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Risk Factors and Underlying Mechanisms for Venous Stasis Syndrome: A Population-Based Case-Control Study

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Abstract

Background—Venous stasis syndrome may complicate deep vein thrombosis (**DVT**; i.e., post-phlebitic syndrome), but in most cases, venous stasis syndrome is not post-phlebitic.

Objective—To determine risk factors (including prior DVT) for venous stasis syndrome, and to assess venous outflow obstruction and venous valvular incompetence as possible mechanisms for venous stasis syndrome.

Design—Case-control study nested within a population-based inception cohort.

Population—232 Olmsted County, MN residents with a first lifetime venous thromboembolism (**VTE**), and 133 residents without VTE.

Measurements—Questionnaire and physical examination for venous stasis syndrome; strain gauge outflow plethysmography, venous continuous wave Doppler ultrasonography and passive venous drainage and refill testing for venous outflow obstruction and venous valvular incompetence.

Results—Altogether, 161 (44%), 43 (12%), and 136 (38%) subjects respectively, had venous stasis syndrome, venous outflow obstruction and venous valvular incompetence. Independent risk factors for venous stasis syndrome included increasing patient age and body mass index (**BMI**), prior DVT, longer time interval since DVT, and varicose veins. Both venous outflow obstruction ($p=0.003$) and venous valvular incompetence ($p<0.0001$) were strongly associated with venous stasis syndrome. Increasing age and prior DVT were significantly associated with venous outflow obstruction, while prior DVT, varicose veins and venous stasis syndrome diagnosed prior to the incident DVT were significantly associated with venous valvular incompetence. The risks of venous outflow obstruction, venous valvular incompetence and venous stasis syndrome were higher with left leg DVT.

Conclusions—Increasing patient age and BMI, prior DVT (particularly left leg DVT), longer time interval since DVT and varicose veins are independent risk factors for venous stasis syndrome. Venous stasis syndrome related to DVT is due to venous outflow obstruction and venous valvular incompetence, while venous stasis syndrome related to older age and to varicose veins is due to venous outflow obstruction and to venous valvular incompetence, respectively.

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Keywords

Deep Vein Thrombosis; Venous Thromboembolism; Venous Stasis Syndrome; Post Thrombotic Syndrome; Risk Factors; Epidemiology

Introduction

Venous stasis syndrome manifests clinically as chronic dependent leg edema with leg pain, skin hyperpigmentation and induration; the most severely affected also develop venous ulcer. Venous stasis syndrome is a major health problem, with an annual incidence of 76 per 100,000[1]. The socio-economic impact of chronic venous diseases is high, with an estimated annual direct cost of US$200 million. Indirect costs are also substantial; at least 2 million workdays are lost annually in the US due to venous ulcer[2]. Furthermore, venous stasis syndrome adversely impacts quality of life[3].

Venous stasis syndrome is typically considered a long-term sequel of deep vein thrombosis (**DVT**; also known as post-thrombotic syndrome or post-phlebitic syndrome in the post-DVT setting). The cumulative incidence of venous stasis syndrome after DVT is 20–50%, with a third being severe venous stasis syndrome[4–9]. Conversely, over three-fourths of venous stasis syndrome patients have no history of DVT[1, 10]. Moreover, approximately 10% of patients with incident venous thromboembolism (**VTE**; DVT or pulmonary embolism) have a diagnosis or evidence of venous stasis syndrome *prior* to the incident VTE event[6]. Ambulatory leg venous pressure has both diagnostic and prognostic significance in patients with venous disease[11–14], suggesting that the main underlying cause of venous stasis syndrome is leg venous hypertension as may occur with increased central venous pressure, leg venous outflow obstruction or leg venous valvular incompetence. Since venous stasis syndrome occurs in individuals with and without a prior history of clinical VTE, the mechanisms leading to venous stasis syndrome in these two patient populations may be different. The objectives of this study were to determine risk factors for venous stasis syndrome, and to assess the role of venous outflow obstruction and venous valvular incompetence as possible underlying mechanisms for venous stasis syndrome, in patients with or without prior incident VTE.

Methods

Study Design and Population

This study was nested within a population-based inception cohort of Olmsted County, MN residents with incident VTE over the 25-year period, 1966 – 1990, as previously described[15]. For each objectively-diagnosed VTE patient, we 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[16]. All living VTE patients and matched residents were invited for study participation, and consenting participants were studied on one occasion within the three-year period 1996–1998. The study was approved by the Mayo Clinic Institutional Review Board.

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[16], and included patient age, gender, body mass index (**BMI**), congestive heart failure, chronic lung disease, pulmonary hypertension, chronic renal

disease, nephrotic syndrome, serious liver disease, superficial vein thrombosis, varicose veins and venous stasis syndrome diagnosed prior to the incident VTE. BMI was based on the most recent height and weight measurements prior to the incident VTE. For subjects missing either a height or weight measurement, BMI was imputed using average values within their sex and ten-year age group strata.

Measurements and Definitions

Venous Stasis Syndrome was assessed by a patient-completed questionnaire for symptoms or signs of venous stasis syndrome, and by physical examination within the Mayo Vascular Laboratory. 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 this swelling. During the physical examination, both legs were examined for edema, stasis pigmentation, dermatoliposclerosis, varicose veins and venous ulcer. Participants were diagnosed with venous stasis syndrome if the questionnaire and physical examination confirmed symptoms, signs and physical findings of venous stasis syndrome, or if either the questionnaire or physical examination confirmed venous stasis syndrome and the other evaluation was not performed.

Deep Venous Outflow Obstruction was assessed in each leg by certified vascular laboratory technicians in the Vascular Laboratory using strain gauge outflow plethysmography (**SGOP**, Phelbotest™, Eureka Company, Sweden) and venous continuous wave (**CW**) Doppler examination (MedaSonics® BF4B general blood flow Doppler, Cooper Surgical, Connecticut, USA). 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 (**V_{sec}**), the thigh cuffs were rapidly deflated and data collected on: a) calf volume change (expelled volume) within the first 4 seconds (**$EV_{4.0}$**), and b) flow rate within the first second (**$F_{1.0}$**). Values for $F_{1.0}$ versus $EV_{4.0}/V_{Sec}$ were plotted and interpreted for venous outflow obstruction as previously described[17]. The sensitivity and specificity of CW Doppler for venous outflow obstruction is at least 80% and 90%, respectively[18]. No venous outflow obstruction was defined as SGOP free flow and a normal venous CW Doppler signal in the femoral region. If venous outflow obstruction 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 venous outflow obstruction was diagnosed. Equivocal venous outflow obstruction, defined as an SGOP indicating as such and absent venous CW Doppler criteria for obstruction, was categorized as no venous outflow obstruction for this analysis. At the patient level, venous outflow obstruction was diagnosed if either leg met criteria for venous outflow obstruction.

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. PD&R was assessed in a tilting power chair (Phelbotest™, 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, as previously described19. The sensitivity and specificity of PD&R for venous valvular incompetence are 92% and 100%, respectively 19. Venous valvular incompetence was also 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. In normal veins with no valve incompetence (scale 0), the flow is phasic with respiration, and

immediately following manual compression or Valsalva maneuver, no flow is detected. With mild (scale −1) valvular incompetence, there is a short time lag between the application of the above maneuvers and the absence of venous flow. The time lag between manual compression/Valsalva maneuver and absent venous flow is longer for moderate (scale −2) valvular incompetence. With severe valvular incompetence (scale −3), venous flow is detected during the manual compression/Valsalva maneuver, with no time period where the venous flow is completely absent. The inter-rater correlation for categorizing venous valvular incompetence by the CW Doppler is 87–93% by the annual quality control studies (data on file). No venous valvular incompetence was defined as a normal PD&R result (<5 mL/100 mL/min) and 0 venous valvular incompetence by venous CW Doppler examination. Mild venous valvular incompetence was defined as a PD&R between 5 and 10 mL/100 mL/min, or a venous CW Doppler incompetence signal of −1. Venous valvular incompetence 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 (common femoral, femoral, popliteal or posterior tibial) vein levels. Superficial venous valvular incompetence 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 venous valvular incompetence was categorized as no valvular incompetence, while mild and moderate-to-severe venous valvular incompetence were combined as venous valvular incompetence. Similar to venous outflow obstruction, a diagnosis of venous valvular incompetence was defined at the patient-level if either leg met criteria for incompetence.

Statistical Analyses

The original matching variables16 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[20], the available previously matched case-control pairs (41 pairs) provided insufficient study power. 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.

We tested venous stasis syndrome, venous outflow obstruction, and venous valvular incompetence for an association with VTE and other baseline characteristics using logistic regression. For each of the endpoints of venous stasis syndrome, venous outflow obstruction and venous valvular incompetence, a multivariable logistic regression model was constructed, initially based on the adjusting variables, VTE case status, and all significant baseline characteristics from the univariate analysis or the multivariable stepwise selection. In addition, baseline characteristics previously identified as independent VTE risk factors[16] were included as covariates for each of venous stasis syndrome, venous outflow obstruction and venous valvular incompetence. For a variable to remain in any of the three models, the level of significance (p-value) was set at ≤ 0.10. Further stepwise selection was carried out to test two-way interactions among the covariates remaining in the model (level of significance cutoff ≤ 0.05 for interaction terms). 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. The multivariable regression modeling was extended to examine the relationship between side-specific leg DVT and study endpoints, using generalized estimating equations which account for the correlation of leg measurements within a subject. An exchangeable covariance structure that assumes the two leg measurements to be equally correlated was used to estimate the working correlation for each endpoint.

Results

Study Population

A total of 1007 subjects (VTE cases, n=503; non-VTE controls, n=504) were solicited for study participation by mailing a questionnaire for symptoms and signs of venous stasis syndrome. Of these, 233 cases (46.3%) and 136 (27.0%) controls completed the questionnaire and the vascular laboratory testing, while among these 168 cases (72.1%) and 136 controls (100%) completed the venous stasis syndrome physical examination. Additionally, two controls did not complete the questionnaire but were evaluated for venous stasis syndrome via physical examination. Of note, there were only 365 unique individuals in this study as four of the controls subsequently developed a VTE event and were considered as both a case and a control.. Three of these individuals developed VTE before their venous stasis syndrome physical examination dates and were treated as VTE cases in the analysis using only data related to their case status. The fourth person became a case after his venous stasis syndrome exam date and was considered solely as a non-VTE control in the analysis. 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% PE, and 12% combined DVT and PE. Cases were significantly younger than controls at the incident VTE event date (median age 50.7 vs. 55.7 years, p=0.03) and marginally younger at the venous stasis syndrome assessment date (64.8 vs. 68.2 years, p=0.12). Baseline characteristics by status are shown in Table 1. The prevalence of prior superficial vein thrombosis and varicose veins was significantly higher among those with VTE.

Frequency of venous stasis syndrome, venous outflow obstruction and venous valvular incompetence

Of the 365 study participants, 161 (44%), 43 (12%) and 136 (37%) had venous stasis syndrome, venous outflow obstruction or venous valvular incompetence, respectively, and their prevalence by VTE case status is shown in Table 1. One hundred and fourteen participants (31%) fulfilled both questionnaire and physical examination criteria for venous stasis syndrome, while 47 (13%) met the criteria for one and were not evaluated for the other. Of the patients with venous stasis syndrome diagnosed by physical examination, all had CEAP clinical class 3 or 4[21]. The prevalence of baseline characteristics by venous stasis syndrome, venous outflow obstruction and venous valvular incompetence status are shown in Table 2. There were 62 individuals who had venous stasis syndrome but with no evidence for venous outflow obstruction or venous valvular incompetence, and with an almost equal gender distribution (32 were females). Forty six (74%) of these individuals had prior VTE, 13 (21%) had varicose veins, seven (11%) had CHF and/or cardiomyopathy, six (10%) had prior superficial vein thrombosis, and five (8%) had chronic lung disease.

Venous stasis syndrome

In univariate analyses (Table 3), increasing patient age and BMI, varicose veins, and superficial vein thrombosis were each associated with venous stasis syndrome. Not surprisingly, venous stasis syndrome diagnosed prior to the original inception cohort study event (i.e., incident VTE event for cases or a corresponding medical visit for controls) was also associated with venous stasis syndrome at the follow up assessment. Adjusting for the matching variables (age, gender and time since VTE event), VTE cases were over six-fold more likely to develop venous stasis syndrome than controls. Moreover, the risk of venous stasis syndrome was higher with an increasing time interval from the VTE event to the follow up assessment. We repeated the analyses using venous stasis syndrome diagnosed by either questionnaire-provided symptoms and signs or by physical examination evidence of venous stasis syndrome and the analyses results were not significantly changed. 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. Venous stasis syndrome was non-significantly higher among patients with incident DVT ± PE compared to PE alone (61.5% vs. 50.0%, p=0.11) and among patients with proximal vs. isolated calf DVT (66.0% vs. 55.0%, p=0.17). In addition, venous stasis syndrome was marginally higher among patients with recurrent VTE compared to those with an incident VTE alone (75.0% vs. 56.3% respectively; p=0.078).

Venous stasis syndrome was significantly associated with venous outflow obstruction (χ^2 p=0.003); 28 of 159 (18%) subjects with venous stasis syndrome had venous outflow obstruction, compared with only 15 of 203 (7%) subjects without venous stasis syndrome. Similarly, venous stasis syndrome was highly associated with venous valvular incompetence (χ^2 p<0.0001); 89 of 158 (56%) venous stasis syndrome subjects had venous valvular incompetence as well, compared with 47 of 204 (23%) non-venous stasis syndrome subjects who had venous valvular incompetence.

Independent risk factors for venous stasis syndrome included advancing patient age at the follow up assessment, higher BMI at the VTE event date, increasing time interval from the VTE event to the follow up assessment, varicose veins, and leg DVT (Table 4). Patients with DVT had nearly a four-fold higher risk for venous stasis syndrome in the DVT-affected (ipsilateral) leg. Interestingly, DVT was also a risk factor for venous stasis syndrome in the contralateral leg. The risk for either left or right leg venous stasis syndrome was highest in those with a left leg DVT.

Venous outflow obstruction

Increasing patient age and male gender were associated with venous outflow obstruction (Table 3). Participants with a greater than 15-year time interval between the VTE event and the follow-up assessment were at highest risk of venous outflow obstruction. Prior varicose veins were marginally associated with venous outflow obstruction. Adjusting for the matching variables, the risk of venous outflow obstruction was over three-fold higher for VTE cases compared to controls. venous outflow obstruction did not differ significantly by VTE event type, but venous outflow obstruction was marginally higher among patients with proximal vs. isolated calf DVT (20.6% vs. 10.0% respectively, p=0.08), and significantly higher among patients with recurrent vs. incident VTE (41.7% vs. 12.6% respectively, <0.001).

Independent risk factors for venous outflow obstruction included ipsilateral leg DVT and increasing patient age at the follow up assessment (Table 5). Participants with ipsilateral DVT had a five-fold higher risk for venous outflow obstruction. Moreover, the risk for venous outflow obstruction was higher for those with a left leg DVT. However, the risk for venous outflow obstruction was not significantly increased in the leg contralateral to the one affected by DVT.

Venous valvular incompetence

Venous stasis syndrome diagnosed prior to the VTE event and varicose veins were significantly associated with venous valvular incompetence (Table 3), and increasing BMI was marginally associated. Similar to venous outflow obstruction, participants with a greater than 15-year interval between the VTE event and the follow-up assessment were at highest risk of venous valvular incompetence. Adjusting for the matching variables, the risk of venous valvular incompetence was nearly four-fold higher for VTE cases compared to controls. There was no significant difference in venous valvular incompetence by VTE event type, but venous valvular incompetence was marginally higher among patients with

proximal vs. isolated calf DVT (57.3% vs. 45.0% respectively, p=0.13), and significantly higher among patients with recurrent vs. incident VTE (83.3% vs. 44.2% respectively, p<0.001).

Independent risk factors for venous valvular incompetence included ipsilateral leg DVT, varicose veins and venous stasis syndrome diagnosed prior to the VTE event (Table 6). The risk of venous valvular incompetence was four-fold higher in the leg affected by DVT. Similar to venous outflow obstruction, the risk of venous valvular incompetence appeared to be highest in those with an ipsilateral left leg DVT. The risk of venous valvular incompetence was also higher in the leg contralateral to the one affected by DVT.

Discussion

In this study designed to evaluate risk factors and underlying mechanisms for venous stasis syndrome, we found that ipsilateral DVT was an independent risk factor for venous stasis syndrome (OR=3.9), venous outflow obstruction (OR=5.0), and venous valvular incompetence (OR=3.9). Furthermore, venous outflow obstruction and venous valvular incompetence were highly associated with venous stasis syndrome. Recognizing the limitations of our study design, we believe that venous outflow obstruction and venous valvular incompetence are the probable mechanisms of DVT-related venous stasis syndrome (i.e., post-phlebitic or post-thrombotic syndrome). Our finding that the risk of venous stasis syndrome is higher (albeit, marginally) with symptomatic proximal DVT compared to isolated calf DVT further supports this hypothesis since the prevalence of venous outflow obstruction and venous valvular incompetence were both higher among patients with proximal DVT. DVT has been shown to be a significant risk factor for venous stasis syndrome [4–6, 8, 10, 22]. However, results on venous stasis syndrome risk by DVT location are conflicting, with some reporting an increased risk of venous stasis syndrome in patients with proximal DVT [7, 23, 24] while others have either shown no risk [5] or an increased venous stasis syndrome risk with isolated calf DVT [25]. A recent study noted an association between residual vein thrombosis and venous stasis syndrome [26], although another did not [27]. A strong association was also observed between severe venous stasis syndrome and venous valvular incompetence [28–31]. However, many patients with severe venous valvular incompetence have only mild symptoms of venous stasis syndrome, suggesting that additional factors may contribute to the development of symptomatic venous stasis syndrome [31].

venous stasis syndrome was marginally higher following incident DVT ± PE compared to incident PE alone (61.5% and 50.0% [p =0.11], respectively), as has been noted in other studies 6, 8. The risk of ipsilateral venous stasis syndrome, venous outflow obstruction and venous valvular incompetence was higher with left leg DVT compared to right leg DVT. This observation may be secondary to the May-Thurner syndrome (i.e., the anatomic compression of the left iliac vein by the overlying right iliac artery) and agrees with a previous report 8. Interestingly, DVT in the contralateral leg was also associated with an increased risk of venous stasis syndrome and venous valvular incompetence, and could reflect occult venous thrombosis in the inferior vena cava or in the test leg, central venous hypertension, or other mechanisms leading to venous stasis syndrome and venous valvular incompetence. A similar finding was also noted by Kahn et al, who reported a 37% and 17% venous stasis syndrome prevalence in the DVT leg and the contralateral (and presumably) unaffected leg, respectively 27. Recurrent DVT was associated with venous outflow obstruction and venous valvular incompetence (p=0.004 and 0.005, respectively) but marginally with venous stasis syndrome (p=0.078). Other studies have reported a 6.4- to 9.6-fold increased risk of venous stasis syndrome with recurrent DVT 5, 32.

Increasing patient age was an independent risk factor for venous stasis syndrome and for venous outflow obstruction. This observation may reflect increasing central venous pressure or other anatomic causes of venous outflow obstruction, or decreased fibrinolysis with advancing age [33], leading to persistent residual vein thrombus and venous outflow obstruction, and to venous stasis syndrome. The association of venous stasis syndrome with advancing age has been observed by some investigators [26, 32] but not others [7, 27]. Our observation that a longer time interval between the VTE event and follow up assessment is an independent risk factor for venous stasis syndrome is consistent with data showing that, although venous stasis syndrome may become apparent soon after DVT [4, 5, 7, 8, 34, 35], the risk of venous stasis syndrome persists for up to 20 years [6]. As seen in other studies, a varicose vein was an independent risk factor for venous stasis syndrome and venous valvular incompetence [10, 22, 36] as was increasing BMI [10, 22, 27, 32, 36, 37], the latter possibly reflecting increased central venous pressure in obese individuals [38]. Moreover, these factors could potentially account for venous stasis syndrome in individuals who do not have a prior history of VTE, although one cannot exclude the possibility of a prior asymptomatic DVT. On the other hand, any other condition potentially associated with central venous hypertension (i.e., congestive heart failure, chronic lung disease/pulmonary hypertension, serious liver disease, or chronic renal disease/nephrotic syndrome) was not a risk factor for venous stasis syndrome (p=0.32).

Our study has several strengths. The study included 365 participants who were drawn from a population-based inception cohort [15, 39], thus avoiding potential referral bias. The venous stasis syndrome, venous outflow obstruction and venous valvular incompetence endpoints were assessed prospectively and systematically at least six years after the incident VTE event, hence avoiding the misclassification of any lingering symptoms of acute DVT as venous stasis syndrome. 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. Finally, 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. Several limitations should also be considered when evaluating the results of this study. Of all the 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. We required concordance in the questionnaire-based symptoms and the physical examination evidence, if both were done, to diagnose venous stasis syndrome, but 29% of participants diagnosed with venous stasis syndrome received only the questionnaire or physical examination evaluation. Because of concern regarding over- or under-diagnosis of venous stasis syndrome, we performed analyses using either venous stasis syndrome diagnosed by questionnaire-provided symptoms and signs or venous stasis syndrome 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 venous stasis syndrome prevalence. Three individuals previously categorized as having venous stasis syndrome prior to their incident VTE event did not meet this study's criteria for venous stasis syndrome at the time of assessment. The definition for venous stasis syndrome diagnosis prior to the index event (i.e., documented venous outflow obstruction, venous valvular incompetence, biopsy stating "venous ulcer", physician diagnosis, or skin stasis changes in absence of other known cause) was different from this study's definition, which may account for this discordance. Finally, the frequency of graduated compression stocking use in our venous stasis syndrome and non venous stasis syndrome study groups is unknown. Graduated compression stocking use has been demonstrated to decrease the incidence of venous stasis syndrome after DVT [34, 35], and may have reduced the magnitude of our estimated association between DVT and venous stasis syndrome. This concern notwithstanding, we observed that prior DVT in the affected leg was strongly associated with venous stasis syndrome, with nearly a 4-fold increased risk.

In summary, DVT (particularly left leg DVT), DVT in the contralateral leg, increasing patient age and time interval since the DVT event, obesity and varicose veins are independent risk factors for venous stasis syndrome, and venous stasis syndrome is due, at least in part, to venous outflow obstruction and venous valvular incompetence. Appropriate graduated compression stocking therapy is effective in preventing venous stasis syndrome after DVT 34, 35, but such therapy has not been widely adopted because many DVT patients do not develop venous stasis syndrome, and because of patient non-compliance. We believe our study results may be useful in stratifying DVT patients into high- and low-risk for venous stasis syndrome (i.e., older and/or overweight individuals, and those with left leg DVT and/or varicose veins), and targeting stocking therapy to those high-risk patients who would benefit most. Specifically, we suggest that older and/or obese patients with leg DVT (particularly, left leg DVT) be considered for stocking therapy, especially if the patient has concomitant varicose veins and/or evidence of venous outflow obstruction (particularly with residual vein thrombosis) or venous valvular incompetence. Furthermore, we believe that reducing the risk of incident and recurrent VTE, and aggressive graduated compression stocking therapy for patients recurrent VTE will reduce the burden of venous stasis syndrome.

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Table 1

Baseline Demographic and Clinical Characteristics by Venous Thromboembolism (VTE) Case or Control Status

	VTE (N=232)	No VTE (N=133)	P-Value
Age at VTE event, *mean (SD)*	50.3 (16.4)	54.1 (14.9)	0.03
Age at follow-up visit, *mean (SD)*	63.6 (14.4)	65.9 (14.9)	0.12
VTE event year, *mean (SD)*	1983 (7.02)	1986 (4.01)	0.02
Gender, *n (%) male*	127 (55%)	65 (49%)	0.32
Body mass index (k/m^2), *mean (SD)*	27.0 (5.2)	26.1 (3.8)	0.09
Prior superficial vein thrombosis (%)	22 (9%)	2 (2%)	0.003
Serious liver disease (%)	1 (.4%)	0 (0%)	1.00
Chronic lung disease/pulmonary hypertension (%)	12 (5%)	7 (5%)	0.98
Chronic renal disease/nephrotic syndrome (%)	1 (0.4%)	0 (0%)	1.00
Congestive heart failure and/or cardiomyopathy (%)	21 (9%)	8 (6%)	0.30
Prior varicose Veins (%)	54 (23%)	15 (11%)	0.005
Prior venous stasis syndrome (%)	14 (6%)	4 (3%)	0.20
Venous stasis syndrome at follow-up visit	135 (58%)	26 (20%)	<0.0001
Venous outflow obstruction at follow-up visit	36 (16%)	7 (5%)	0.004
Venous valvular incompetence at follow-up visit	111 (48%)	25 (19%)	<0.0001

Table 2

Baseline Characteristics by Venous Stasis Syndrome, Venous Outflow Obstruction and Venous Valvular Incompetence Status

Baseline Characteristic		Venous Stasis Syndrome		Venous Outflow Obstruction		Venous Valvular Incompetence	
		Yes (n=161)	No (n=204)	Yes (n=43)	No (n=319)	Yes (n=136)	No (n=226)
Age at Visit (years)	*Mean*(*SD*)	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*)	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* (%)	89 (55.3%)	103 (50.5%)	29 (67.4%)	160 (50.2%)	78 (57.4%)	112 (49.6%)
Time Since Event (years)	*Mean*(*SD*)	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*)	12.9 (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 (47.6%)	36 (83.7%)	195 (61.1%)	111 (81.6%)	119 (52.7%)
Congestive Heart Failure and/or cardiomyopathy	*n* (%)	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*)	27.7 (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*)	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)	28.5 (23.3,28.6)
Prior Superficial Thrombosis	*n* (%)	18 (11.2%)	6 (2.9%)	3 (7.0%)	21 (6.6%)	13 (9.6%)	11 (4.9%)
Prior Varicose Veins	*n* (%)	48 (29.8%)	21 (10.3%)	13 (30.2%)	56 (17.6%)	41 (30.2%)	28 (12.4%)
Lung Disease / Pulmonary Hypertension	*n* (%)	12 (7.6%)	7 (3.4%)	3 (7.0%)	15 (4.7%)	8 (5.9%)	11 (4.9%)
Venous Stasis Syndrome prior to the incident VTE event	*n* (%)	15 (9.3%)	3 (1.5%)	4 (9.3%)	14 (4.4%)	14 (10.3%)	4 (1.8%)
Chronic Renal Disease	*n* (%)	1 (0.6%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Serious Liver Disease	*n* (%)	0 (0.0%)	1 (0.5%)	1 (2.3%)	0 (0.0%)	1 (0.7%)	0 (0.0%)

Table 3

Univariate Analyses of Demographic and Baseline Characteristics as Potential Risk Factors for Venous Stasis Syndrome, Venous Outflow Obstruction and Venous Valvular Incompetence

Variable [$$]	Endpoints		
	Venous Stasis Syndrome	**Venous Outflow Obstruction**	**Venous Valvular Incompetence**
	---------- *Odds Ratios (95% Confidence Intervals)* ----------		
Age at Visit *Δ per 10 years*	1.2 (1.1, 1.4)[†]	1.7 (1.3, 2.2)[†]	1.1 (0.96, 1.3)
Male	1.2 (0.8, 1.8)	2.1 (1.05, 4.0)[*]	1.4 (0.9, 2.1)
Time Since VTE Event			
Δ per 5 years	1.2 (1.03, 1.5)[*]		
10 vs 5		0.6 (0.4, 0.96)[*]	0.7 (0.5, 1.01)
15 vs 10		0.9 (0.6, 1.2)	1.0 (0.8, 1.2)
20 vs 15		1.3 (1.03, 1.7)[*]	1.4 (1.1, 1.7)[*]
25 vs 20		2.0 (1.3, 3.1)[*]	2.0 (1.3, 2.9)[*]
VTE Case *Unadjusted*	5.7 (3.5, 9.5)[‡]	3.3 (1.4, 7.6)[†]	4.0 (2.4, 6.6)[‡]
VTE Case *Adjusted for age, gender, and time since event*	6.4 (3.8, 10.8)[‡]	3.2 (1.3, 7.8)[*]	3.6 (2.1, 6.2)[‡]
BMI	1.1 (1.04, 1.1)[‡]	1.0 (0.9, 1.1)	1.0 (0.99, 1.1)
Prior Superficial Vein Thrombosis	4.2 (1.6, 10.7)[†]	1.1 (0.3, 3.7)	2.1 (0.9, 4.8)
Prior Varicose Veins	3.7 (2.1, 6.5)[‡]	2.0 (1.00, 4.2)	3.0 (1.8, 5.2)[‡]
Lung Disease / Pulmonary Hypertension	1.5 (0.4, 5.4)	1.2 (0.5, 3.2)	2.3 (0.9, 6.0)
Prior venous stasis syndrome prior to the incident event	2.2 (0.7, 7.1)	6.4 (2.1, 19.8)[†]	6.9 (2.0, 24.2)[†]

[$$] Only variables that were significant in at least one analysis are shown

[*] p-value<0.05

[†] p-value<0.01

[‡] p-value<0.001

Table 4

Multivariate Analysis of Demographic and Baseline Characteristics as Potential Risk Factors for Venous Stasis Syndrome

Characteristic		Venous Stasis Syndrome in Left Leg Only	Venous Stasis Syndrome in Right Leg Only	Venous Stasis Syndrome in Either Leg
		---------- *Odds Ratio (95% Confidence Intervals)* ----------		
DVT Same Leg		5.3 (2.9, 9.7)‡	2.4 (1.2, 4.6)†	3.9 (2.4, 6.3)‡
DVT Opposite Leg		1.7 (0.9, 3.3)	3.6 (2.0, 6.6)‡	2.6 (1.6, 4.2)‡
Age at Follow-up Visit	*Δ per 10 years*	1.3 (1.1, 1.6)*	1.3 (1.05, 1.6)*	1.3 (1.1, 1.5)*
Male		1.3 (0.8, 2.2)	1.2 (0.7, 2.2)	1.3 (0.8, 2.2)
Time Since Event	*Δ per 5 years*	1.4 (1.1, 1.8)†	1.4 (1.1, 1.8)†	1.4 (1.1, 1.8)†
BMI	*Δ per unit increase*	1.1 (1.01, 1.14)*	1.1 (1.01, 1.14)*	1.1 (1.01, 1.14)*
Varicose Veins		3.3 (1.6, 6.6)†	4.2 (2.1, 8.4)‡	3.7 (1.9, 7.2)‡

*p-value<0.05

†p-value<0.01

‡p-value<0.001

Table 5

Multivariate Analysis of Demographic and Baseline Characteristics as Potential Risk Factors for Venous Outflow Obstruction

Characteristic		Venous Outflow Obstruction in Left Leg Only	Venous Outflow Obstruction in Right Leg Only	Venous Outflow Obstruction in Either Leg
		---------- *Odds Ratio (95% Confidence Intervals)* ----------		
DVT Same Leg		6.7 (2.7, 16.6)‡	3.6 (1.4, 9.5)†	5.0 (2.6, 9.6)‡
DVT Opposite Leg		2.1 (0.8, 5.8)	1.6 (0.6, 4.2)	1.8 (0.9, 3.7)
Age at Visit	*Δ per 10 years*	1.8 (1.2, 2.6)†	2.0 (1.4, 3.0)‡	1.8 (1.4, 2.4)‡
Male		2.1 (0.8, 5.3)	1.6 (0.6, 3.9)	1.9 (0.9, 4.0)
Time Since Event	*Δ per 5 years*			
	10 vs 5	0.9 (0.5, 1.9)	1.0 (0.5, 2.0)	1.0 (0.6, 1.6)
	15 vs 10	1.1 (0.8, 1.6)	1.0 (0.7, 1.4)	1.0 (0.8, 1.4)
	20 vs 15	1.2 (0.9, 1.7)	1.0 (0.6, 1.4)	1.1 (0.9, 1.5)
	25 vs 20	1.4 (0.8, 2.5)	1.0 (0.5, 2.0)	1.2 (0.8, 2.0)

* p-value<0.05

† p-value<0.01

‡ p-value<0.001

Table 6

Multivariate Analysis of Demographic and Baseline Characteristics as Potential Risk Factors for Venous Valvular Incompetence

Characteristic		Venous Valvular Incompetence in Left Leg Only	Venous Valvular Incompetence in Right Leg Only	Venous Valvular Incompetence in Either Leg
		---------- *OR (95% CI)* ----------		
DVT Same Leg		4.8 (2.8, 8.4)‡	3.1 (1.7, 5.7)‡	3.9 (2.6, 6.0)‡
DVT Opposite Leg		1.7 (0.9, 3.3)	2.2 (1.2, 4.0)†	2.0 (1.3, 3.1)†
Age at Visit	*Δ per 10 years*	1.1 (0.9, 1.3)	0.9 (0.7, 1.1)	1.0 (0.8, 1.1)
Male		1.4 (0.8, 2.3)	1.5 (0.9, 2.6)	1.4 (0.9, 2.2)
	Δ per 5 years			
	10 vs 5	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	1.0 (0.7, 1.4)
Time Since Event	*15 vs 10*	1.1 (0.8, 1.4)	1.0 (0.8, 1.3)	1.1 (0.9, 1.3)
	20 vs 15	1.2 (0.95, 1.5)	1.1 (0.9, 1.4)	1.2 (0.96, 1.4)
	25 vs 20	1.4 (0.9, 2.1)	1.2 (0.8, 1.9)	1.2 (0.9, 1.8)
Varicose Veins		2.3 (1.2, 4.3)*	2.1 (1.1, 4.0)*	2.2 (1.3, 3.6)†
Prior Venous Stasis Syndrome		2.4 (0.8, 7.0)	4.8 (1.6, 14.3)†	3.4 (1.5, 8.0)†

*p-value<0.05

†p-value<0.01

‡p-value<0.001