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Impact of Venous Thromboembolism, Venous Stasis Syndrome, Venous Outflow Obstruction and Venous Valvular Incompetence on Quality of Life and Activities of Daily Living: A Nested Case-Control Study

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Abstract

The role of venous stasis syndrome (**VSS**) mechanisms (i.e. venous outflow obstruction [**VOO**] and venous valvular incompetence [**VVI**]) on quality of life (**QoL**) and activities of daily living (**ADL**) is unknown. The objective of this study was to test the hypotheses that venous thromboembolism (**VTE**), VSS, VOO and VVI are associated with reduced QoL and ADL. This study is a follow-up of an incident VTE case–control study nested within a population-based inception cohort of incident residents from Olmsted County, MN, USA, between 1966 and 1990. The study comprised 232 Olmsted County residents with a first lifetime VTE and 133 residents without VTE. Methods included a questionnaire and physical examination for VSS; vascular laboratory testing for VOO and VVI; assessment of QoL by SF36 and of ADL by pertinent sections from the Older Americans Resources and Services (**OARS**) and Arthritis Impact Measurement Scales (**AIMS2**) questionnaires. Of the 365 study participants, 232 (64%), 161 (44%), 43 (12%) and 136 (37%) had VTE, VSS, VOO and VVI, respectively. Prior VTE was associated with reduced ADL and increased pain, VSS with reduced physical QoL and increased pain, and VOO with reduced physical QoL and ADL. VVI was not associated with QoL or ADL. In conclusion, VSS and VOO are associated with worse physical QoL and increased pain. VOO and VTE are associated with impaired ADL. We hypothesize that rapid clearance of venous outflow obstruction in individuals with acute VTE will improve their QoL and ADL.

Keywords

Deep Vein Thrombosis; Venous Thromboembolism; Venous Stasis Syndrome; Post Thrombotic Syndrome; Quality of Life; Activities of Daily Living; Epidemiology

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Introduction

Venous stasis syndrome (**VSS**) is a major health problem, with an annual incidence of 76 per 100,000 [1]. Its clinical features include chronic dependent leg edema, leg pain, skin hyperpigmentation and induration, and in severe cases, venous ulcer. The principal mechanism for VSS is thought to be leg venous hypertension, as may occur with leg venous outflow obstruction or venous valvular incompetence [2]. However, VSS is most often regarded as a long-term consequence of deep vein thrombosis (**DVT)** and is also known as post-thrombotic syndrome or post-phlebitic syndrome in the post-DVT setting. While the estimated cumulative incidence of VSS following DVT is 20–50% [3–8], over three-fourths of VSS patients have no prior history of DVT [1,9]. VSS secondary to DVT adversely impacts quality of life [10–13]. Since VSS also occurs in individuals without a prior history of clinical VTE, we hypothesized that poorer quality of life (**QoL**) and/or impaired activities of daily living (**ADL**) are associated with the potential underlying mechanisms associated with VSS (i.e., venous outflow obstruction **[VOO]** and venous valvular incompetence **[VVI]** as well as DVT). The objectives of this study were to assess the QoL and ADL in patients with or without prior history of incident venous thromboembolism (**VTE**). Among these individuals, VSS was determined by a patient-completed questionnaire and by physical examination, and VOO and VVI were measured, allowing us to assess their relationship with QoL and ADL as well. The data from this study will help identify risk factors associated with poorer QoL and/or ADL in individuals with VTE, VSS, VOO and/or VVI, and thus target high-risk groups with more aggressive therapy.

Methods

Study Design and Population

This case-control study was nested within a population-based inception cohort of Olmsted County, MN residents. The original cases had an incident VTE over the 25-year period, 1966 – 1990 [2,14]. For each objectively-diagnosed VTE patient, we have previously identified one Olmsted County resident without prior VTE who most closely matched the VTE patient on age, gender and duration of prior medical history in the community [15]. There is a risk of misclassification of any lingering symptoms of acute DVT as VSS if the assessment is conducted soon after the acute VTE event. Moreover, although VSS may become apparent soon after VTE, symptomatic VSS takes time to develop [3,4,6,7,16,17]. Therefore, following approval by the Mayo Clinic Institutional Review Board, all living VTE patients and matched residents were invited for study participation at least five years after their VTE event for VTE cases and index event for controls. The latter was within ± 1 year of the incident VTE of the case to whom they were originally matched. Consenting participants were assessed for VSS, VVI, VOO, ADL and QoL on one occasion within the three-year period, 1996–1998.

Baseline Characteristics

For each participant, data on demographic and baseline clinical characteristics at the time of the incident VTE event (or for matched residents, the corresponding medical visit) were abstracted from their complete (inpatient and outpatient) medical records in the community as previously described [15], and included patient age, gender, body mass index (**BMI**), congestive heart failure (**CHF**), chronic lung disease, pulmonary hypertension, chronic renal disease, serious liver disease, superficial vein thrombosis, varicose veins and VSS diagnosed prior to the incident VTE.

Measurements and Definitions

Venous Stasis Syndrome was assessed by a patient-completed questionnaire for symptoms or signs of VSS, and by physical examination as described previously [2]. Briefly, the questionnaire obtained patient responses (yes – no) to questions addressing: a) leg or ankle skin pigmentation; b) leg or ankle skin thickening; c) leg or ankle slow-healing ulcer; d) leg or ankle swelling, and if such swelling was present, e) overnight resolution of the swelling (Supplement 1). During the physical examination, both legs were examined for edema, stasis pigmentation, dermatoliposclerosis, varicose veins and venous ulcer. Participants were diagnosed with VSS if both questionnaire and physical examination confirmed symptoms, signs and physical findings of VSS, or if either the questionnaire or physical examination confirmed VSS and the other evaluation was not performed. To diagnose VSS, we required concordance in the questionnaire-based symptoms and its evidence by physical examination if both were done. However, 29% of participants diagnosed with VSS received only the questionnaire or physical examination evaluation. Because of concern regarding over- or under-diagnosis of VSS, we performed analyses using either VSS diagnosed by questionnaire-provided symptoms and signs or VSS diagnosed by physical examination evidence of venous stasis syndrome, and the analyses results were not significantly changed. Consequently, we only report the most conservative estimate of VSS prevalence.

Deep Venous Outflow Obstruction was assessed in each leg by certified vascular laboratory technicians in the Mayo Clinic Vascular Laboratory using strain gauge outflow plethysmography (**SGOP**, Phlebotest™, Eureka Company, Sweden) and venous continuous wave (**CW**) Doppler examination (MedaSonics® BF4B general blood flow Doppler, Cooper Surgical, Connecticut, USA) as described previously [2]. Briefly, for SGOP, appropriately-sized blood pressure cuffs were placed around both thighs and inflated to 45 mmHg, allowing arterial inflow but occluding venous outflow. Changes in calf volumes were determined by strain gauges. Following recording of a steady state calf volume ($\mathbf{V_{sec}}$), the thigh cuffs were rapidly deflated and data collected on: a) calf volume change (expelled volume) within the first 4 seconds ($\mathbf{EV_{4.0}}$), and b) flow rate within the first second ($\mathbf{F_{1.0}}$). Values for $F_{1.0}$ versus $EV_{4.0}/V_{Sec}$ were plotted and interpreted for VOO as previously described [18]. No VOO was defined as SGOP free flow and a normal venous CW Doppler signal in the femoral region. If VOO by SGOP was noted, or if the venous CW Doppler examination showed either a ≤ -1 reduction in spontaneous or phasic venous signal at the femoral level or ≤ -2 insufficient venous signal augmentation at the common femoral, femoral or popliteal vein level with calf compression, then VOO was diagnosed. Equivocal VOO, defined as an SGOP indicating as such and absent venous CW Doppler criteria for obstruction, was categorized as no VOO for this analysis. At the patient level, venous outflow obstruction was diagnosed if either leg met criteria for VOO.

Deep Venous Valvular Incompetence was assessed in each leg by venous CW Doppler examination at the common femoral, femoral, popliteal, and posterior tibial veins and by passive drainage and refill (**PD&R**) testing using strain gauge plethysmography as previously described [2]. Briefly, PD&R was assessed in a tilting power chair (Phlebotest™, Eureka Company, Sweden; distributor: Osborn Medical Corporation, Utica, MN, USA) by passively tilting the subject from the supine sitting position to the upright sitting position and measuring the venous refill rate [19]. In addition, VVI was gauged by the presence of significant, sustained venous flow reversal occurring at or distal to the common femoral vein in response to either the Valsalva maneuver or manual compression of the limb performed proximally to the site of CW Doppler examination. No VVI was defined as a normal PD&R result (<5 mL/100 mL/min) and 0 (on a scale of 0 to −3, with −3 being severe) VVI by venous CW Doppler examination. Mild VVI was defined as a PD&R between 5 and 10 mL/100 mL/min, or a venous CW Doppler incompetence signal of −1. VVI was considered moderate-to-severe if the PD&R was >10 mL/100 mL/min, or a −2 or −3 CW Doppler

incompetence signal was present at two or more (femoral, popliteal or posterior tibial) vein levels. Superficial VVI was defined as a normal PD&R and a variable CW Doppler incompetence signal at any of the aforementioned venous levels, or abnormal PD&R results with no CW Doppler incompetence signal. For purposes of the analysis, superficial VVI was categorized as no valvular incompetence, while mild and moderate-to-severe VVI were combined as venous valvular incompetence. Similar to VOO, VVI was defined at the patient-level if either leg met criteria for incompetence.

The Health-Related Quality of Life was assessed using a standardized, self-administered QoL instrument, Short Form Health Survey-36 version 1 (**SF-36**; Supplement 1) [20, 21]. The SF-36 generates Physical Component and Mental Component Summary scores, which reflect the physical and mental health status of individuals.

Activities of Daily Living was measured by questionnaire, "Study of Blood Clots in Legs or in the Lungs" (Supplement 1) that contained items taken from pertinent sections of established assessment tools, such as the ADL section of the “Older Americans Resources and Services” (**OARS**) questionnaire [22, 23]. The participants were also asked to report restricted activity, missed work/school days and bed-days in the preceding 15 days. In addition, a series of questions where adapted from the second version of the “Arthritis Impact Measurement Scales” (**AIMS2**) instrument in order to assess overall and lower extremity functional limitations, including mobility, walking/bending, and leg pain [24].

Statistical Analyses

The matching variables for the original case-control study [15] included patient age at incident VTE event, gender, and year of incident VTE event. For this study, all available cases and controls were invited to participate. Due to lower participation rates in the controls and low survival in the cases [25], however, only 41 previously matched complete case-control pairs were available. Consequently, the matching was not retained in the analysis, and age, gender, and time from VTE event to follow-up assessment were treated as adjusting variables in the analysis of the 232 VTE case patients and the 133 community residents who served as controls. For each of the four analyses performed in this study, “case” status was defined, respectively, by either presence or absence of prior history of VTE or by current VSS, by VOO or by VVI. Thus, this is a nested case-control study within an inception population based cohort.

QoL was represented by the SF-36 physical and mental composite scores, and were computed using standard scoring algorithms [20,21] that were age- and gender-adjusted, with higher scores indicating a better QoL. The ADL assessed by the items in the AIMS2 scale were categorized into patient's mobility, walking and bending capacity, and leg pain scores, utilizing scoring methods developed for the AIMS2 instrument [24]. The scores were then normalized on a scale from 0 to10, with higher values indicating better ADL. While the OARS instrument assesses an individual’s physical, mental, economic and social health in addition to the activities of daily living, we utilized only the ADL section for this study. Therefore, a revised scoring system was created based on questions in the OARS instrument relevant to lower extremity physical functioning. Scores were calculated based upon simple summation of the pertinent survey responses and then normalized on a scale of 0 to 10 with higher scores indicating better ADL. Due to missing data, scores could not be computed on 11 VTE cases and four controls for SF 36; eight cases and four controls for AIMS2 Mobility; 11 cases and two controls for AIMS2 Walking/Bending; six cases and four controls for AIMS2 Leg Pain; nine cases and eight controls for overall OARS Daily Activity; and seven cases and six controls for OARS Daily Lower Extremity Activity.

We tested VTE, VSS, VOO and VVI for an association with each of the QoL and ADL scores using logistic regression, both unadjusted and adjusted for potential confounders. Potential confounders were identified via multivariable logistic regression based on the following model selection techniques: For each of the four endpoints (i.e., VTE, VSS, VOO and VVI), a multivariable model was constructed based initially on the adjusting variables, hypothesized VTE risk factors, and all significant baseline characteristics from stepwise selection (with a retention criterion of $p \leq 0.10$). In addition, the functional form of all continuous variables was assessed for a nonlinear relationship with the endpoint, and all pair-wise interaction terms were considered for entry in stepwise selection (retention criterion of $p \leq 0.05$). Lastly, bootstrap resampling was used to identify a final model consisting of only factors retained in stepwise selection in at least 60% of all bootstrap samples, thus reducing the chance of type I error [26]. Each of the QoL or ADL scores were then added to the endpoint-specific final models separately and evaluated for an independent association. For ease of interpretation, the scales of QoL and ADL were inverted such that higher scores reflected poorer QoL/ADL and thus a higher risk ratio represented worse outcome.

As multiple hypotheses were tested for the six QoL/ADL scores on four disease endpoints with a type I error (alpha value) set at 0.05 for each hypothesis, the Bonferroni correction (alpha ÷ k, where k=number of tests; k=6×4=24, Bonferroni corrected alpha=0.002) was applied in order to reduce the likelihood of finding apparently significant differences due to random chance.

Results

Study Population

A total of 1007 subjects (VTE cases, n=503; non-VTE controls, n=504) were solicited for study participation. Of these, 233 cases (46%) and 136 (27%) controls completed the questionnaire and the vascular laboratory testing. There were 365 unique individuals in this study as four of the controls subsequently developed a VTE event and could be considered as both a case and a control. Three of these individuals developed VTE eight years, seven and one-half years, and nearly one year before their VSS physical examination dates and were treated as VTE cases in the analysis using only data related to their case status (136-3=133). The fourth person became a case after his VSS exam date and was considered solely as a non-VTE control in the analysis (233-1=232). Thus, of the 365 study participants, 232 had a VTE and 133 did not at the time of completing the questionnaire and vascular laboratory testing. Fifty-nine percent of the incident VTE events were DVT, 28% pulmonary embolism (**PE**), and 12% combined DVT and PE. Surviving VTE cases were younger than participating controls at the incident VTE event date (mean age ±SD, 50.3±16.4 vs. 54.1±14.9 years, p=0.03) and marginally younger at the VSS, QoL and ADL assessment date (63.6±14.4 vs. 65.9±14.9 years, p=0.15). One hundred and six of the study participants wore graduated compression stocking.

In an attempt to address possible selection bias, we compared the baseline characteristics of individuals included in the original inception cohort but not participating in this study versus those who did participate in the study (Table 1). Among non-participant VTE cases from the original inception cohort, nearly 90% of those with incident PE±DVT and 56% of those with DVT alone were deceased prior to the launch of the study, compared to 45% of non-participant controls. Individuals who were alive and consented to participate in this nested case-control study were younger in age at the time of their index VTE event, and had higher BMI levels and a lower frequency of comorbidities (e.g., lung disease and/or pulmonary hypertension, active malignancy, and CHF and/or cardiomyopathy; Table 1). In addition, VTE cases who participated in the study had a slightly higher rate of prior superficial vein

thrombosis compared to the non-participants. In contrast, the consenting non-VTE controls had a lower rate of prior varicose veins at the time of the index event compared to the non-participants (Table 1).

Frequency of VSS, VOO and VVI

Of the 365 study participants, 161 (44%), 43 (12%) and 136 (37%) had VSS, VOO or VVI, respectively. Twenty-six (7%) had both VOO and VVI. The prevalence of baseline characteristics by VSS, VOO and VVI status are shown in Table 2. Individuals with VSS were older and had a higher BMI. In addition, they had a higher frequency of prior VTE, varicose veins and superficial vein thrombosis. VOO was noted more frequently in older individuals, males, and those with prior VTE. VVI was detected more frequently in individuals with higher BMI, prior VTE, varicose veins and those with VSS diagnosed prior to the VTE event. Furthermore, the risk of VSS, VOO and VVI was higher with an increasing time interval from the VTE event to the follow-up assessment [2].

QoL and ADL in individuals with VTE, VSS, VOO and VVI

The distribution of QoL and ADL scores are summarized in Table 3, and the association between each score and venous endpoint tested via logistic regression, both unadjusted and adjusted for potential confounders, are shown in Table 4.

QoL and ADL in individuals with prior VTE—Though not significant with the Bonferroni correction, prior VTE was associated with worse AIMS2 Pain scores (p=0.003), OARS Daily Activities (p=0.005) and Daily Lower Extremity Activities scores (p=0.004) (Table 4).

Adjusting for age, gender, BMI, time since VTE event, and graduated compression stocking use, prior VTE was not associated with increased pain (p=0.017), or with worse SF-36 physical (p=0.058), AIMS2 Walking/Bending (p=0.009) or Mobility (p=0.051) scores (Table 4). However, prior VTE was independently associated with worse OARS Daily Activities (p=0.002) and Daily Lower Extremity Activities scores (p=0.002).

We also tested for an association with VTE event type (DVT ± PE vs. PE alone), DVT location (proximal vs. isolated calf DVT) and VTE recurrence. AIMS2 Pain score was marginally worse among patients with DVT ± PE compared to PE alone (8.0±2.4 vs. 8.7±1.6 respectively; p=0.08). The AIMS2 Mobility and Walking/Bending scores were non-significantly worse among patients with isolated calf vs. proximal DVT (8.9±1.9 vs. 9.4±1.4; p=0.13, and 6.5±3.3 vs. 7.5±2.7; p=0.09, respectively). AIMS2 Pain score was worse among patients with recurrent VTE compared to those with an incident VTE alone (8.3+2.1 vs. 6.9+2.9 respectively; p=0.03), along with marginally poorer AIMS2 Walking/Bending scores (6.5±3.1 vs. 7.4±2.9 respectively; p= 0.11). Interestingly, individuals with an incident VTE had marginally poorer SF-36 mental QoL compared to those with prior recurrent VTE (53.2±8.5 versus 55.6±9.9 respectively; P = 0.12).

QoL and ADL in individuals with VSS—From univariate analysis, VSS was significantly associated with worse SF-36 physical QoL scores (p<0.001) and with impaired ADL (Table 4), as measured by the AIMS2 Pain (p<0.001) and Walking/Bending (p<0.001) scales. Though not significant with the Bonferroni correction, VSS was marginally associated with worse OARS Daily Activities (p=0.003) and Daily Lower Extremity Activities scores (p=0.003).

Adjusting for age, gender, BMI, time since VTE event, VTE case status, varicose veins, and graduated compression stocking use, VSS was significantly associated with increased pain

(p<0.001) but not with worse physical QoL (p=0.01) or any of the other ADL scales (Table 4).

QoL and ADL in individuals with VOO—Similar to VSS in univariate analysis, VOO was associated with impaired physical QoL (p<0.001) but not with mental QoL, as measured by the SF-36 questionnaire (Table 4). Further, VOO was significantly associated with worse AIMS2 Walking/Bending scores (p<0.001) and marginally associated with worse OARS Daily Lower Extremity Activities scores with the Bonferroni correction (p=0.005). In contrast to VSS, VOO was associated with worse AIMS2 Mobility scores (p<0.001) but was not associated with increased pain (p=0.037) or the OARS Daily Activities scale (p=0.015).

Adjusting for age, gender, BMI, time since VTE event (quadratic), VTE case status, and graduated compression stocking use, VOO was only marginally associated with worse AIMS2 walking/bending (p=0.004; see Table 4). There was not a significant association of VOO with physical QoL (p=0.015), AIMS2 Mobility (p=0.009) or OARS Daily Lower Extremity Activities (p=0.279) scores, independent of the adjusting factors.

QoL and ADL in individuals with VVI—None of the SF-36 QoL, AIMS2 ADL, or OARS daily activities scores differed significantly between individuals with or without venous valvular incompetence (Table 3).

Adjusting for age, gender, BMI, time since VTE event (quadratic), VTE case status, BMI, varicose veins, prior VSS, and graduated compression stocking use, there was no association between any of the QoL or ADL scores with VVI (Table 4).

QoL and ADL in individuals with concomitant VOO and VVI—Twenty six of the study participants were noted to have both VOO and VVI. Concomitant VOO and VVI was marginally associated with worse SF-36 physical QoL (p=0.005) and AIMS2 walking/bending scores (p=0.004) with the Bonferroni correction, but not associated with AIMS2 Mobility (p=0.016), Pain (p=0.075) or OARS Daily Lower Extremity Activities (p=0.135; see Table 4).

Adjusting for age, gender, BMI, time since VTE event (quadratic), VTE case status, and graduated compression stocking use, concomitant VOO and VVI was not associated with worse SF-36 physical QoL (p=0.033), AIMS2 walking/bending (p=0.054), AIMS2 Mobility (p=0.029), Pain (p=0.398) or OARS Daily Lower Extremity Activities scores (p=0.848; see Table 4).

Discussion

VSS secondary to DVT, also known as post-thrombotic syndrome, has been shown to adversely impact quality of life [10–13]. In this nested case-control study, VSS was associated with increased pain and probably poorer physical QoL but did not affect ADL (i.e., walking/bending, and daily activities overall and specific to lower extremities), adjusted for potential confounders. We speculate that although the pain from VSS was impacting the affected individuals' physical QoL, they could still carry out their ADL without limitation. With respect to potential underlying mechanisms for VSS, prior VTE was associated with impaired ADL (i.e., overall daily activities and daily activities involving lower extremities) and probably increased pain, but not with worse SF-36 QoL, independent of confounding factors. We speculate that prior VTE may lead to persistent residual vein thrombosis and increased pain, and thus impact the daily activities involving lower extremities and overall daily activities. Alternatively, one could speculate that as relative immobility is risk factor for VTE, the impaired ADL may have predisposed these

individuals to venous thrombosis. Similarly, VOO was marginally associated with worse ADL in the form of walking/bending and mobility but not physical QoL after adjustment for potential confounders. We think that VOO is secondary to residual vein thrombus from prior DVT, and that decreased ADL could probably reflect one of the underlying risk factors for the affected individual's VTE. In contrast, VVI was not associated with QoL, pain or ADL. In support of this lack of association, many patients with severe VVI have been noted to have only mild symptoms of VSS, suggesting that additional factors may contribute to the development of symptomatic VSS [27]. We did not note adverse QoL and ADL in individuals with concomitant VOO and VVI, and this may be due to inadequate power for detecting an association as only 7% of all participants had both VOO and VVI.

We also noted that individuals with prior DVT ± PE had worse pain scores compared to individuals with PE alone. A similar finding was noted in individuals with prior recurrent VTE compared to individuals with an incident VTE episode. These findings may be related to the slightly higher frequency of VSS in patients with DVT ± PE and in those with recurrent VTE [2]. In addition, individuals with recurrent VTE had worse walking/bending scores, which may be due to a higher rate of VOO in individuals with recurrent VTE [2]. Interestingly, individuals with a single episode of VTE had a marginally poorer mental QoL compared to those with recurrent VTE, and may reflect that individuals with recurrent VTE may have acclimatized to the clinical symptoms of VTE, or alternatively, may be on chronic, long term anticoagulation for secondary VTE prevention, which in turn, may provide a sense of security against repeat episodes.

Our study has several strengths. The study included 365 participants who were drawn from a population-based inception cohort [14,28], thus avoiding potential referral bias. In addition, we have documented true VTE case status for both cases and controls by thorough medical record review. Furthermore, we have reliable medical record documentation of recurrent VTE and can accurately measure effects on individuals with the first, incident VTE and those with recurrent VTE. While based on data from no later than 1998, the findings of this study are still relevant as there have been no major changes in the management of either VTE or VSS since then. The most conservative way of assessing VSS status was used; and the analyses results did not change appreciably based on whether diagnosis of VSS was based on questionnaire-provided symptoms and signs, or by its evidence on physical examination. VOO and VVI endpoints were assessed prospectively and systematically by established protocol using validated tests at least six years after the incident VTE event, hence avoiding the misclassification of any lingering symptoms of acute DVT as VSS. The QoL and ADL were measured systematically using standard, well-documented and validated scales that were available at the time. A large number of baseline characteristics collected at the time of the initial VTE event were assessed as potential risk factors for the study end-points. Furthermore, we adjusted for the use of graduated compression stocking in our analyses, which has been demonstrated to decrease the incidence of VSS, a major determinant of QoL [13], after DVT [16,17]. Our modeling strategy required that the risk factors included in our final model be present in at least 60% or more of separate bootstrap validations, thus reducing the chance of type 1 error. Finally, as multiple hypotheses were tested, the conservative Bonferroni correction (Bonferroni corrected alpha=0.002) was applied in order to reduce the likelihood of finding apparently significant differences due to random chance.

Several limitations should also be considered when evaluating the results of this study. Of all potential subjects who were initially invited to participate in the study, only 46% of the VTE cases and 27% of the non-VTE controls agreed to take part in the study, introducing potential selection bias. In an attempt to address this potential bias, we compared the baseline characteristics of individuals included in the original inception cohort that did

versus did not participate in this nested case-control study (Table 1). Individuals who participated tended to be younger, have higher BMI levels, and have less comorbidity (e.g., lung disease and/or pulmonary hypertension, active malignancy, and CHF and/or cardiomyopathy). We speculate that the older individuals and ones with significant comorbidities at the index event were probably deceased prior to the launch of this study. Of the surviving older individuals and those with higher rates of comorbidities may have had poorer QoL and/or ADL and their potential participation in this study may have resulted in worse QoL and/or ADL scores than that observed in the participants. The VTE cases who participated in the study had a slightly higher frequency of prior superficial thrombosis compared to the non-participants, which could also have caused a shift in QoL and pain scores. In contrast, the participating non-VTE controls had lower frequency of prior varicose veins compared to the non-participants, which in turn, could have improved the QoL and pain scores. Furthermore, our study may be subject to survival bias as VTE cases have a significantly poorer survival than their matched controls [25]. Among non-participant VTE cases from the original inception cohort, nearly 90% of those with incident PE±DVT and 56% of those with DVT alone were deceased prior to the launch of the study, compared to 45% of non-participant controls. Uniquely, our study can assess this participation bias. Finally, the application of the conservative Bonferroni to reduce the type I error may have increased the type II error.

In summary, individuals with VSS have increased pain and poorer physical QoL. Individuals with prior history of VTE, a potential underlying mechanism of VSS, have decreased ADL and increased pain, and those with VOO have worse ADL. Therefore, we hypothesize that the use of thrombolytic agents and/or mechanical thrombectomy to clear venous outflow obstruction rapidly in individuals with acute DVT will improve their QoL and ADL. However, these potential benefits of aggressive treatment have to be balanced by an increased risk for hemorrhagic complications. To address these questions, a randomized, multi-institutional, NIH sponsored clinical trial is currently being conducted [29]. In addition, as the risk of VSS and VOO is higher with left leg DVT compared to right leg DVT [2], presumably due to the May-Thurner syndrome (i.e., the anatomic compression of the left iliac vein by the overlying right iliac artery), we speculate that proactive screening and correction of May-Thurner syndrome in individuals with left leg DVT will improve their QoL and ADL. Furthermore, we suggest that older and/or obese patients with leg DVT (particularly, left leg DVT), who are at increased risk for VSS and/or VOO [2] be considered for compression stocking therapy to improve their QoL and ADL, particularly those with evidence of ongoing VOO.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADL	Activities of daily living
AIMS2	Second version of “Arthritis Impact Measurement Scales”
CW Doppler	Continuous wave Doppler

DVT	Deep vein thrombosis
OARS	“Older Americans Resources and Services” questionnaire
PE	Pulmonary embolism
QoL	Quality of life
SF-36	Short Form Health Survey-36
VOO	Venous outflow obstruction
VSS	Venous stasis syndrome
VTE	Venous thromboembolism
VVI	Venous valvular incompetence

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Table 1

Baseline Characteristics of the Individuals of the Original Inception Cohort Not Participating versus those Participating in the Study

Variable	VTE Cases					VTE Controls		
	DVT alone		PE±DVT					
	Non-Participants (n=344)	Participants (n=138)	Non-Participants (n=767)	Participants (n=94)	*p-value*	Non-Participants (n=761)	Participants (n=133)	*p-value*
Age at Time of VTE Event^	66.1 (44.0, 78.0)	49.6 (35.7, 63.1)	74.5 (62.6, 82.9)	51.8 (41.5, 62.4)	*<.001*	71.8 (52.5, 81.4)	55.8 (43.4, 66.1)	*<.001*
Male	149 (43.3%)	77 (55.8%)	371 (48.4%)	50 (53.2%)	*0.06*	364 (47.8%)	65 (48.9%)	*0.82*
BMI^	25.1 (22.1, 28.7)	27.3 (24.3, 30.3)	22.9 (19.5, 26.7)	25.9 (23.5, 29.6)	*<.001*	25.0 (22.3, 28.2)	26.3 (23.6, 28.2)	*0.01*
Obese (BMI≥30)	60 (17.4%)	38 (27.5%)	109 (14.2%)	21 (22.3%)	*<.001*	111 (14.6%)	20 (15.0%)	*0.89*
Death prior to VSS Study	193 (56.1%)	-	687 (89.6%)	-	*<.001*	344 (45.2%)	-	-
Liver disease	6 (1.7%)	0 (0.0%)	14 (1.8%)	1 (1.1%)	*0.43*	8 (1.1%)	0 (0.0%)	*0.23*
Lung Disease and/or Pulmonary Hypertension	59 (17.2%)	12 (8.7%)	161 (21.0%)	7 (7.4%)	*<.001*	99 (13.0%)	9 (6.8%)	*0.04*
Active Malignancy	82 (23.8%)	9 (6.5%)	224 (29.2%)	3 (3.2%)	*<.001*	32 (4.2%)	0 (0.0%)	*0.02*
Congestive Heart Failure and/or cardiomyopathy	48 (14.0%)	1 (0.7%)	223 (29.1%)	1 (1.1%)	*<.001*	84 (11.0%)	0 (0.0%)	*<.001*
Prior Varicose Veins	88 (25.6%)	27 (19.6%)	189 (24.6%)	32 (34.0%)	*0.09*	152 (20.0%)	16 (12.0%)	*0.03*
Superficial Thrombosis	29 (8.6%)	15 (10.9%)	41 (5.4%)	7 (7.4%)	*0.05*	27 (3.6%)	2 (1.5%)	*0.21*
Venous Stasis Syndrome prior to the incident VTE	25 (7.3%)	11 (8.0%)	70 (9.1%)	3 (3.2%)	*0.22*	47 (6.2%)	4 (3.0%)	*0.15*

^Median (Q1, Q3); K–W test

Table 2

Baseline Characteristics of Study Participants by Venous Thromboembolism, Venous Stasis Syndrome, Venous Outflow Obstruction and Venous Valvular Incompetence Status

Baseline Characteristic		Venous Thromboembolism		Venous Stasis Syndrome		Venous Outflow Obstruction		Venous Valvular Incompetence	
		Yes (n=232)	No (n=133)	Yes (n=161)	No (n=204)	Yes (n=43)	No (n=319)	Yes (n=136)	No (n=226)
Age at Diagnosis (years)	*Mean (SD)*	50.3 (16.4)	54.1 (14.9)	67.2 (14.3)	62.6 (14.6)	72.7 (12.4)	63.2 (14.5)	65.7 (14.3)	63.6 (14.7)
	Median (Q1,Q3)	50.7 (37.6,62.9)	55.7 (43.4,66.1)	68.4 (58.5,78.2)	64.2 (50.8,74.0)	76.2 (64.9,80.7)	64.8 (51.6,74.4)	67.9 (55.5,76.8)	65.1 (53.8,74.8)
Male	*n (%)*	127 (54.7%)	65 (48.9%)	89 (55.3%)	103 (50.5%)	29 (67.4%)	160 (50.2%)	78 (57.4%)	112 (49.6%)
Time Between VTE Event and Venous Endpoint Assessment (years)	*Mean (SD)*	13.7 (7.0)	11.8 (3.9)	13.9 (7.0)	12.4 (5.2)	13.5 (7.9)	12.6 (5.9)	13.4 (7.1)	12.3 (5.5)
	Median (Q1,Q3)	12.8 (8.0,19.6)	10.7 (8.7,14.3)	12.9 (8.4,15.2)	11.3 (8.5,15.2)	11.5 (8.1,20.2)	11.5 (8.3,16.6)	11.9 (8.1,17.7)	11.1 (8.3,15.4)
VTE Case	*n (%)*	--	--	135 (83.9%)	97 (47.5%)	36 (83.7%)	195 (61.1%)	111 (81.6%)	119 (52.7%)
Congestive Heart Failure and/or cardiomyopathy	*n (%)*	21 (9.1%)	8 (6.0%)	15 (9.3%)	14 (6.9%)	6 (14.0%)	23 (7.2%)	15 (11.0%)	14 (6.2%)
Body Mass Index (kg/m^2)	*Mean (SD)*	27.0 (5.2)	26.1 (3.8)	27.7 (5.0)	25.9 (4.4)	26.8 (4.2)	26.6 (4.9)	27.3 (5.5)	26.3 (4.3)
	Median (Q1,Q3)	26.6 (23.5,30.0)	26.3 (23.5,27.9)	27.5 (24.2,30.9)	25.7 (23.0,28.1)	26.1 (22.8,30.1)	26.4 (23.5,29.2)	27.1 (23.6,30.4)	26.2 (23.3,28.6)
Prior Superficial Thrombosis	*n (%)*	22 (9.5%)	2 (1.5%)	18 (11.2%)	6 (2.9%)	3 (7.0%)	21 (6.6%)	13 (9.6%)	11 (4.9%)
Prior Varicose Veins	*n (%)*	54 (23.3%)	15 (11.3%)	48 (29.8%)	21 (10.3%)	13 (30.2%)	56 (17.6%)	41 (30.1%)	28 (12.4%)
Lung Disease / Pulmonary Hypertension	*n (%)*	12 (5.2%)	7 (5.3%)	12 (7.5%)	7 (3.4%)	3 (7.0%)	15 (4.7%)	8 (6.0%)	11 (4.9%)
Venous Stasis Syndrome prior to the incident VTE event	*n (%)*	14 (6.0%)	4 (3.0%)	15 (9.3%)	3 (1.5%)	4 (9.3%)	14 (4.4%)	14 (10.3%)	4 (1.8%)
Chronic Renal Disease	*n (%)*	1 (0.4%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Serious Liver Disease	*n (%)*	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.3%)	1 (0.7%)	0 (0.0%)

Table 3

Distribution of QoL and ADL Scores for Individuals With or Without Venous Thromboembolism, Venous Stasis Syndrome, Venous Outflow Obstruction and Venous Valvular Incompetence

Score		Venous Thromboembolism		Venous Stasis Syndrome		Venous Outflow Obstruction		Venous Valvular Incompetence	
		Yes (n=232)	No (n=133)	Yes (n=161)	No (n=204)	Yes (n=43)	No (n=319)	Yes (n=136)	No (n=226)
SF-36 Physical	*Mean (SD)*	44.3 (11.4)	46.6 (10.1)	42.0 (11.6)	47.6 (9.9)	38.6 (11.0)	45.9 (10.8)	43.8 (11.2)	45.8 (10.8)
	Median (Q1,Q3)	46.8 (37.0, 52.9)	49.6 (40.8, 54.7)	43.7 (34.3, 51.5)	50.3 (44.7, 55.0)	39.1 (33.7, 46.5)	49.1 (40.7, 54.0)	46.2 (36.9, 52.5)	49.0 (38.8, 54.5)
SF-36 Mental	*Mean (SD)*	53.5 (8.6)	54.8 (7.6)	53.3 (9.0)	54.5 (7.6)	52.9 (10.8)	54.0 (8.0)	52.8 (9.2)	54.6 (7.6)
	Median (Q1,Q3)	56.1 (49.1, 59.5)	56.3 (52.1, 59.4)	55.7 (48.3, 59.4)	56.4 (51.9, 59.5)	55.9 (46.6, 59.9)	56.1 (50.8, 59.4)	55.9 (46.9, 59.5)	56.3 (51.9, 59.4)
AIMS2 Mobility	*Mean (SD)*	9.2 (1.6)	9.5 (1.1)	9.2 (1.5)	9.4 (1.4)	8.5 (2.3)	9.4 (1.2)	9.3 (1.5)	9.4 (1.4)
	Median (Q1,Q3)	10.0 (9.0, 10.0)	10.0 (9.5, 10.0)	10.0 (9.0, 10.0)	10.0 (9.5, 10.0)	10.0 (8.0, 10.0)	10.0 (9.5, 10.0)	10.0 (9.0, 10.0)	10.0 (9.5, 10.0)
AIMS2 Walking/ Bending	*Mean (SD)*	7.3 (2.9)	8.1 (2.4)	6.9 (2.9)	8.1 (2.5)	5.8 (3.1)	7.8 (2.6)	7.4 (2.8)	7.7 (2.7)
	Median (Q1,Q3)	8.1 (5.6, 10.0)	9.4 (6.9, 10.0)	7.5 (5.0, 9.7)	9.4 (7.5, 10.0)	6.3 (4.4, 8.1)	8.8 (6.3, 10.0)	8.1 (5.6, 10.0)	8.8 (6.3, 10.0)
AIMS2 Pain	*Mean (SD)*	8.2 (2.3)	8.9 (1.8)	7.7 (2.3)	9.0 (1.8)	7.8 (2.6)	8.5 (2.1)	8.2 (2.2)	8.6 (2.1)
	Median (Q1,Q3)	9.1 (6.9, 10.0)	10.0 (8.1, 10.0)	8.1 (6.3, 10.0)	10.0 (8.8, 10.0)	9.4 (5.6, 10.0)	9.4 (7.5, 10.0)	9.4 (6.9, 10.0)	10.0 (7.5, 10.0)
OARS Daily Activities	*Mean (SD)*	9.5 (1.1)	9.8 (0.5)	9.5 (1.2)	9.8 (0.6)	9.3 (1.3)	9.7 (0.9)	9.6 (0.9)	9.7 (1.0)
	Median (Q1,Q3)	10.0 (9.3, 10.0)	10.0 (10.0, 10.0)	10.0 (9.3, 10.0)	10.0 (10.0, 10.0)	10.0 (9.3, 10.0)	10.0 (10.0, 10.0)	10.0 (9.3, 10.0)	10.0 (10.0, 10.0)
OARS Daily Lower Extremity Activities	*Mean (SD)*	9.3 (1.5)	9.7 (0.8)	9.2 (1.5)	9.6 (1.0)	8.9 (1.9)	9.5 (1.2)	9.4 (1.4)	9.5 (1.2)
	Median (Q1,Q3)	10.0 (8.8, 10.0)	10.0 (10.0, 10.0)	10.0 (8.8, 10.0)	10.0 (10.0, 10.0)	10.0 (8.8, 10.0)	10.0 (10.0, 10.0)	10.0 (8.8, 10.0)	10.0 (10.0, 10.0)

TABLE 4

Unadjusted and Adjusted Measures of QoL and ADL Associated with Venous Thromboembolism, Venous Stasis Syndrome, Venous Outflow Obstruction and Venous Valvular Incompetence

Score		Endpoints				
		Venous Thromboembolism[1]	**Venous Stasis Syndrome[2]**	**Venous Outflow Obstruction (VOO)[3]**	**Venous Valvular Incompetence (VVI)[4]**	**VOO and VVI [5]**
		OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
SF-36 Physical	*Unadjusted*	1.02 (1.00, 1.04)	1.05 (1.03, 1.07)***	1.05 (1.02, 1.08)***	1.02 (1.00, 1.04)	1.05 (1.01, 1.09)**
	Adjusted	**1.02 (1.00, 1.05)**	**1.03 (1.01, 1.06)****	**1.04 (1.01, 1.08)***	**1.00 (0.98, 1.02)**	**1.05 (1.00, 1.09)***
SF-36 Mental	*Unadjusted*	1.02 (0.99, 1.05)	1.02 (0.99, 1.04)	1.02 (0.98, 1.06)	1.03 (1.00, 1.05)*	1.03 (0.99, 1.08)
	Adjusted	**1.02 (0.99, 1.05)**	**1.01 (0.98, 1.04)**	**1.00 (0.96, 1.04)**	**1.02 (0.99, 1.05)**	**1.01 (0.96, 1.06)**
AIMS2 Mobility	*Unadjusted*	1.18 (0.99, 1.41)	1.14 (0.98, 1.32)	1.35 (1.14, 1.59)***	1.05 (0.90, 1.21)	1.28 (1.05, 1.56)*
	Adjusted	**1.22 (1.00, 1.48)**	**0.97 (0.81, 1.16)**	**1.30 (1.07, 1.59)****	**0.94 (0.79, 1.12)**	**1.32 (1.03, 1.68)***
AIMS2 Walking/ Bending	*Unadjusted*	1.11 (1.02, 1.21)*	1.18 (1.09, 1.28)***	1.26 (1.13, 1.40)***	1.05 (0.97, 1.13)	1.21 (1.06, 1.37)**
	Adjusted	**1.14 (1.03, 1.25)****	**1.10 (1.00, 1.21)**	**1.19 (1.06, 1.34)****	**0.98 (0.90, 1.08)**	**1.16 (1.00, 1.34)**
AIMS2 Pain	*Unadjusted*	1.19 (1.06, 1.34)**	1.34 (1.20, 1.50)***	1.15 (1.01, 1.31)*	1.08 (0.98, 1.19)	1.16 (0.99, 1.36)
	Adjusted	**1.16 (1.03, 1.32)***	**1.25 (1.10, 1.41)*****	**1.09 (0.94, 1.27)**	**1.01 (0.90, 1.13)**	**1.09 (0.90, 1.32)**
OARS Daily Activities	*Unadjusted*	1.83 (1.20, 2.79)**	1.57 (1.17, 2.11)**	1.39 (1.06, 1.81)*	1.08 (0.86, 1.36)	1.23 (0.89, 1.70)
	Adjusted	**2.23 (1.35, 3.69)*****	**1.23 (0.90, 1.67)**	**1.14 (0.85, 1.53)**	**0.87 (0.66, 1.15)**	**1.01 (0.67, 1.52)**
OARS Daily Lower Extremity Activities	*Unadjusted*	1.46 (1.13, 1.88)**	1.33 (1.10, 1.60)**	1.32 (1.09, 1.59)**	1.08 (0.92, 1.27)	1.20 (0.94, 1.53)
	Adjusted	**1.64 (1.21, 2.23)*****	**1.11 (0.90, 1.37)**	**1.13 (0.91, 1.40)**	**0.92 (0.76, 1.12)**	**1.03 (0.77, 1.37)**

* p-value<0.05

** p-value<0.01

*** p-value<0.002* (* *0.002 was used as the level of significance based on the Bonferroni correction for multiple comparisons (k=24))*

[1] **Adjusted** for age, gender, BMI, time since VTE event and stocking use

[2] **Adjusted** for age, gender, BMI, time since VTE event, VTE case status, varicose veins and stocking use

[3] **Adjusted** for age, gender, BMI, time since VTE event (quadratic), VTE case status and stocking use

[4] **Adjusted** for age, gender, BMI, time since VTE event (quadratic), VTE case status, varicose veins, prior VSS and stocking use

[5] **Adjusted** for age, gender, BMI, time since VTE event (quadratic), VTE case status, and stocking use