosis, hypodermitis). Includes white atrophy and lipodermatosclerosis	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf

Active ulcer number	0	1	2	≥ 3
Active ulcer duration	N/A	< 3 months	> 3 months but <1 year	Not healed for > 1 year
Active ulcer size	N/A	Diameter < 2cm	Diameter 2-6 cm	Diameter > 6cm
Use of compression therapy	Not used	Intermittent use of stockings	Wears stockings most days	Full compliance: stockings

2.7.5 Villalta Scale

The Villalta Scale was specifically developed to evaluate patients with PTS. The Villalta scale can both diagnose and classify the severity of PTS. It is comprised of five symptoms (pain, cramps, heaviness, paresthesia, and pruritus) and six clinical signs (pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, pain on calf compression). Each of the 11 items is graded from 0 (not present) to 3 points (severe), for a maximum total score of 33 points (Table 6). The diagnosis of PTS corresponds to a Villalta score of ≥5 or presence of an ulcer. The three categories of disease severity are mild (score 5-9), moderate (score 10-14) and severe (score ≥15) (128).

Table 6: Villalta Scale

Symptoms/ Signs	**None**	**Mild**	**Moderate**	**Severe**
	Points			
Pain	0	1	2	3
Cramps	0	1	2	3
Heaviness	0	1	2	3
Paresthesia	0	1	2	3
Pruritus	0	1	2	3
Pretibial edema	0	1	2	3
Skin induration	0	1	2	3
Hyperpigmentation	0	1	2	3
Redness	0	1	2	3
Venous ectasia	0	1	2	3
Pain on calf compression	0	1	2	3

Note: Venous ulcer - absent (0), present (15)

The inter-rater reliability of the Villalta scale measured by the weighted kappa statistic was good to excellent for total score, sum of signs scores, sum of symptoms score, PTS severity categories, absence versus presence of PTS and moderate/severe PTS versus no PTS/mild PTS (128, 135). The Villalta scale is responsive to change in PTS severity (136). Worsening severity (i.e. increased Villalta scale scores) was correlated to statistically and clinically significant changes in generic physical QoL and venous disease specific QoL (99). Likewise, improvement of PTS captured by the Villalta scale was associated with an increase in venous disease specific QoL (137).

Given the lack of a "gold-standard" diagnostic test for PTS, the validity of the Villalta scale is gauged by the ability of its designed thresholds and scores to correlate with related health outcomes and anatomical/pathological changes seen in chronic venous disease (136). Increase in Villalta scores (i.e. worsening PTS) has a strong negative correlation with generic and venous disease-specific QoL, measured by the Short-Form Health Survey-36 version 2 (SF-36) and the Venous Insufficiency Epidemiological and Economic Study-QoL/Symptoms (VEINES-QoL/Sym) questionnaire, respectively (92, 98, 138, 139). PTS defined as a Villalta score ≥ 5 was found to be associated with an increased frequency of residual vein thrombosis and/or popliteal valvular reflux on Duplex ultrasound (140). Furthermore, in patients with prior DVT, the mean ambulatory venous pressure increased in a step-wise fashion in response to the increase in Villalta severity category (141). The reliability, validity, acceptability and responsiveness to changes in PTS are the bases for the recommendation by the International Society on Thrombosis and Haemostasis (ISTH) to use the Villalta scale to diagnose and categorize the severity of PTS (75). This call for standardization by the ISTH was intended to facilitate the exchange of information between researchers, clinicians and studies.

In summary, DVT is a common cardiovascular disease. DVT can be objectively diagnosed using imaging such as ultrasound and is treated for many months or longer with anticoagulants. Despite anticoagulation, up to 50% of patients will go on to develop PTS, a chronic condition with a high economic and societal burden of diseases. To date, there are few effective ways to prevent or treat PTS. Diagnosis and grading the severity of PTS is achieved using clinical PTS scales; most commonly used are the Villalta scale and the VCSS. Of interest, hematology and thrombosis researchers have tended to rely on the Villalta scale, while interventional radiologists and vascular surgeons tend to use the VCSS. Independently, each of the Villalta Scale and the VCSS have demonstrated a correlation with patient reported QoL outcomes (92, 138, 142, 143), however, thus far, it has not been directly established which of these two measures best captures PTS. The overall objective of this thesis is to determine which of these two measures best identifies and characterizes clinically important PTS and PTS severity.

Chapter 2 – Rationale and Objectives

The incidence of PTS is 20-50% following proximal DVT, despite anticoagulation treatment (81, 85, 89, 110, 144). PTS is a chronic condition that is characterized by clinical symptoms and signs which may be severe (128). Previously, ISTH recommended diagnosing and categorizing PTS severity using the Villalta scale (75, 128, 136). As presented above, the Villalta scale is a composite score of five symptoms (pain, cramps, heaviness, paresthesia, and pruritus) and six clinical signs (pretibial edema, skin induration, redness, hyperpigmentation, venous ectasia, pain on calf compression), each graded out of 3 points. The diagnosis of PTS corresponds to a Villalta score of ≥5 or the presence of a venous ulcer (136). The categories of PTS severity are mild, moderate and severe. Despite the ISTH's call for standardization and recommendation to use the Villalta scale, many investigators continue to use other clinical scales such as the VCSS to diagnose PTS and assess its severity. The VCSS was developed for chronic venous disease, and not specifically PTS; the VCSS has no validated threshold value to diagnose PTS (145).

To our knowledge, there have been no large studies that have directly compared whether the Villalta scale or the VCSS better identifies and characterizes clinically important PTS and PTS severity. Hence, this thesis will firstly describe the Villalta and the VCSS scores at each assessment time in the ATTRACT trial study population (as explained in next section) and in relevant patient subgroups. We will also evaluate the correlation between the Villalta and VCSS during study follow-up. Then, we will analyze the relationship between 1) Villalta scores and QoL scores (using generic and disease specific measures), and 2) VCSS and QoL scores in the ATTRACT study population.

My thesis project will help to better characterize and compare the performance and value

of tools that are commonly used to diagnose and grade the severity of PTS. Our results will be useful in standardizing the approach to diagnosing, assessing and following PTS in patient populations in research and clinical settings.

Chapter 3 – Methodology

1. Study Design

This study is a secondary analysis of the ATTRACT randomized controlled clinical trial (NCT00790335) (82). The ATTRACT trial was designed to assess whether treatment of proximal DVT with PCDT in addition to standard DVT treatment decreases the incidence of PTS compared to standard DVT treatment alone. Secondary efficacy outcomes were the proportions of patients with moderate-to-severe PTS, the combined outcome of PTS or major non-PTS treatment failure, and of most relevance to this thesis, VCSS scores and patient-reported health-related quality of life (QoL). Other secondary efficacy outcomes as well as safety outcomes were reported in the main publication (82). The rationale and study design for the ATTRACT Trial have been reported in detail elsewhere (146).

2. Population

Between December 2009 and December 2014, patients between 16 years to 75 years old with symptomatic proximal DVT of the femoral, common femoral, or iliac vein in 56 clinical centers in the United States were enrolled in the ATTRACT Trial. Exclusion criteria included, but were not limited to, pregnant patients, patients with non-acute symptomatic DVT (symptomatic for >14 days), active bleeding or high bleeding risk, or diagnosis of PTS or previous DVT in the index leg in the past 2 years (82).

3. Randomization and Treatment

Eligible patients were randomly assigned in a 1:1 ratio to one of two treatment groups: pharmacomechanical catheter-directed thrombolysis (PCDT) (active intervention) or control

group. All patients received standard anticoagulation and compression stockings. Additionally, the PCDT treatment group underwent a procedure which included the delivery of recombinant tissue plasminogen activator (rt-PA) into the thrombus by a Trellis catheter or an AngioJet Rheolytic Thrombectomy System. Following the initial rt-PA delivery, one of multiple adjunctive treatments such as bolus rt-PA, aspiration or mechanical thrombectomy and balloon maceration could be conducted, at the discretion of the endovascular physician, to remove residual thrombus. However, the total rt-PA dose could not exceed 35mg. Treatment was stopped when 1) $\geq$ 90% of the thrombus was removed with restoration of flow; 2) the maximum dose of 35mg of rt-PA was administered or 30 hour maximum infusion duration was reached; or 3) the patient suffered from overt bleeding or any other complication that necessitated cessation of therapy. All procedures were performed by board-certified endovascular physicians that were reviewed and approved by an Interventions Credentialing Committee. Randomization was stratified by clinical center and extent of thrombus (i.e. presence or absence of common femoral vein and/or iliac vein involvement). The randomization process was computer generated and overseen by an independent statistician to ensure concealment.

4. Post-Thrombotic Syndrome Measures

ATTRACT Trial patients were followed for 24 months. Patients and assessors completed the Villalta scale at baseline, and then subsequently at 10 days, 1, 6, 12, 18 and 24-month follow-up visits. PTS was defined by a Villalta score $\geq$ 5 or development of an ulcer at any time from the 6-month post-randomization follow-up visit up to the 24-month visit. All patients that underwent an unplanned endovascular intervention to treat severe symptomatic disease in the index DVT leg 6 months or later following randomization were considered to have PTS. The

VCSS was administered to patients at the 6, 12, 18 and 24-month follow-up visits. The descriptor "use of compression stockings" was not tallied into the VCSS score because the use of compression stockings was standardized in the trial. Patients were instructed not to wear their compression socks on the day of their follow-up visit. This was to allow for their symptoms and signs to manifest, for more accurate evaluation of venous symptoms and signs.

Clinical assessors were trained prior to their first administration of the Villalta Scale and VCSS through a web-based training module. Standardized graphic depictions of the Villalta Scale clinical signs and instructions on grading the VCSS clinical signs were provided to all enrolling centers and made available to clinical assessors. All clinical assessors were blinded to patient treatment allocation. Furthermore, patients were instructed not to divulge which leg was the index DVT leg to the assessor.

5. Quality of Life Measures

QoL was assessed using general and venous disease-specific QoL measures: the Short-Form Health Survey-36 version 2 (SF-36) and the Venous Insufficiency Epidemiological and Economic Study-QoL/Symptoms (VEINES-QoL/Sym) questionnaire, respectively. The SF-36 is a generic health related QoL measure which was constructed based on the Medical Outcome Study (147). It consists of eight health scales: physical functioning (10 items), role limitations–physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role limitations–emotional (3 items), and mental health (5 items). The scores from these 8 health scales are combined into two components: physical component summary (SF-36 PCS) and mental component summary (SF-36 MCS). The VEINES-QoL/Sym is a questionnaire containing 26 questions regarding venous symptoms, limitations in daily

activities, time of day of greatest intensity, change over the past year, and psychological impact. The VEINES-Sym is a validated subset that looks solely at the symptoms of the VEINES-QoL. The VEINES-QoL/Sym have been previously validated in PTS (138). Both the SF-36 and the VEINES-QoL/Sym were administered at baseline and at the 1, 6, 12, 18 and 24-month follow-up visits. Table 7 shows the schedule of assessments of the Villalta scale, VCSS, and QoL measures.

Table 7: Assessment Schedule of Different Scales

Scales	Clinical Follow-Up Visit					
	Baseline	**1-month**	**6-month**	**12-month**	**18-month**	**24-month**
Villalta Scale	✓	✓	✓	✓	✓	✓
VCSS			✓	✓	✓	✓
General QoL SF-36v2 36 (SF- 36 PCS/MCS)	✓	✓	✓	✓	✓	✓
Venous QoL VEINES-QoL/Sym	✓	✓	✓	✓	✓	✓

6. Statistical Analysis

This secondary analysis of the ATTRACT Trial was overseen by Chu-Shu Gu PhD (McMaster University), the trial's statistician. For the secondary analysis, all patients randomized into either the control arm or the intervention arm were included. This was to maximize the power of the study. Furthermore, the ATTRACT trial previously demonstrated that the severity of PTS denoted by the mean Villalta Scale and the VCSS was significantly lower in the intervention arm compared to the control group at all follow-up visits. Hence, by including patients that underwent PCDT, we were able to capture more mild severity of disease that may not have been sufficiently represented by solely the control arm. Additionally, all the assessment scales are used in a clinical context to assess medically treated, surgically treated and untreated

patients. The Pearson correlation coefficient analysis was used to calculate the association, at the various assessment points, between 1) the Villalta score and the VCSS score; 2) the Villalta score and QoL scores (SF-36 PCS/MCS; VEINES-QoL/Sym); and 3) the VCSS and QoL scores (SF-36 PCS/MCS; VEINES-QoL/Sym).

The correlation between the Villalta Scale and the VCSS were analyzed using combinations of each scale as a continuous, dichotomous (absence of disease or presence of disease), and/or ordinal scale (severity groups). The Pearson correlation coefficient was calculated between the Villalta scale and VCSS as continuous scales. Its confidence interval was obtained through Fisher z-transformation. Spearman's rank correlation coefficient was calculated for the remaining conditions. Their confidence interval was obtained through Bonett and Wright Transformation. T-test and one-way ANOVA were used for comparisons between/among groups for continuous scores.

In the published ATTRACT Trial univariate longitudinal model, the outcome was modeled as a growth curve model with a piece-wise linear regression (82). Alternatively, for the ease of exploration of the relationship between two scales, the multivariate longitudinal model in this work was a growth curve model with a polynomial function to model time. Given the stronger association between the disease severity scores and the venous disease specific QoL measure, the Villalta score, VCSS score, VEINES-QoL and VEINES-Sym were modelled as a quadratic curve of time using multivariate longitudinal modelling. The correlation between the random effects from the different scales was adjusted for the covariates of age, sex and body mass index (BMI). In all analyses, to account for multiple testing, the two-sided P value of $\leq$ 0.01 was considered to indicate statistical significance in all analyses.

6.1 Missing Data

In the situation where the PTS questionnaire was only partially completed, a simple imputation algorithm was used to complete the questionnaire. If the symptom responses were missing, then each missing response would be assigned the mean score of the completed symptom responses. Similarly, if any sign responses were missing, then they would be assigned the mean score of the sign responses. If all the symptom responses were missing, then each incomplete response would take on the value of the mean of the completed sign responses, and vice versa. If all responses for both the symptoms and signs portion were missing, then the evaluation was considered missing. In the context of a partially-completed SF-36 and VEINES-QoL, scores were generated using standard imputation algorithms (82).

Chapter 4 – Results

1. Baseline Characteristics

Of the 691 patients analyzed in the ATTRACT trial, 336 patients were randomized to PCDT and 355 patients were randomized to control (Table 8). One patient that was randomized to PCDT was removed from analyses because on blinded review of the pre-randomization assessments, the patient did not meet DVT inclusion criteria.

The mean age at enrolment was 51 years of age, 78% were white, 62% were male, the mean BMI was 32 kg/m^2, 57% had iliofemoral DVT, 19% had a previous ipsilateral DVT, mean time between DVT diagnosis and randomization was 6.9 (standard deviation, SD = 4.2) days, and 93% were taking one or more anticoagulation therapies prior to randomization. At baseline, 35% of the patients reported mild disease as per the Villalta Scale severity categories. The VCSS was only administered starting at the 6-month follow-up visit. Further details are shown in Table 8.

Table 8: Baseline Characteristics

Characteristics	All Patients N=691
Age at Enrollment, years: *mean (SD)*	51 (13)
Age Group: *n (%)*	
< 45	204 (30)
45 – 54	171 (25)
55 – 64	194 (28)
65 – 75	121 (17)
Unknown	1 (<1)
Sex: *n (%)*	
Female	265 (38)
Male	426 (62)
Ethnicity: *n (%)*	
Hispanic/Latino	41 (6)
Not Hispanic/Latino	629 (91)
Not reported or refused	21 (3)
Race: *n (%)*	

Characteristics	All Patients N=691
American Indian/Alaska Native	4 (1)
Asian	5 (1)
Black/African-American	123 (18)
Native Hawaiian/Other Pacific Islander	0
White	541 (78)
Not reported or refused	18 (3)
Race: *n (%)*	
White	541 (78)
Black/African-American	123 (18)
Other	27 (4)
Medical History: *n (%)**	
Diabetes	113 (16)
Angina/MI	28 (4)
Congestive Heart Failure	32 (5)
Weight, kg: *mean (SD)*	97 (24)
BMI, kg/m^2: *mean (SD)*	32 (7.6)
BMI Class: *n (%)*	
< 25 kg/m^2	115 (17)
25 to < 30 kg/m^2	208 (30)
≥ 30 kg/m^2	364 (53)
Unknown	4 (1)
Villalta (PTS) Class: *n (%)*	
None (score 0-4)	126 (18)
Mild (score 5-9)	239 (35)
Moderate (score 10-14)	192 (28)
Severe (score ≥ 15)	132 (19)
Unknown	2 (<1)
Extent of DVT: *n (%)*	
Iliofemoral DVT	391 (57)
Femoropopliteal DVT	300 (43)
Treatment Group: *n (%)*	
PCDT arm	336 (49)
Control arm	355 (51)
Previous Ipsilateral DVT: *n (%)*	19 (3)
Pre-Rand Anticoagulant Therapy: *n (%)**	645 (93)
LMWH	385 (60)
UFH	198 (31)
Fondaparinux	7 (1)
Rivaroxaban	27 (4)
Warfarin	333 (52)
Other	27 (4)

**Subjects may fit into more than one category*

2. Comparison of the Villalta Scale and VCSS

The correlation between the Villalta Scale and the VCSS was assessed (Table 9). The VCSS was analyzed as a continuous, dichotomous (absence of disease < 4 or presence of disease ≥ 4), and ordinal scale (none < 4, mild-moderate 4-7 and severe ≥ 8). Comparably, the Villalta Scale was analyzed as a continuous, dichotomous (absence of disease <5 or presence of disease ≥5), ordinal 1 (none < 5, mild 5-9, moderate 10-14 and severe ≥ 15), and ordinal 2 scale (none < 5, mild-moderate 5-14 and severe ≥15). The strength of correlation between continuous Villalta Scale and continuous VCSS was consistently >0.7 at all follow-up visits, which corresponds to strong correlation. The majority of correlation coefficients between continuous, dichotomous, and/or ordinal scales at the different time points ranged from 0.5-0.7 which corresponds to moderate correlation. The correlation between the continuous Villalta Scale and continuous VCSS had a tendency to be stronger than other combinations. There was minimal change in the correlation coefficient between the 6-month and the 24-month follow-up visit for a given pairing of Villalta and VCSS categorization.

Table 9: Correlation Between Villalta Score and VCSS Score by Follow-up Visit

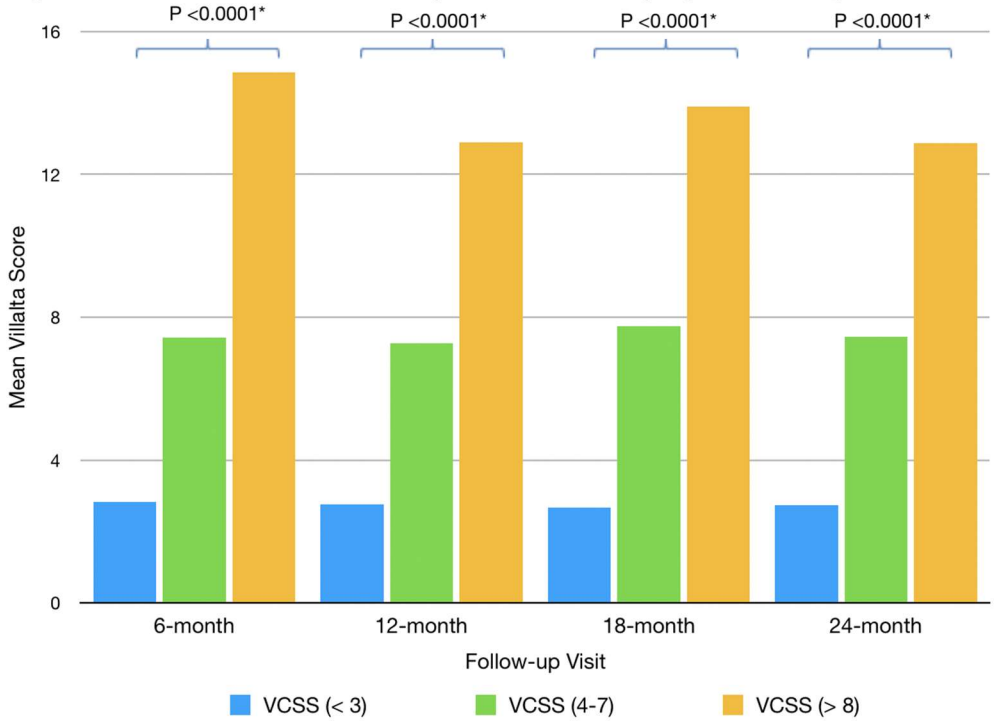
Villalta*	**VCSS****	**Visit**	**Pearson's / Spearman's rank correlation coefficient**	
			Estimate	*95% CI*
Continuous	Continuous	6 m	0.71	0.66, 0.75
		12 m	0.70	0.66, 0.74
		18 m	0.74	0.69, 0.78
		24 m	0.72	0.67, 0.76
Dichotomous	Continuous	6 m	0.51	0.44, 0.57
		12 m	0.55	0.48, 0.61
		18 m	0.57	0.50, 0.63
		24 m	0.59	0.52, 0.65
Ordinal 1	Continuous	6 m	0.53	0.47, 0.59
		12 m	0.57	0.51, 0.63
		18 m	0.60	0.53, 0.66
		24 m	0.60	0.54, 0.66

Dichotomous	Dichotomous	6 m	0.51	0.45, 0.58
		12 m	0.49	0.42, 0.56
		18 m	0.58	0.51, 0.64
		24 m	0.52	0.45, 0.59
Dichotomous	Ordinal	6 m	0.52	0.46, 0.58
		12 m	0.50	0.43, 0.56
		18 m	0.59	0.52, 0.65
		24 m	0.53	0.46, 0.59
Ordinal 2	Dichotomous	6 m	0.53	0.47, 0.59
		12 m	0.51	0.44, 0.58
		18 m	0.60	0.54, 0.66
		24 m	0.54	0.47, 0.60
Ordinal 2	Ordinal	6 m	0.55	0.48, 0.61
		12 m	0.52	0.45, 0.59
		18 m	0.62	0.55, 0.68
		24 m	0.55	0.48, 0.61

**Dichotomous: < 5 vs ≥ 5; Ordinal 1: None (< 5), Mild (5-9), Moderate (10-14) and Severe (≥ 15); Ordinal 2: None (< 5), Mild-Moderate (5-14) and Severe (≥ 15)*
*** Dichotomous: < 4 vs ≥ 4; Ordinal: None (< 4), Mild-Moderate (4-7) and Severe (≥ 8)*

The mean Villalta score was calculated for the different VCSS severity categories at the 6, 12, 18 and 24-month follow-up visits (Figure 1). The mean Villalta score ranged from 2.66 to 2.82 for VCSS ≤3 (absence of disease). This corresponds to a Villalta severity category of absence of PTS. For VCSS 4-7 (mild-moderate), the mean Villalta score ranged from 7.26 to 7.75, which corresponds to mild PTS as per the Villalta severity categories. VCSS ≥8 (severe) yielded a mean Villalta score which ranged from 12.90 to 14.86. This corresponds with moderate PTS as per the Villalta Scale. The proportion of patients in VCSS ≤3 was 0.75 to 0.77 patients depending on the follow-up visit. VCSS 4-7 ranged from 0.17 to 0.20 patients. VCSS ≥8 ranged from 0.04 to 0.06 patients (Appendix 1). At the 6-month follow-up visit and all subsequent visits, ANOVA detected at least one group as statistically significant different in mean Villalta scores among the VCSS severity categories (Figure 1).

Figure 1: Mean Villalta Score by VCSS Severity by Follow-up Visit



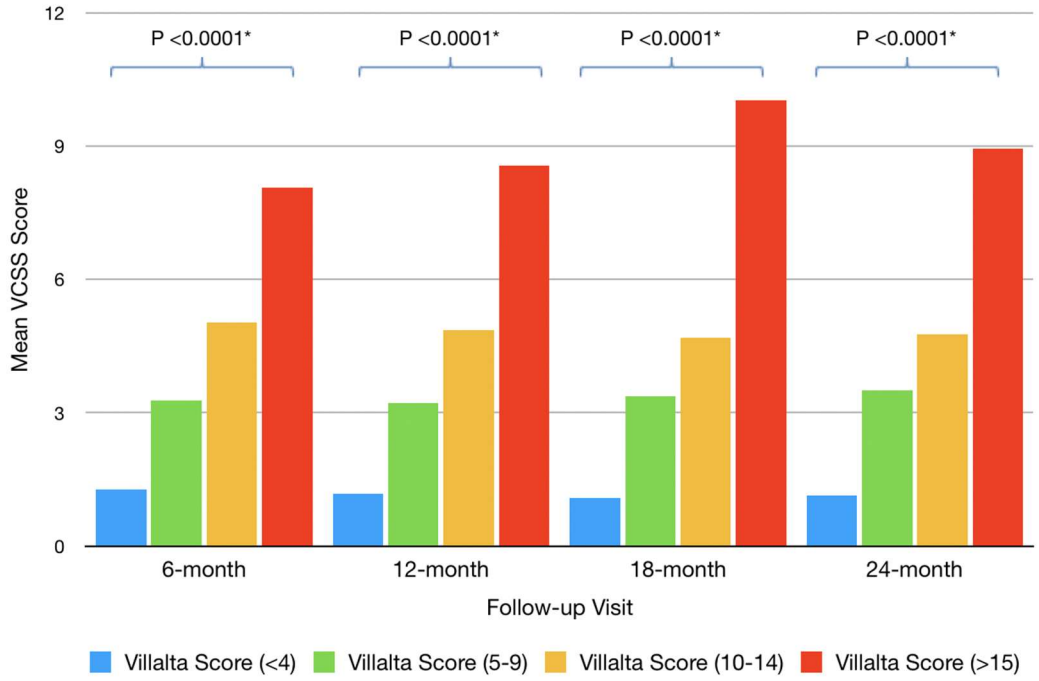
**P-value from ANOVA testing*

Similarly, the mean VCSS score was determined for each Villalta severity category at time points 6, 12, 18 and 24-month (Figure 2). Villalta ≤4 (absence of disease) had a VCSS score ranging from 1.08 to 1.27. This corresponds to an absence of disease as per VCSS severity categorizations. Villalta 5-9 (mild disease) yielded a VCSS score ranging from 3.22-3.51, which represents absence of disease. Villalta 10-14 (moderate disease) had a VCSS ranging from 4.69-5.03, corresponding with VCSS mild-moderate disease. Villalta ≥15 (severe disease) had a VCSS score ranging from 8.06 to 10.04, signifying severe disease. At the 6-month follow-up visit and all subsequent visits, ANOVA detected at least one group is statistically significant difference in mean VCSS scores among the Villalta severity categories.

The proportion of patients in Villalta score ≤4 ranged from 0.18 to 0.67 patients (Appendix 2). The proportion of patients with Villalta 5-9 ranged from 0.20 to 0.35 patients. The proportion of patients with Villalta 10-14 ranged from 0.08 to 0.28 patients. The proportion of

patients with Villalta ≥15ranging from 0.03 to 0.19 patients. The larger range of proportion of patients within a particular Villalta severity group compared with VCSS is because the Villalta score was also assessed at baseline and at 1-month follow-up visits. Whereas, the VCSS was only administered from 6-month to 24-month follow-up visits. The initial DVT event can take up to 6 months to resolve, therefore, the proportion of patients with disease (Villalta score ≥4) as per the Villalta Scale at baseline was 0.82 and at 1-month follow-up visits was 0.44. From 6-month to 24-month follow-up visits, the proportion of patients with disease is consistently between 0.33 to 0.34.

Figure 2: Mean VCSS Score by Villalta severity



**P-value from ANOVA testing*

3. Quality of Life Scores and the Villalta Scale

When the VEINES-QoL scores were compared in patients whose Villalta score denoted absence of disease (Villalta score < 5) vs. presence of disease (Villalta score ≥ 5), the mean of

the baseline VEINES-QoL score was 69.00 and 46.89 respectively (Table 10). The difference of the mean VEINES-QoL scores in these two groups were statistically significant at all time points (P <0.0001). A lower VEINES-QoL score indicates worse QoL. In both groups, VEINES-QoL scores increased (indicating improvement) until the 6- and/or 12-month follow-up visits, after which the scores tended to plateau. At baseline, 555 patients of 676 patients (82.1%) were categorized has having venous disease as per the Villalta Scale. The percentage of patients with disease as per the Villalta Scale at 6 months was 33.2% and at 12 months was 32.9%. A similar overall trend in which there was an increase of the scores until 6 months, proceeded by stabilization of scores until 24-month follow-up was seen with the VEINES-Sym, SF-36 PCS and SF-36 MCS scores (Appendix 3).

Table 10: Summary of VEINES-QoL Scores by Dichotomous Villalta Scale Categories

Visit	Villalta Score < 5		Villalta Score ≥ 5		Difference	
	n	*mean (SD)*	*n*	*mean (SD)*	*Estimate*	*P value*
Baseline	121	69.00 (20.42)	555	46.89 (22.60)	22.10	<.0001
30 days	356	74.34 (19.22)	279	48.02 (22.79)	26.31	<.0001
6 months	382	84.77 (15.05)	190	55.54 (25.03)	29.23	<.0001
12 months	347	88.02 (13.74)	179	57.80 (24.35)	30.22	<.0001
18 months	306	89.29 (13.64)	161	59.01 (23.21)	30.27	<.0001
24 months	322	88.71 (13.00)	158	59.72 (23.02)	28.99	<.0001

Note: Villalta Score < 5 is absence of disease. Villalta Score ≥ 5 is presence of disease.

VEINES-QoL scores were also analyzed by Villalta Score severity categories (Table 11). The percentage of patients in the no disease category (Villalta Score <5) was 34.8% at baseline, 66.8% at 6-month and 67.1% at 24-month follow-up visits. Consequently, the percentage of patients with mild, moderate or severe disease decreased at 6 months, but then remained the same until 24 months. Additionally, within each Villalta severity category, VEINES-QoL scores

showed improvement from baseline to 6 months. Subsequently, the VEINES-QoL scores remained relatively constant until the final 24-month follow-up visit. Similar trends were seen with VEINES-Sym, SF-36 PCS and SF-36 MCS scores. Through pairwise testing, the difference in VEINES-QoL scores and also VEINES-Sym scores in the various Villalta disease severity categories were demonstrated to be significantly different between all pairs, at all time points, with exception of the comparison between the Villalta score 10-14 and Villalta score ≥ 15 (Appendix 4). However, the SF-36 PCS and SF-36 MCS (generic QoL scales) scores were not consistently different between the pairings of Villalta mild-moderate disease, mild-severe disease and moderate-mild disease throughout time (Appendix 4).

Table 11: VEINES-QoL Scores by Villalta Scale Severity Category

Visit	Villalta Score (<5)		Villalta Score (5-9)		Villalta Score (10-14)		Villalta Score (≥ 15)	
	n	*mean (SD)*	*n*	*mean (SD)*	*n*	*mean (SD)*	*n*	*mean (SD)*
Baseline	121	69.00	235	55.95	190	43.34	130	35.70
30 days	356	74.34	186	53.25	55	41.64	38	31.69
6 months	382	84.77	119	63.13	38	47.00	33	37.97
12 months	347	88.02	116	67.43	45	42.27	18	34.55
18 months	306	89.29	98	66.21	40	45.33	23	52.14
24 months	322	88.71	94	67.07	38	51.02	26	45.87

Note: Villalta score <5 is no disease. Villalta score 5-9 is mild disease. Villalta score 10-14 is moderate disease. Villalta score ≥15 is severe disease.

4. Quality of Life Scores and VCSS

At 6 months, the first VCSS assessment, the mean VEINES-QoL scores of patients without disease defined by a VCSS <4 was 79.13 (Table 12). This score was significantly greater than the mean VEINES-QoL score of 61.80 in patients with disease (VCSS ≥ 4). The difference in VEINES-QoL scores between the two groups was statistically different at all follow-up visits

(Appendix 5). Mean VEINES-QoL scores had a tendency to stay constant or slightly improve throughout time within each group. The same trend was seen in the VEINES-Sym, SF-36 PCS and SF-36 MCS scores (Appendix 5). The trend seen between mean QoL scores and dichotomous VCSS categories was similar to the relationship between mean QoL scores and dichotomous Villalta categories at 6-month to 24-month follow-up visits. The proportion of patients without disease (VCSS <4) at 6-month and 24-month was 77.4% and 77.8% respectively.

Table 12: Summary of VEINES-QoL Scores by Dichotomous VCSS Severity

VEINES-QoL score	VCSS < 4		VCSS ≥ 4		Difference	
	n	*mean (SD)*	*n*	*mean (SD)*	*Estimate (SD)*	*P value*
6 months	435	79.13 (20.90)	131	61.80 (26.32)	17.33 (22.27)	<.0001
12 months	389	82.10 (20.13)	126	64.81 (26.02)	17.29 (21.71)	<.0001
18 months	341	83.42 (20.07)	114	65.81 (24.36)	17.61 (21.22)	<.0001
24 months	347	83.19 (19.33)	102	66.20 (23.74)	16.99 (20.41)	<.0001

Note: VCSS <4 is absence of disease. VCSS ≥4 is presence of disease.

The mean VEINES-QoL score for each VCSS severity category was determined (Table 13). The proportion of patients in each severity category remained constant from 6 months to 24 months and their VEINES-QoL scores remained constant throughout the different time points. The only exception was the increase in mean VEINES-QoL score from 6 months to 12 months for VCSS ≥8. The same pattern was seen for VEINES-SYM, SF-36 PCS and SF-36 MCS scores (Appendix 5).

Table 13: Summary of VEINES-QoL Scores by VCSS Severity

VEINES-QoL	VCSS (≤ 3)		VCSS (4-7)		VCSS (≥ 8)	
	n	*mean (SD)*	*n*	*mean (SD)*	*n*	*mean (SD)*
6 months	435	79.13 (20.90)	103	66.66 (24.72)	28	43.93 (24.64)
12 months	389	82.10 (20.13)	105	65.64 (25.20)	21	60.66 (30.14)
18 months	341	83.42 (20.07)	88	66.94 (22.87)	26	62.00 (29.01)
24 months	347	83.19 (19.33)	76	67.00 (23.24)	26	63.86 (25.45)

Note: VCSS ≤ 3 is no disease. VCSS 4-7 is mild-moderate disease. VCSS ≥8 is severe disease.

Upon pairwise comparison of the mean VEINES-QoL scores by VCSS severity category, a statistical difference was detected in VEINES-QoL score between VCSS ≤3 and VCSS 4-7 and between VCSS ≤3 and VCSS ≥8. However, there was no statistical difference in VEINES-QoL score between VCSS 4-7 and VCSS ≥8. The same was applicable to VEINES-Sym and SF-36 PCS score (Appendix 6). The difference in SF-36 MCS scores in all pairwise comparisons were inconsistent or absent.

5. Relationship between Villalta Score/QoL and VCSS Score/QoL

The correlation between the Villalta score and all QoL scales analysed continuously tended to increase over time until the correlation reached a maximum correlation at the 12-month follow-up visit (Table 14). At 18-month follow-up, there was a decrease in the strength of correlation that was comparable to that at 6-month follow-up. Then the correlation at the 24-month follow-up is similar to the correlation at 18-month follow-up. The strength of the correlation coefficient ranged from -0.51 to -0.73 (moderate to strong negative correlation) throughout time. As the Villalta score increased, there was an associated decrease in the VEINES-QoL score, denoting worsening QoL. Similarly, the correlation coefficient between Villalta scores and VEINES-Sym scores ranged from -0.50 to -0.76 (moderate to strong correlation) throughout the follow-up visits. The correlation between the Villalta score and the

SF-36 PCS score tended to be weaker, with a correlation coefficient ranging from -0.35 to -0.54 (weak to moderate correlation) at the different follow-up visits. The correlation coefficient between the Villalta score and the SF-36 MCS ranged from -0.21 to -0.38 (none/very weak to weak) throughout time. The venous disease specific QoL scale tended to have a stronger correlation with the Villalta score than the generic QoL scale.

Table 14: Correlation between Villalta Score/QoL and VCSS Score/QoL by Visit

QoL Scale	Visit	Pearson Correlation Coefficient			
		Villalta Score		VCSS Score	
		Estimate	*95% CI*	*Estimate*	*95% CI*
VEINES-QoL	Baseline	-0.51	-0.56, -0.45		
	1 m	-0.61	-0.65, -0.56		
	6 m	-0.68	-0.72, -0.63	-0.37	-0.44, -0.30
	12 m	-0.73	-0.77, -0.69	-0.39	-0.46, -0.31
	18 m	-0.68	-0.73, -0.63	-0.39	-0.46, -0.31
	24 m	-0.70	-0.75, -0.66	-0.39	-0.46, -0.31
VEINES-Sym	Baseline	-0.50	-0.55, -0.44		
	1 m	-0.66	-0.70, -0.61		
	6 m	-0.70	-0.74, -0.66	-0.36	-0.43, -0.29
	12 m	-0.76	-0.79, -0.72	-0.41	-0.48, -0.33
	18 m	-0.71	-0.76, -0.67	-0.40	-0.47, -0.32
	24 m	-0.74	-0.78, -0.70	-0.41	-0.49, -0.33
SF-PCS	Baseline	-0.35	-0.41, -0.28		
	1 m	-0.46	-0.52, -0.40		
	6 m	-0.49	-0.55, -0.42	-0.31	-0.38, -0.23
	12 m	-0.54	-0.60, -0.48	-0.32	-0.39, -0.24
	18 m	-0.54	-0.60, -0.48	-0.32	-0.40, -0.23
	24 m	-0.52	-0.58, -0.45	-0.31	-0.40, -0.23
SF-MCS	Baseline	-0.21	-0.28, -0.14		
	1 m	-0.27	-0.34, -0.20		
	6 m	-0.31	-0.38, -0.24	-0.14	-0.22, -0.06
	12 m	-0.38	-0.45, -0.30	-0.15	-0.23, -0.06
	18 m	-0.31	-0.39, -0.23	-0.12	-0.21, -0.03
	24 m	-0.32	-0.40, -0.24	-0.12	-0.21, -0.02

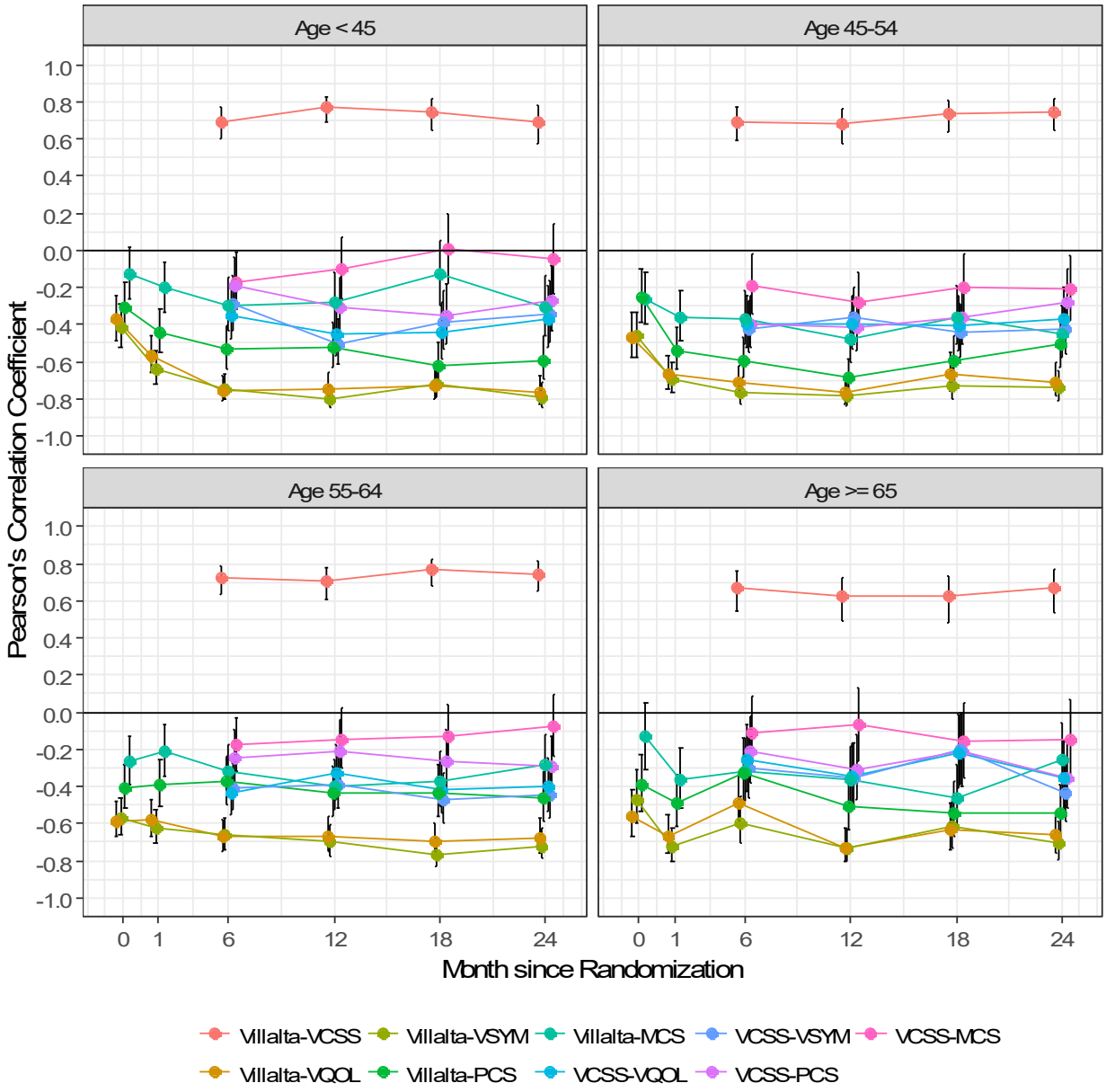
The correlation between the VCSS score and all QoL scales remained relatively constant throughout time. The VCSS score and VEINES-QoL score correlation coefficients ranged from -

0.37 to -0.39. The correlation coefficients for VCSS score and VEINES-Sym ranged from -0.36 to -0.41 (weak correlation). The SF-36 PCS also had a weak correlation to the VCSS; the estimated correlation coefficient ranged from -0.31 to -0.32. The SF-36 MCS, however, had a no or very weak correlation to the VCSS. The venous specific QoL scale and the SF-36 PCS component of the generic QoL scale tended to have a similar correlation strength in relation to the VCSS. The correlation between SF-36 MCS and VCSS scores were minimal.

Overall, the Villalta score had a tendency to have a greater level of correlation with both the generic and venous specific QoL scales at baseline and all subsequent follow-up visits.

The correlation between QoL and Villalta score or VCSS were further stratified by age categories (<45years, 45-54 years, 55-64 years, ≥ 65years), sex (male or female), BMI categories (<25, 25-<30, ≥30 kg/m^2), ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported), race (white, black, other), extent of DVT (iliofemoral, isolated femoral-popliteal), previous ipsilateral DVT (yes, no) and by follow-up visit. Pairwise comparisons were conducted. Pairwise comparison of subgroups by age (Figure 3), sex, ethnicity, race, extent of DVT or previous ipsilateral DVT did not lead to significant changes in the correlation between the QoL scales and the Villalta or VCSS scores. Upon stratification by BMI and pairwise comparison of the categories, there were sporadic tendencies for the BMI category to affect the correlation between QoL measurements and disease measurement scores at certain follow-up visits (Appendix 7). However, there were no identifiable patterns and these tendencies were minimal.

Figure 3: Correlation of Scales Among Scales by Age and Visit



To explore the relationship between the different disease, each pair of scales was treated as a multivariate outcome in a multivariate longitudinal model. The quadratic function was found to be sufficient for all these scores. The impact of covariates (i.e. age, sex and BMI) were also examined. A random intercept and random slope were present in all these multivariate

longitudinal models. The correlation of the random intercept and random slope among different scales are shown in Table 15.

Table 15: Correlation between Random Effects (Multivariate Longitudinal Model)

Category	Correlation			
	Intercept		*Slope*	
	Unadjusted Estimate (95% CI)	Adjusted* Estimate (95% CI)	Unadjusted Estimate (95% CI)	Adjusted* Estimate (95% CI)
Villalta Score vs VCSS Score	0.74 (0.70, 0.77)	0.69 (0.65, 0.73)	0.72 (0.68, 0.76)	0.84 (0.82, 0.86)
Villalta Score vs VEINES-QoL	-0.73 (-0.77, -0.70)	-0.72 (-0.76, -0.69)	-0.74 (-0.77, -0.71)	-0.76 (-0.79, -0.73)
Villalta Score vs VEINES-Sym	-0.76 (-0.79, -0.73)	-0.76 (-0.79, -0.73)	-0.82 (-0.84, -0.79)	-0.83 (-0.85, -0.81)
VCSS Score vs VEINES-QoL	-0.37 (-0.43, -0.30)	-0.38 (-0.44, -0.31)	-0.35 (-0.41, -0.28)	-0.42 (-0.48, -0.36)
VCSS Score vs VEINES-Sym	-0.38 (-0.44, -0.32)	-0.38 (-0.44, -0.32)	-0.33 (-0.39, -0.26)	-0.46 (-0.51, -0.39)
VEINES-QoL vs VEINES-Sym	0.93 (0.92, 0.94)	0.93 (0.91, 0.94)	0.94 (0.93, 0.95)	0.94 (0.93, 0.95)

** adjusted by age, sex and BMI*

The Villalta score and VCSS score have a positive correlation between their random intercepts and between their random slopes. This suggests that patients with a higher average Villalta score also tend to have a higher average VCSS score (correlation is 0.74, and 0.69 if adjusted). Those that have a higher rate of change in Villalta score over time tend to have a higher rate of change in VCSS (correlation is 0.72, and 0.84 if adjusted). The impact of adjustment appears to be minor. The negative correlation of the random intercept, as seen between Villalta score and VEINES-QoL, is interpreted such that patients with a higher average

Villalta score also tend to have a lower VEINES-QoL score. Similarly, a negative correlation for the random slope suggests that patient with a higher rate of change in Villalta score over time also tend to have a higher rate of decrease in their VEINES-QoL score.

Chapter 5 – Discussion

The overall purpose of this thesis was to 1) describe the Villalta and the VCSS scores at each assessment time in the ATTRACT trial study population, 2) evaluate the correlation between the Villalta and VCSS during study follow-up, and 3) analyze the relationship between 3a) Villalta scores and QoL scores and 3b) VCSS and QoL scores in the ATTRACT study population. Despite the strong correlation between the continuous Villalta Scale and VCSS scores, their respective relationship with QoL scores differed.

When mean VCSS scores were calculated for each Villalta severity category, the mean VCSS scores for the mild disease Villalta severity category would have been classified as absence of disease as per the VCSS severity category. The finding suggests that the Villalta scale categorizes less degrees of disease as mild disease, compared to VCSS. Upon examination of the scales in a dichotomous manner (absence or presence of disease), the percentage of patients diagnosed with PTS by the Villalta scale was consistently 10 percentage points higher than with the VCSS. This higher rate of PTS diagnosis using the Villalta scale is in line with the literature and has been a point of contention from critics of the Villalta scale (132, 148, 149).

Conversely, when the mean Villalta score was calculated for severe disease as categorized by VCSS, this translated to moderate PTS as per the Villalta scale. This finding suggests that the VCSS categorizes less severe disease into the severe category when compared to the Villalta scale. However, the percentages of patients diagnosed with severe PTS between 6-month to 24-month follow up were comparable with both scales. Therefore, it is likely that the Villalta Scale and VCSS are identifying different patients as having severe PTS. In a previous study by Jayaraj *et al.*, there was a strong correlation between mild and moderate PTS as diagnosed by the Villalta Scale and VCSS, but only moderate correlation for the diagnosis of

severe disease (150). This discrepancy may be attributable to the design of the two different scales. The Villalta Scale considers both subjective and objective criteria, whereas the VCSS is more reliant on objective criteria. Arguments have been made in favor of both PTS scales. Groups in support of the Villalta Scale emphasize the importance of symptoms experienced by patients, as PTS is a clinical diagnosis with proven negative impact on QoL (98, 139, 151), whereas, VCSS is criticized for not adequately integrating the patient perspective in its evaluation of the disease (151). Conversely, supporters of the VCSS emphasize that the VCSS tends to capture more severe disease compare to the Villalta Scale and therefore, it identifies more clinically significant disease (150).

Taken together, the results of my project found that there was a significant difference in the degree of correlation between the Villalta Scale and the QoL measurements compared to the VCSS and QoL measurements within the same patients. Previously there have been studies that examined the association between the Villalta Scale and QoL measurements, or the VCSS and QoL measurements. However, my project assesses these relationships within the same patient population and directly compares these relationships. The Villalta Scale tended to correlate more strongly with VEINES-QoL, VEINES-Sym, SF-36 PCS and SF-36 MCS, compared to VCSS. In particular, the Villalta Scale strongly correlated with the venous disease-specific VEINES-QoL/Sym scale, which is in keeping with the findings of previous studies (98, 139). VCSS, however, only weakly correlated with VEINES-QoL/Sym; these results are in keeping with a study that solely evaluated the relationship of the VCSS to the VEINES-QoL/Sym (152). The poor correlation between VCSS and the VEINES-QoL/Sym are not unexpected, given that VCSS does not take patient symptoms into account. Previous studies in the literature have demonstrated that , in descending order of effect size, VEINES-QoL, VEINES-Sym and SF-36

PCS scores are responsive to changes in Villalta scores (138). SF-36 MCS had a small effect size and was the least responsive to clinical change.

Additionally, we conducted stratified analysis by age categories, sex, BMI categories, ethnicity, race, extent of DVT or previous ipsilateral DVT. Age categories, sex, ethnicity, race, extent of DVT and previous ipsilateral DVT were not confounding factors in the correlation between Villalta scores and QoL scores. BMI categories had an inconsistent effect on the correlation between the Villalta score and QoL scores over time, however, no pattern could be identified. The multivariate model of the correlation between random effects adjusted for age, sex and BMI have shown minimal effect on the correlation between the Villalta score and QoL scores.

Strengths of this project include that the ATTRACT Trial was a rigorously conducted multi-center randomized controlled trial that included 691 patients. The original protocol was designed to collect data on potential confounders such as age categories, sex, BMI categories, ethnicity, race, extent of DVT and/or previous ipsilateral DVT. The ATTRACT Trial is one of the only studies to assess various patient-important measures in PTS concurrently. Both the VEINES-QoL/Sym and the SF-36 are validated measures of QoL. All clinical assessors that administered the disease severity measurements and QoL measurements were uniformly trained.

However, these are some limitations. Despite the large size of the ATTRACT Trial study population, at subsequent follow-up visits, there was drop-off in completed Villalta Scale and VCSS assessments. For example, at the 24-month follow-up visit, only 451 patients had completed both the Villalta Scale and VCSS. Also, the overwhelming majority of the ATTRACT trial population was homogenous in terms of race and ethnicity. As a result, this limited our ability to determine the effects of race and ethnicity in our stratified analyses. This thesis project

was a secondary, *post hoc* analysis of the ATTRACT Trial. Hence, to mitigate the chance of multiple testing error, we considered that $p \leq 0.01$ denoted statistical significance, rather than $p \leq 0.05$. Nevertheless, this may not have been adequately conservative. The ATTRACT Trial was designed and powered to detect a decrease in the development of PTS from 30% to ≤20% in the intervention arm between 6-month and 24-month follow-up. Therefore, the sample size may not have afforded sufficient power to capture statistically significant differences between the various measures in rarer outcomes such as severe PTS. Despite this, my thesis provides valuable new data on relationships over time between the Villalta scale, VCSS, and QoL measures used in PTS.

Chapter 6 - Conclusion

To our knowledge, my team and I are the first to directly analyze the relationships between Villalta Scale, VCSS and QoL measurements relevant to PTS in a large, rigorously documented population of patients with proximal DVT. The Villalta Scale has previously been reported to be a valid, reliable, acceptable and responsive tool to diagnose and follow PTS and to assess the impact of PTS on patients' QoL. Taken together, my research results support the use of the Villalta Scale to diagnose and follow patients with PTS, compared to VCSS, as it better captures the impact of PTS on the QoL of the patient. Given the absence of a gold standard test for PTS, PTS remains a clinical diagnosis. Therefore, it is important for the subjective experience of the patient to be incorporated into clinical assessments at diagnosis and follow-up. Currently, treatment of PTS is aimed at improving QoL, as PTS is a chronic disease. Thus, researchers should also strive to use a diagnostic scale that best reflects and correlates with QoL measures. Our findings suggested that there was no significant difference in mean VEINES-QoL/Sym scores when comparing moderate PTS to severe PTS as per the Villalta Scale. However, the ATTRACT Trial was powered to detect a 20% or lower decrease in the treatment arm if the incidence of PTS in the control arm was 30%. Further large prospective studies are needed to explore the relationship between patients with severe PTS and its clinical implications on QoL and patient outcomes.

In the clinical and research fields, there are two prevalent schools of thought regarding how best to diagnose and follow PTS. Thrombosis clinicians and researchers tend to favor the Villalta Scale and surgical specialists and researchers are more inclined to use the VCSS. As a result, there has been a divergence in the literature between medical and surgical evaluations and approaches to PTS. Our findings support the use of the Villalta scale to assess PTS and PTS

severity in preference to VCSS. The Villalta scale better captures the impact of PTS on patient reported QoL, a key consideration in patients suffering from PTS. Our head-to-head analysis of the Villalta Scale and VCSS in relation to the QoL of patients with PTS is crucial to promote the standardized use of diagnostic and assessment tools for PTS. This facilitates the transfer of information from clinician to clinician and/or to researcher and helps promote best practices in patient-oriented care.

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Appendix 1: Summary of VCSS Score by Villalta Severity

Visit	Villalta Score (≤ 4)		Villalta Score (5-9)		Villalta Score (10-14)		Villalta Score (≥ 15)		P value
	n	*mean (SD)*	*n*	*mean (SD)*	*n*	*mean (SD)*	*n*	*mean (SD)*	
6 months	379	1.27 (1.49)	118	3.28 (2.43)	39	5.03 (3.26)	32	8.06 (4.57)	<0.0001
12 months	341	1.18 (1.45)	116	3.22 (2.18)	43	4.86 (2.85)	18	8.56 (4.82)	<0.0001
18 months	297	1.08 (1.39)	97	3.38 (2.42)	39	4.69 (2.90)	22	10.04 (4.47)	<0.0001
24 months	304	1.14 (1.53)	87	3.51 (2.46)	37	4.76 (2.78)	22	8.95 (4.84)	<0.0001

Appendix 2: Summary of Villalta Score by VCSS Severity

Visit	VCSS (≤ 3)		VCSS (4-7)		VCSS (≥ 8)		P value
	n	*mean (SD)*	*n*	*mean (SD)*	*n*	*mean (SD)*	
At 6 months	436	2.82 (3.08)	103	7.42 (4.22)	29	14.86 (5.6)	<0.0001
At 12 months	392	2.76 (3.00)	105	7.26 (4.32)	21	12.90 (5.43)	<0.0001
At 18 months	341	2.66 (3.01)	88	7.75 (4.16)	26	13.89 (5.01)	<0.0001
At 24 months	348	2.74 (3.25)	76	7.45 (4.34)	26	12.88 (5.13)	<0.0001

Appendix 3: Summary of QoL by the Absence or Presence of Disease as Per the Villalta Scale (< 5 vs ≥ 5)

Outcome Measure	Villalta Score < 5		Villalta Score ≥ 5		Difference	
	n	*mean (SD)*	*n*	*mean (SD)*	*Estimate (SD)*	*P value*
VEINES-QoL						
Baseline	121	69.00 (20.42)	555	46.89 (22.60)	22.10 (22.23)	<.0001
30 days	356	74.34 (19.22)	279	48.02 (22.79)	26.31 (20.87)	<.0001
6 months	382	84.77 (15.05)	190	55.54 (25.03)	29.23 (18.95)	<.0001
12 months	347	88.02 (13.74)	179	57.80 (24.35)	30.22 (18.06)	<.0001
18 months	306	89.29 (13.64)	161	59.01 (23.21)	30.27 (17.53)	<.0001
24 months	322	88.71 (13.00)	158	59.72 (23.02)	28.99 (16.96)	<.0001
VEINES-Sym						
Baseline	121	73.71 (19.07)	553	53.02 (24.70)	20.69 (23.79)	<.0001
30 days	356	80.16 (16.85)	278	52.49 (24.07)	27.67 (20.34)	<.0001
6 months	382	85.41 (14.92)	190	56.46 (25.77)	28.95 (19.21)	<.0001
12 months	347	86.82 (13.57)	179	56.28 (24.14)	30.54 (17.88)	<.0001
18 months	306	88.01 (14.32)	161	55.94 (24.14)	32.06 (18.30)	<.0001
24 months	322	88.21 (12.97)	158	59.26 (22.81)	28.95 (16.85)	<.0001
SF-36 PCS						
Baseline	120	43.15 (10.48)	555	34.95 (10.89)	8.20 (10.82)	<.0001
30 days	356	46.32 (9.76)	279	37.58 (10.69)	8.73 (10.18)	<.0001
6 months	382	50.11 (9.46)	190	39.93 (11.78)	10.18 (10.29)	<.0001
12 months	347	51.66 (8.43)	179	40.12 (11.32)	11.54 (9.51)	<.0001
18 months	306	52.54 (7.73)	160	40.18 (11.61)	12.36 (9.25)	<.0001
24 months	322	51.93 (8.04)	158	40.73 (11.72)	11.20 (9.41)	<.0001
SF-36 MCS						
Baseline	121	51.87 (11.35)	555	47.54 (13.45)	4.33 (13.10)	0.0003
30 days	356	51.10 (10.96)	279	44.92 (13.21)	6.18 (12.00)	<.0001
6 months	382	53.10 (9.42)	190	45.74 (12.98)	7.36 (10.73)	<.0001
12 months	347	53.59 (9.36)	179	46.26 (13.18)	7.32 (10.81)	<.0001
18 months	306	54.08 (8.60)	160	47.31 (12.50)	6.77 (10.11)	<.0001
A24 months	322	54.76 (7.34)	158	48.23 (11.58)	6.53 (8.96)	<.0001

Appendix 4: Summary of QoL by Villalta Score Severity (pairwise comparison)

Outcome Measure	(≤ 4) – (5-9)		(≤ 4) – (10-14)		(≤ 4) – (≥ 15)	
	Diff (95% CI)	*p*	*Diff (95% CI)*	*p*	*Diff (95% CI)*	*p*
VEINES-QoL						
Baseline	13.04 (7.00, 19.08)	<0.0001	25.66 (19.38, 31.94)	<0.0001	33.29 (26.47, 40.11)	<0.0001
30 days	21.09 (16.37, 25.80)	<0.0001	32.70 (25.15, 40.25)	<0.0001	42.65 (33.76, 51.54)	<0.0001
6 months	21.63 (16.75, 26.51)	<0.0001	37.77 (29.86, 45.68)	<0.0001	46.80 (38.36, 55.23)	<0.0001
12 months	20.59 (16.07, 25.11)	<0.0001	45.75 (39.07, 52.43)	<0.0001	53.47 (43.28, 63.66)	<0.0001
18 months	23.08 (18.08, 28.08)	<0.0001	43.95 (36.71, 51.20)	<0.0001	37.14 (27.83, 46.46)	<0.0001
24 months	21.64 (16.75, 26.53)	<0.0001	37.69 (30.54, 44.84)	<0.0001	42.84 (34.34, 51.34)	<0.0001
VEINES-Sym						
Baseline	11.46 (4.98, 17.95)	<0.0001	23.87 (17.13, 30.61)	<0.0001	32.89 (25.54, 40.24)	<0.0001
30 days	21.14 (16.62, 25.67)	<0.0001	37.51 (30.28, 44.73)	<0.0001	45.24 (36.72, 53.75)	<0.0001
6 months	19.75 (14.91, 24.59)	<0.0001	40.10 (32.26, 47.94)	<0.0001	49.29 (40.93, 57.66)	<0.0001
12 months	20.41 (16.01, 24.82)	<0.0001	46.32 (39.81, 52.82)	<0.0001	56.32 (46.39, 66.24)	<0.0001
18 months	22.98 (17.88, 28.09)	<0.0001	48.32 (40.93, 55.71)	<0.0001	42.48 (32.98, 51.99)	<0.0001
24 months	20.40 (15.66, 25.14)	<0.0001	37.49 (30.55, 44.43)	<0.0001	47.38 (39.14, 55.63)	<0.0001
SF-36 PCS						
Baseline	5.35 (2.29, 8.41)	<0.0001	10.09 (6.90, 13.27)	<0.0001	10.61 (7.15, 14.06)	<0.0001
30 days	6.94 (4.61, 9.27)	<0.0001	10.16 (6.43, 13.90)	<0.0001	15.45 (11.05, 19.85)	<0.0001
6 months	8.31 (5.56, 11.07)	<0.0001	11.31 (6.85, 15.78)	<0.0001	15.59 (10.83, 20.35)	<0.0001
12 months	8.64 (6.08, 11.19)	<0.0001	16.50 (12.72, 20.27)	<0.0001	17.85 (12.09, 23.60)	<0.0001
18 months	10.49 (7.75, 13.23)	<0.0001	16.29 (12.32, 20.25)	<0.0001	13.52 (8.31, 18.73)	<0.0001
24 months	8.56 (5.77, 11.35)	<0.0001	15.89 (11.80, 19.97)	<0.0001	13.91 (9.06, 18.77)	<0.0001
SF-36 MCS						
Baseline	2.27 (-1.46, 6.00)	0.40	4.10 (0.22, 7.98)	0.033	8.37 (4.16, 12.58)	<0.0001
30 days	4.89 (2.10, 7.67)	<0.0001	7.73 (3.27, 12.19)	<0.0001	10.25 (5.00, 15.51)	<0.0001
6 months	5.80 (2.90, 8.69)	<0.0001	10.22 (5.54, 14.90)	<0.0001	9.71 (4.72, 14.71)	<0.0001
12 months	4.44 (1.51, 7.36)	0.0006	12.03 (7.71, 16.35)	<0.0001	14.12 (7.53, 20.72)	<0.0001
18 months	5.06 (2.07, 8.06)	<0.0001	11.38 (7.05, 15.72)	<0.0001	5.96 (0.27, 11.66)	0.036
24 months	5.78 (3.07, 8.48)	<0.0001	7.15 (3.19, 11.11)	<0.0001	8.38 (3.67, 13.09)	<0.0001

Appendix 4 continued: Summary of QoL by Villalta Score Severity (pairwise comparison)

Outcome Measure	(5-9) – (10-14)		(5-9) – (≥ 15)		(10-14) – (≥ 15)	
	Diff (95% CI)	*p*	*Diff (95% CI)*	*p*	*Diff (95% CI)*	*p*
VEINES-QoL						
Baseline	12.62 (7.35, 17.88)	<0.0001	20.25 (14.35, 26.15)	<0.0001	7.63 (1.49, 13.77)	0.0079
30 days	11.61 (3.62, 19.61)	<0.0001	21.56 (12.29, 30.84)	<0.0001	9.95 (-1.04, 20.94)	0.092
6 months	16.14 (7.47, 24.80)	<0.0001	25.16 (16.02, 34.31)	<0.0001	9.03 (-2.03, 20.09)	0.15
12 months	25.15 (17.75, 32.55)	<0.0001	32.87 (22.20, 43.55)	<0.0001	7.72 (-4.03, 19.47)	0.33
18 months	20.88 (12.80, 28.96)	<0.0001	14.07 (4.09, 24.05)	0.0018	-6.81 (-18.08, 4.46)	0.40
24 months	16.05 (8.03, 24.07)	<0.0001	21.20 (11.96, 30.44)	<0.0001	5.15 (-5.46, 15.77)	0.59
VEINES-Sym						
Baseline	12.41 (6.75, 18.06)	<0.0001	21.43 (15.06, 27.80)	<0.0001	9.02 (2.39, 15.65)	0.0027
30 days	16.36 (8.70, 24.03)	<0.0001	24.10 (15.21, 32.98)	<0.0001	7.73 (-2.79, 18.26)	0.23
6 months	20.35 (11.76, 28.94)	<0.0001	29.54 (20.47, 38.61)	<0.0001	9.19 (-1.78, 20.16)	0.14
12 months	25.91 (18.70, 33.11)	<0.0001	35.91 (25.51, 46.30)	<0.0001	10.00 (-1.45, 21.45)	0.11
18 months	25.34 (17.09, 33.59)	<0.0001	19.50 (9.31, 29.69)	<0.0001	-5.84 (-17.35, 5.67)	0.56
24 months	17.09 (9.32, 24.87)	<0.0001	26.99 (18.02, 35.95)	<0.0001	9.89 (-0.40, 20.19)	0.065
SF-36 PCS						
Baseline	4.74 (2.08, 7.40)	<0.0001	5.26 (2.28, 8.24)	<0.0001	0.52 (-2.59, 3.63)	0.97
30 days	3.22 (-0.73, 7.18)	0.15	8.51 (3.93, 13.10)	<0.0001	5.29 (-0.15, 10.73)	0.060
6 months	3.00 (-1.89, 7.89)	0.39	7.28 (2.12, 12.44)	0.0017	4.28 (-1.97, 10.52)	0.29
12 months	7.86 (3.68, 12.04)	<0.0001	9.21 (3.18, 15.24)	0.0005	1.35 (-5.29, 7.99)	0.95
18 months	5.80 (1.37, 10.23)	0.0044	3.03 (-2.53, 8.60)	0.50	-2.77 (-9.03, 3.50)	0.67
24 months	7.33 (2.75, 11.90)	0.0003	5.35 (0.07, 10.63)	0.046	-1.98 (-8.04, 4.08)	0.83
SF-36 MCS						
Baseline	1.83 (-1.43, 5.08)	0.47	6.10 (2.45, 9.74)	<0.0001	4.27 (0.48, 8.07)	0.020
30 days	2.85 (-1.88, 7.57)	0.41	5.37 (-0.11, 10.85)	0.057	2.52 (-3.97, 9.01)	0.75
6 months	4.43 (-0.70, 9.56)	0.12	3.92 (-1.50, 9.33)	0.25	-0.51 (-7.06, 6.04)	1.0
12 months	7.59 (2.80, 12.38)	0.0003	9.68 (2.78, 16.59)	0.0019	2.09 (-5.51, 9.70)	0.89
18 months	6.32 (1.48, 11.16)	0.0046	0.90 (-5.18, 6.99)	0.98	-5.42 (-12.27, 1.43)	0.17
24 months	1.37 (-3.07, 5.81)	0.86	2.60 (-2.51, 7.72)	0.56	1.23 (-4.65, 7.11)	0.95

Appendix 5: Summary of QoL by Absence of Presence of Disease as Per the VCSS (< 4 vs ≥ 4)

Outcome Measure	VCSS < 4		VCSS ≥ 4		Difference	
	n	*mean (SD)*	*n*	*mean (SD)*	*Estimate (SD)*	*P value*
VEINES-QoL						
6 months	435	79.13 (20.90)	131	61.80 (26.32)	17.33 (22.27)	<.0001
12 months	389	82.10 (20.13)	126	64.81 (26.02)	17.29 (21.71)	<.0001
18 months	341	83.42 (20.07)	114	65.81 (24.36)	17.61 (21.22)	<.0001
24 months	347	83.19 (19.33)	102	66.20 (23.74)	16.99 (20.41)	<.0001
VEINES-Sym						
6 months	435	79.71 (20.93)	131	62.68 (26.99)	17.03 (22.47)	<.0001
12 months	389	80.54 (20.23)	126	64.11 (26.10)	16.43 (21.80)	<.0001
18 months	341	81.56 (21.16)	114	63.41 (25.82)	18.15 (22.42)	<.0001
24 months	347	82.45 (19.24)	102	65.51 (24.01)	16.93 (20.42)	<.0001
SF-36 PCS						
6 months	435	48.33 (10.32)	131	41.79 (12.84)	6.53 (10.95)	<.0001
12 months	389	49.56 (9.79)	126	42.58 (12.34)	6.98 (10.47)	<.0001
18 months	341	50.22 (10.01)	113	43.13 (11.36)	7.09 (10.36)	<.0001
24 months	347	49.97 (9.68)	102	42.96 (11.99)	7.01 (10.24)	<.0001
SF-36 MCS						
6 months	435	51.50 (10.67)	131	47.82 (12.70)	3.68 (11.17)	0.0029
12 months	389	52.02 (10.48)	126	48.57 (13.25)	3.45 (11.22)	0.0084
18 months	341	52.44 (10.44)	113	49.42 (10.90)	3.03 (10.56)	0.011
24 months	347	53.33 (9.01)	102	50.78 (10.08)	2.55 (9.27)	0.023

Appendix 6: Summary of QoL by VCSS Severity (Pairwise Comparison)

Outcome Measure	(≤ 3) – (4-7)		(≤ 3) – (≥ 8)		(4-7) – (≥ 8)	
	Diff (95% CI)	*p*	*Diff (95% CI)*	*p*	*Diff (95% CI)*	*p*
VEINES-QoL						
6 months	12.47 (6.85, 18.09)	<0.0001	35.20 (25.19, 45.20)	<0.0001	22.72 (11.79, 33.66)	<0.0001
12 months	16.46 (10.85, 22.07)	<0.0001	21.44 (10.00, 32.87)	<0.0001	4.98 (-7.22,17.18)	0.60
18 months	16.49 (10.52, 22.45)	<0.0001	21.43 (11.27, 31.58)	<0.0001	4.94 (-6.20,16.08)	0.55
24 months	16.19 (10.10, 22.27)	<0.0001	19.33 (9.56, 29.09)	<0.0001	3.14 (-7.77,14.05)	0.78
VEINES-Sym						
6 months	12.18 (6.50, 17.86)	<0.0001	34.87 (24.77, 44.97)	<0.0001	22.69 (11.65, 33.73)	<0.0001
12 months	14.99 (9.36, 20.62)	<0.0001	23.61 (12.15, 35.07)	<0.0001	8.62 (-3.61, 20.85)	0.22
18 months	16.13 (9.84, 22.42)	<0.0001	24.98 (14.28, 35.68)	<0.0001	8.85 (-2.89, 20.59)	0.18
24 months	15.01 (8.94, 21.08)	<0.0001	22.56 (12.82, 32.30)	<0.0001	7.55 (-3.34, 18.44)	0.23
SF-36 PCS						
6 months	4.34 (1.57, 7.11)	0.0008	14.59 (9.66, 19.53)	<0.0001	10.25 (4.86, 15.65)	<0.0001
12 months	6.54 (3.83, 9.24)	<0.0001	9.20 (3.69, 14.71)	0.0003	2.66 (-3.22, 8.54)	0.54
18 months	7.19 (4.27, 10.12)	<0.0001	6.76 (1.80, 11.72)	0.0041	-0.43 (-5.89, 5.02)	0.98
24 months	6.86 (3.80, 9.91)	<0.0001	7.44 (2.54, 12.35)	0.0012	0.58 (-4.90, 6.06)	0.97
SF-36 MCS						
6 months	3.07 (0.19, 5.94)	0.033	5.95 (0.83, 11.06)	0.018	2.88 (-2.71, 8.47)	0.45
12 months	3.57 (0.67, 6.47)	0.011	2.85 (-3.06, 8.76)	0.49	-0.72 (-7.03, 5.59)	0.96
18 months	3.35 (0.37, 6.33)	0.023	1.94 (-3.11, 7.00)	0.64	-1.41 (-6.96, 4.15)	0.82
24 months	2.85 (0.08, 5.61)	0.042	1.69 (-2.74, 6.13)	0.64	-1.15 (-6.11, 3.80)	0.85

Appendix 7: Pairwise Comparison for Correlation by BMI Group

Outcome Measure	Visit	(< 25) – (25 – < 30)		(< 25) – (≥ 30)		(25 – < 30) – (≥ 30)	
		Diff (95% CI)	*p*	*Diff (95% CI)*	*p*	*Diff (95% CI)*	*p*
Villalta vs VCSS	6 m	-0.34(-0.52, -0.17)	0	-0.26(-0.44, -0.1)	0.0009	0.08(-0.01, 0.16)	0.070
	12 m	-0.23(-0.44, -0.05)	0.0097	-0.26(-0.45, -0.09)	0.0015	-0.02(-0.13, 0.07)	0.63
	18 m	-0.18(-0.37, -0.01)	0.033	-0.2(-0.38, -0.04)	0.0088	-0.02(-0.12, 0.07)	0.70
	24 m	-0.4(-0.63, -0.19)	0.0001	-0.42(-0.65, -0.22)	0	-0.02(-0.13, 0.07)	0.65
Villalta vs VEINES-QoL	Baseline	-0.04(-0.19, 0.13)	0.64	-0.12(-0.26, 0.04)	0.13	-0.08(-0.21, 0.05)	0.22
	1 m	0.1(-0.06, 0.27)	0.24	0.08(-0.06, 0.25)	0.29	-0.02(-0.12, 0.1)	0.79
	6 m	0.01(-0.13, 0.16)	0.91	0.02(-0.1, 0.16)	0.78	0.01(-0.09, 0.12)	0.85
	12 m	-0.08(-0.21, 0.05)	0.22	0(-0.1, 0.13)	0.94	0.09(-0.01, 0.2)	0.075
	18 m	0.03(-0.08, 0.16)	0.63	-0.15(-0.27, -0.01)	0.034	-0.18(-0.28, -0.07)	0.001
	24 m	0.13(0, 0.28)	0.047	-0.03(-0.16, 0.12)	0.66	-0.16(-0.25, -0.06)	0.0011
Villalta vs VEINES-Sym	Baseline	-0.01(-0.17, 0.17)	0.91	-0.05(-0.2, 0.11)	0.52	-0.04(-0.17, 0.09)	0.52
	1 m	0.09(-0.06, 0.25)	0.27	0.11(-0.03, 0.26)	0.125	0.02(-0.08, 0.13)	0.69
	6 m	0.09(-0.05, 0.25)	0.23	0.11(-0.02, 0.26)	0.11	0.02(-0.08, 0.12)	0.74
	12 m	0.02(-0.11, 0.16)	0.80	0.07(-0.04, 0.2)	0.21	0.05(-0.03, 0.15)	0.22
	18 m	0.04(-0.05, 0.15)	0.40	-0.18(-0.29, -0.06)	0.0047	-0.22(-0.31, -0.13)	0
	24 m	0.13(0.02, 0.28)	0.022	-0.01(-0.13, 0.14)	0.94	-0.14(-0.22, -0.06)	0.0012
Villalta vs SF-36 PCS	Baseline	-0.08(-0.26, 0.11)	0.39	-0.22(-0.38, -0.04)	0.019	-0.14(-0.28, 0.02)	0.083
	1 m	0.04(-0.15, 0.24)	0.70	0.06(-0.11, 0.25)	0.48	0.03(-0.11, 0.17)	0.72
	6 m	0.02(-0.18, 0.23)	0.85	0.07(-0.11, 0.26)	0.47	0.05(-0.1, 0.2)	0.53
	12 m	-0.11(-0.28, 0.08)	0.26	-0.1(-0.26, 0.07)	0.23	0(-0.14, 0.15)	0.99
	18 m	-0.03(-0.2, 0.16)	0.78	-0.12(-0.28, 0.06)	0.18	-0.1(-0.24, 0.05)	0.20
	24 m	-0.06(-0.22, 0.12)	0.52	-0.21(-0.36, -0.03)	0.023	-0.15(-0.29, 0)	0.047
Villalta vs SF-36 MCS	Baseline	0.03(-0.19, 0.26)	0.78	0.03(-0.17, 0.24)	0.78	0(-0.17, 0.17)	0.97
	1 m	0.04(-0.18, 0.26)	0.74	-0.05(-0.24, 0.16)	0.65	-0.09(-0.25, 0.08)	0.31
	6 m	-0.14(-0.35, 0.08)	0.21	-0.14(-0.33, 0.06)	0.16	0(-0.17, 0.18)	0.98
	12 m	-0.12(-0.33, 0.12)	0.32	-0.05(-0.24, 0.16)	0.62	0.06(-0.1, 0.24)	0.46
	18 m	-0.21(-0.41, 0.01)	0.062	-0.34(-0.52, -0.13)	0.0019	-0.13(-0.31, 0.06)	0.18
	24 m	0.17(-0.09, 0.42)	0.20	0.11(-0.12, 0.36)	0.37	-0.06(-0.23, 0.13)	0.54

VCSS vs VEINES-QoL	6 m	0.16(-0.06, 0.39)	0.16	0.09(-0.12, 0.31)	0.40	-0.07(-0.23, 0.09)	0.39
	12 m	0.05(-0.19, 0.3)	0.67	0.11(-0.11, 0.34)	0.33	0.06(-0.11, 0.23)	0.50
	18 m	0.12(-0.12, 0.38)	0.34	0.05(-0.18, 0.29)	0.69	-0.07(-0.24, 0.11)	0.42
	24 m	0.36(0.1, 0.62)	0.0055	0.2(-0.05, 0.45)	0.12	-0.16(-0.33, 0.01)	0.066
VCSS vs VEINES-Sym	6 m	0.19(-0.03, 0.43)	0.097	0.13(-0.08, 0.35)	0.23	-0.06(-0.22, 0.1)	0.45
	12 m	0.18(-0.06, 0.43)	0.15	0.18(-0.04, 0.42)	0.11	0(-0.16, 0.17)	0.95
	18 m	0.14(-0.09, 0.39)	0.25	-0.01(-0.23, 0.23)	0.92	-0.15(-0.32, 0.03)	0.092
	24 m	0.4(0.15, 0.66)	0.0013	0.2(-0.05, 0.45)	0.11	-0.2(-0.36, -0.04)	0.017
VCSS vs SF-36 PCS	6 m	0.23(-0.01, 0.47)	0.064	0.23(0, 0.45)	0.046	0(-0.17, 0.17)	0.97
	12 m	0.01(-0.24, 0.27)	0.95	0.05(-0.18, 0.29)	0.68	0.04(-0.14, 0.23)	0.65
	18 m	0.04(-0.22, 0.31)	0.77	0.06(-0.17, 0.31)	0.63	0.02(-0.17, 0.21)	0.84
	24 m	0.3(0.03, 0.57)	0.027	0.21(-0.05, 0.46)	0.11	-0.1(-0.28, 0.09)	0.31
VCSS vs SF-36 MCS	6 m	-0.12(-0.36, 0.13)	0.35	-0.1(-0.31, 0.13)	0.40	0.02(-0.17, 0.21)	0.83
	12 m	0.03(-0.23, 0.3)	0.80	-0.01(-0.25, 0.24)	0.94	-0.04(-0.23, 0.15)	0.66
	18 m	0.05(-0.23, 0.33)	0.74	-0.01(-0.26, 0.26)	0.97	-0.05(-0.26, 0.16)	0.62
	24 m	0.15(-0.13, 0.43)	0.30	0.04(-0.22, 0.3)	0.77	-0.11(-0.31, 0.1)	0.30