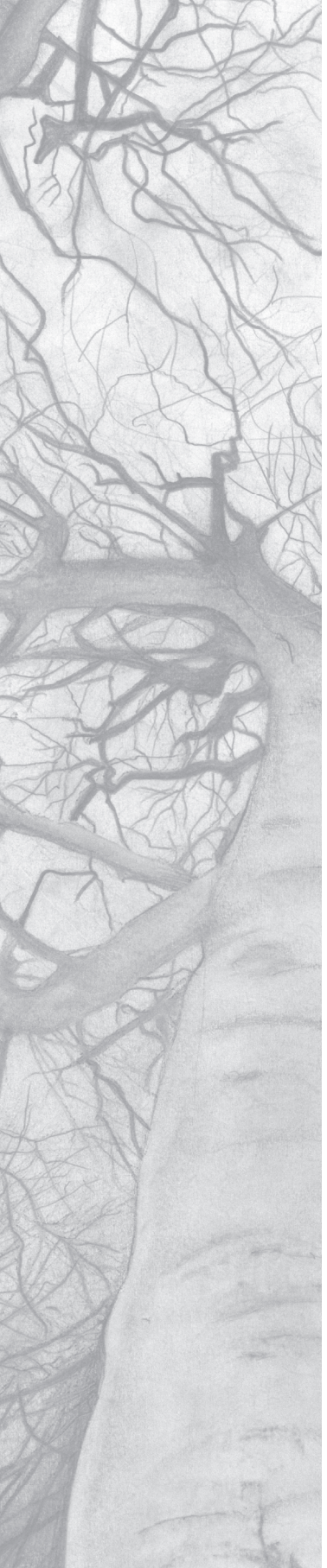

CHAPTER 5

Clinical features of venous insufficiency and risk of venous thrombosis in older people

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ABSTRACT

Venous thrombosis is common in older age, with an incidence of 0.5-1% per year in those aged ≥70 years. Stasis of blood flow is an important contributor to the development of thrombosis and may be due to venous insufficiency in the legs. The risk of thrombosis associated with clinical features of venous insufficiency i.e., varicose veins, leg ulcer, and leg oedema obtained with a standardised interview was assessed in the AT-AGE study. The AT-AGE study is a case-control study in 70 years and older individuals (401 cases with a first-time venous thrombosis and 431 control subjects). We calculated odds ratios (ORs) and corresponding 95% confidence intervals (CI95) adjusted for age, sex, and study centre. Varicose veins were associated with a 1.6-fold (CI95 1.2-2.3) and a leg ulcer with a 3.3-fold increased risk of thrombosis (CI95 1.6-6.7), while the risk was 3.0-fold (CI95 2.1-4.5) increased in the presence of leg oedema. The risk of thrombosis was highest when all three risk factors occurred simultaneously (OR: 10.5; CI95 1.3-86.1). In conclusion, clinical features of venous insufficiency, i.e., varicose veins, leg ulcer, and leg oedema are risk factors for venous thrombosis in older people.

INTRODUCTION

The incidence of venous thrombosis increases steeply with age, with an incidence of 0.5-1% per year in people aged over 70 years. [1] More than 60% of all thrombotic events occur in this age group. [2]

Stasis of blood flow is, together with hypercoagulability and endothelial injury, an important contributor to the development of venous thrombosis according to Virchow's triad. [3] Stasis can occur due to external pressure on the vein during, e.g., prolonged immobilisation or pregnancy, or due to venous insufficiency in the legs. Venous insufficiency comprises a spectrum of clinical features, including varicose veins, venous ulcer, and leg oedema. [4-6] Like venous thrombosis, the prevalence of venous insufficiency increases steeply with age. [7-9] There is limited information on the role of venous insufficiency in the development of venous thrombosis. In young and middle aged individuals, varicose veins strongly predispose to superficial thrombosis and are also associated with an increased risk of deep vein thrombosis. [10-12] The contribution of venous insufficiency to the incidence of venous thrombosis in the older population is unknown.

The aim of this study was to investigate whether clinical features of venous insufficiency defined as a history of varicose veins, leg ulcer, or leg oedema are risk factors for venous thrombosis in individuals aged 70 years and older. In addition, the contribution of these factors to the incidence of deep venous thrombosis was evaluated.

METHODS

Participants

The Age and Thrombosis Acquired and Genetic risk factors in the Elderly (AT-AGE) study is a two centre population-based case-control study. The study has been described in detail previously. [13] In brief, between 2008 and 2011 all consecutive cases aged 70 years or older with an episode of deep venous thrombosis in the leg (DVT) or a pulmonary embolism (PE) were identified in defined geographical areas in Leiden, the Netherlands and Burlington, Vermont, US. In Leiden, cases were identified in two anticoagulation clinics (Leiden and Haarlem). In Vermont, cases were resided in a 45 km radius of Burlington, and were diagnosed at the University of Vermont Medical Centre in Burlington, the only diagnostic centre in that area. Presence of DVT required positive compression ultrasonography or Doppler ultrasound. PE was considered definite in case of a positive spiral computed tomographic or high probability ventilation-perfusion lung scan. We defined venous thrombosis as DVT alone or PE with or without a proven DVT by ultrasound (PE±DVT). We invited the population-based control subjects randomly from primary care practices in the same geographic areas (five in Leiden and four in Vermont).

We defined the index date for the cases as the date of diagnosis of the thrombotic event. For control subjects the index date was the date of completing the interview at home. Individuals with active malignancy, defined as diagnosis of cancer, or chemotherapy or radiation therapy for cancer within six months before the index date, and those with severe psychiatric or cognitive disorders were excluded from participation, as were individuals who self-reported previous DVT or PE within the past 10 years.

Of 1187 identified cases, 689 (58%) were eligible. In Leiden, 398 (71%) of the 561 invited cases and 321 (76%) of the 422 invited control subjects participated. In Burlington, 128 cases were invited and 75 (59%) participated, while 140 (67%) of the 209 invited control subjects participated. Detailed information about the reasons for exclusion or not participating in the study can be found elsewhere. [13] All participants provided written informed consent. The study was approved by the Medical Ethical Committee of the Leiden University Medical Centre and by the Committee on Human Research of the University of Vermont.

Data collection

During a home visit an extensive interview was performed by trained personnel. For the analyses on the aetiology of venous thrombosis we included the cases and control subjects without a history of venous thrombosis and who completed the interview at home (401 cases and 431 control subjects). For the cases, the median duration between the index date and the home visit was 5 weeks (range 1–44 weeks), 75% were visited within 7 weeks, and 90% were visited within 10 weeks.

In the interview information about the presence of well-known risk factors, such as recent hospitalisation, surgery, and fracture was obtained and a blood sample or buccal swab was collected. [13] The participants were asked about any prior history of varicose veins or leg ulcer or whether they had a history of leg oedema that lasted until at least the three months before the index date. Leg oedema was classified by participants as "daily oedema,""intermittent oedema", or "no oedema". In the first version of the interview questionnaire of the control subjects the question of oedema was not incorporated yet. For this reason, for 24 control subjects we could not report this data.

We used self-assessed information on clinical features of venous insufficiency, a strategy that has been previously validated. [14] Additionally, among cases we obtained self-assessed information on the type and duration (in days) of possible thrombotic complaints prior to the diagnosis of the thrombotic event. The thrombotic event was defined as provoked if in the three months before the thrombosis one of these conditions was present: hospitalisation, surgery, a fracture, plaster cast or splint use, a minor injury or immobilisation in the home situation. [13] Physical measurements were performed including weight (measured with a calibrated scale) and height. Body mass index (BMI) was calculated by dividing body weight (kg) by squared height (m^2).

Statistical Analysis

To provide insight into the source population at the two study sites, we compared participant characteristics of control subjects, in Leiden and in Vermont. We studied the associations between potential confounders, i.e., sex and BMI and features of venous insufficiency in the complete control group.

The risk of venous thrombosis associated with the presence of history of varicose veins, leg ulcer, and leg oedema in the three months before the thrombosis was determined. We assessed a dose-response relation for oedema across groups of those with none, intermittent or daily oedema. The risk of thrombosis associated with the presence of one, two, or three of the symptoms of venous insufficiency was assessed.

Odds ratios (OR) and 95% confidence intervals (95CI) were calculated as an estimate of the relative risk of venous thrombosis. We used a multiple logistic regression model to calculate adjusted odds ratios. All reported ORs in the manuscript were adjusted for age (continuous), sex and study centre. Additionally, we adjusted for BMI (continuous), smoking status and the presence of the factor V Leiden or prothrombin 20210A mutation. Stratified analyses were performed by type of thrombosis (DVT and PE±DVT) and the presence of provoking factors, i.e. provoked and unprovoked first venous thrombosis.

We performed two analyses to address whether other causes of leg oedema than venous insufficiency explained our findings. Firstly, heart failure is associated with an increased risk of venous thrombosis and leg oedema can be present in individuals with heart failure. [15] To assess the risk of venous thrombosis associated with leg oedema as a symptom of venous insufficiency, we excluded participants with a self-reported history of heart failure. Secondly, to assess whether the presence of daily leg oedema might have been a (pre)clinical sign of the venous thrombosis (rather than due to venous insufficiency), we determined the risk of thrombosis associated with daily leg oedema in the individuals who reported a clinically asymptomatic event of venous thrombosis, e.g. individuals that did not reported any acute thrombotic complaints of the legs, or lungs before the diagnosis.

To assess the contribution of venous insufficiency to the incidence of venous thrombosis in this older population, we estimated the population attributable risk (PAR) of a history of varicose veins, leg ulcers, and daily leg oedema and the number of these symptoms combined. The PAR was calculated as *pd* (OR-1)/(OR), in which the *pd* is the prevalence of the risk factor among cases, and OR is the adjusted OR found in the study population. [16] All statistical analyses were performed using SPSS 20 for Windows (SPSS Inc, Chicago, Ill).

RESULTS

Characteristics of the control subjects of the two AT-AGE study centres are shown in table 1. In both centres, one third of the control subjects were 80 years or older. Median BMI was 25.9 kg/m2 (range 17.0-42.0 kg/m2) in Leiden, and 27.3 kg/m2 (19.0-49.7 kg/m2) in Vermont. The prevalence of intermittent and daily leg oedema was similar at the two study centres, while the prevalence of varicose veins and leg ulcers was higher in Leiden than Vermont.

Tabel 1. Characteristics of control subjects by study centre

	Leiden (NL)	Vermont (US)
Controls, n	**306**	**125**
Median Age (Range)	76 (70-94)	76 (70-96)
70-75 years, n (%)	126 (41.2)	49 (39.2)
75-80 years, n (%)	90 (29.4)	39 (31.2)
80-85 years, n (%)	61 (19.9)	24 (19.2)
>85 years, n (%)	29 (9.5)	13 (11.4)
Men, n (%)	147 (48.0)	62 (49.6)
Median BMI (kg.m-2)(Range)*	25.9 (17.0-42.0)	27.3 (19.0-49.7)
Varicose veins, n (%)	73 (23.9)	20 (16.0)
Leg ulcer, n (%)	10 (3.3)	1 (0.8)
Leg oedema†		
Never, n (%)	216 (76.6)	93 (74.4)
Intermittent, n (%)	35 (12.4)	13 (10.4)
Daily, n (%)	31 (11.0)	19 (15.2)

NL= the Netherlands, US= United States, n = number, BMI = Body Mass Index
*BMI 8 missings, †Leg oedema 24 missings

Symptoms of venous insufficiency were associated with sex and BMI. Women more often had varicose veins and leg oedema than men (varicose veins: women: 28.4%, men 14.4%; oedema women: 17.1%, men 7.1%). Leg ulceration was rare and more common in men (3.3%) than women (1.8%). Individuals with obesity more often had leg oedema and leg ulceration than normal weight individuals but this association was less clear for varicose veins (BMI>30 compared with <25 kg/m^2: oedema: 38.3% versus 16.1%, leg ulceration: 5.3% versus 1.3 %; varicose veins: 23.4% versus 20.6%). Symptoms of venous insufficiency were not associated with smoking status.

In table 2 the risk of venous thrombosis associated with symptoms of venous insufficiency are shown. Individuals with varicose veins had a 1.6-fold increased risk of venous thrombosis compared with individuals without varicose veins (OR 1.6; CI95 1.2-2.3). A history of a leg ulcer was associated with a 3-fold increased risk of thrombosis (OR 3.3; CI95 1.6-6.7). Leg oedema during the three months before thrombosis (daily and inter-

Table 2. Clinical features of venous insufficiency and the risk of venous thrombosis

	Cases n = 401	Controls n = 431	OR crude (95CI)	OR adjusted* (95CI)	OR adjusted† (95CI)
Varicose Veins, n (%)	131 (32.7)	93 (21.6)	1.8 (1.3-2.4)	1.6 (1.2-2.3)	1.6 (1.2-2.3)
Leg Ulcer, n (%)	35 (8.7)	11 (2.6)	3.7 (1.8-7.3)	3.3 (1.6-6.7)	3.0 (1.5-6.2)
Leg Oedema, n (%)‡§	111 (33.0)	50 (13.9)	3.0 (2.1-4.4)	3.0 (2.1-4.5)	2.9 (1.9-4.3)
Leg Oedema‡§					
Never, n (%)	225 (56.8)	309 (75.9)	1 (ref)	1 (ref)	1 (ref)
Intermittent, n (%)	60 (15.2)	48 (11.8)	1.7 (1.1-2.6)	1.6 (1.0-2.5)	1.4 (0.9-2.2)
Daily, n (%)	111 (28.0)	50 (12.3)	3.0 (2.1-4.4)	3.1 (2.1-4.5)	2.9 (1.9-4.4)

n = number, OR = odds ratio, CI = confidence interval, ref= reference group.

*Adjusted for age (continuous), sex, and study centre.

†Further adjustment: BMI (body mass index)(continuous) and smoking status.

‡Leg oedema: no versus daily leg oedema. §Leg oedema: 29 missings.

mittent oedema combined) was associated with a 3.0 fold (CI95 2.1-4.5) increased risk of venous thrombosis compared with no oedema. There was a dose-response relationship of severity of oedema and the risk of venous thrombosis. Compared with individuals without oedema, individuals with intermittent oedema had a 1.6-fold increased risk of venous thrombosis (CI95 1.0 -2.5) while this risk was 3.1-fold increased for individuals with daily oedema (CI95 2.1-4.5). The associations between the clinical features of venous insufficiency and thrombosis remained present after adjustment for BMI and smoking (Table 2). Adjustment for the presence of the factor V Leiden and prothrombin 20210A mutation showed similar risk estimates: varicose veins: OR 1.7 (CI95 1.3-2.4), leg ulcer: OR 3.4 (CI95 1.7-6.8), leg oedema: OR 3.1 (CI95 2.1-4.6). Excluding individuals with heart failure (20 cases and 19 controls) did not change the risk associated with leg oedema, i.e., compared with no oedema, the risk of venous thrombosis was 1.5-fold increased for intermittent oedema (OR 1.5; CI95 1.0-2.3) and 3.2-fold increased for daily oedema (OR 3.2; CI95 2.1-4.8). For 376 cases (93.8%), information on the presence or absence of thrombotic complaints prior to the diagnosis of venous thrombosis was available. Of the cases, 322 (85.6%) reported leg complaints specifically attributable to the subsequent diagnosis of venous thrombosis, whereas 54 (14.4%) did not. Among the latter, daily leg oedema was associated with a 2.6 fold (CI95 1.3-5.2) increased risk of venous thrombosis compared with no leg oedema. Of the cases, 219 (54.6%) had an unprovoked venous thrombotic event. Varicose veins were associated with a 1.3-fold (CI95 0.9-2.0) increased risk of an unprovoked venous thrombosis. For leg ulcer this risk was 3.2-fold increased (CI95 1.4-6.9) and for leg oedema (daily and intermittent oedema combined) 3.4-fold (CI95 2.1-5.3). For provoked venous thrombosis we found a 2.0-fold (CI95 1.4-2.9) increased risk for varicose veins, and a 3.4-fold increased risk (CI95 1.5-7.4) for leg ulcer. Leg oedema was associated with a 2.8-fold (CI95 1.7-4.4) increased risk of provoked thrombosis.

To assess the association of severity of venous insufficiency with risk of venous thrombosis, we determined the risk associated with number of venous insufficiency symptoms. The presence of one, two or three of the clinical features gradually increased the risk of thrombosis with the highest risk of venous thrombosis associated with the presence of all three clinical features compared with none of the features (OR: 10.5; CI95 1.3-86.8) (Table 3). Of the cases, 166 (41%) were diagnosed with DVT only, and 235 (59%) with PE±DVT. The associations of venous insufficiency features with thrombosis risk were similar for both types of thrombosis except that the association of leg ulcer with DVT appeared stronger than the association with PE±DVT (Table 4).

The PAR of the three manifestations of venous insufficiency was 12.3% for varicose veins, 6.0% for a leg ulcer and 22.0% for the presence of leg oedema. The PAR of presence of two symptoms of venous insufficiency was 22.7%, and for presence of three symptoms, 4.6%.

Table 3. Joint associations of the presence of varicose veins, leg ulcer and leg oedema with thrombosis

	Cases n=396	**Controls n=407**	**OR crude (95CI)**	**OR adjusted* (95CI)**
No risk factor	149 (47.2)	249 (66.9)	1 (ref)	1 (ref)
One risk factor, n (%)	167 (52.8)	123 (33.1)	2.3 (1.7-3.1)	2.2 (1.6-3.0)
Two risk factors, n (%)	72 (32.6)	34 (12.0)	3.5 (2.2-5.6)	3.3 (2.1-5.3)
Three risk factors, n (%)	8 (5.1)	1 (0.4)	13.4 (1.7-108.0)	10.5 (1.3-86.1)

n = number, OR = odds ratio, CI = confidence interval, ref= reference group.
*Adjusted for age (continuous), sex, and study centre.

Table 4. Odds ratios of thrombosis with venous insufficiency stratified by type of thrombosis

	N, DVT/total VT (%)	**DVT OR adjusted (CI95)***	**PE±DVT OR adjusted (CI95)***
Varicose veins	52/131 (39.7)	1.7 (1.1-2.5)	1.6 (1.1-2.3)
Leg ulcer	18/35 (51.4)	4.3 (2.0-9.4)	2.4 (1.1-5.3)
Leg oedema† Intermittent	26/60 (43.3)	1.7 (1.0-3.0)	1.5 (0.9-2.5)
Leg oedema† Daily	42/111 (37.8)	2.8 (1.8-4.6)	3.2 (2.1-5.0)

N = number, DVT = deep vein thrombosis of the leg, PE= pulmonary embolism, OR = odds ratio, CI = confidence interval.
*Adjusted for age (continuous), sex and study centre.
†Leg oedema: 29 missings.

DISCUSSION

In this population-based case-control study among individuals aged 70 and older, symptoms of venous insufficiency, i.e., a history of varicose veins, leg ulcer, and oedema increased the risk of venous thrombosis (both DVT and PE), with ORs ranging from 1.6 to 3.0. The risk of venous thrombosis increased with severity of the venous insufficiency, defined as the number of clinical features. The risk was highest in individuals with all three clinical features combined (OR 10.5), although presence of all three features was uncommon. In agreement with the literature, venous insufficiency was common, both in the cases and control subjects, [8] leading to a high PAR of venous thrombosis associated with varicose veins and leg oedema. Adjustments for potential confounders did not influence the finding that clinical features of venous insufficiency are risk factors for thrombosis. Moreover, restricting the analysis to cases with unprovoked venous thrombosis demonstrated that the risks associated with symptoms of venous insufficiency are not explained by the presence of other major risk factors of thrombosis in the older population, such as recent hospitalisation and surgery. [13]

Some, but not all, studies have reported that varicose veins are associated with an increased risk of DVT and PE in the young and middle-aged. [12, 17-20] Heit et al. demonstrated a 4-fold increased risk of venous thrombosis associated with varicose veins in middle-aged up to age 60 years, but in contrast to the current study, they observed no increased risk in those 70 years and older. [12] This difference in findings may be due to a difference in data collection. Heit et al. used medical record to assess chronic venous insufficiency, and we collected data on clinical features of venous insufficiency by an interview. Mild disorders, such as varicose veins, may be documented less often in medical records of older individuals, particularly when other co-morbidities are present, potentially resulting in underestimation of relative risks.

To our knowledge, presence of leg oedema due to chronic venous insufficiency has not been investigated as a risk factor for venous thrombosis in the older population. Leg oedema could be a pre-clinical sign of thrombosis; however, we showed that among individuals who did not report any thrombotic complaints prior to the diagnosis of venous thrombosis, leg oedema was still associated with a more than two-fold increased risk of thrombosis compared with no oedema. This indicates that our findings are not likely explained by leg oedema being a symptom of deep vein thrombosis. Heart failure as an underlying cause of leg oedema may explain the association between leg oedema and venous thrombosis. However, in our study excluding the individuals with heart failure did not change the results. We hypothesise several mechanisms by which venous insufficiency may increase the risk of venous thrombosis. Firstly, varicose veins, due to dysfunction of the venous valves, lead to low sheer stress in the veins and reduced blood flow, which subsequently lead to a pro thrombotic state. [21,22] It has been hy-

pothesised that damage to the valves results in hypoxia especially in the valve pockets, which promotes thrombus formation at this location. [23] Secondly, inflammation may play an important role. Leg oedema as a result of long-term venous insufficiency could lead to mediator release and inflammation in the veins. [24,25] Leg ulceration is also associated with local inflammatory processes. [26] We hypothesise that this inflammatory state could initiate local thrombus formation within the leg veins. A leg ulcer is the most severe expression of venous insufficiency of the three clinical features that we assessed in this study. [27] In concordance with this, among the venous insufficiency features evaluated, the strongest association with thrombosis risk was found for leg ulcer. Finally, it has been suggested that venous insufficiency in the absence of a prior history of DVT may be due in part to prior undiagnosed DVT, which might increase the risk of future clinically apparent DVT. [28]

In the AT-AGE study we achieved high participation rates, which is challenging in older people. [29] As venous thrombosis and venous insufficiency are both associated with immobility, performing home visits to both cases and control subjects, minimised selection bias due to selection of only mobile older individuals. Moreover, by performing interviews we were able to determine risk factors that are not reported regularly in medical reports. Limitations of the current study require consideration. Recall bias may have affected our results, although we minimised this by performing standardised interviews, in both the cases and the control subjects. Referral bias could play a role in our results, e.g., if individuals with varicose veins are more likely to be referred for ultra sound of the legs, resulting in an overestimation of the risks. However, as we also found an increased risk for pulmonary embolism with clinical features of venous insufficiency, we do not expect a major influence. As the clinical features of venous insufficiency were all self-reported, over or under reporting of the clinical features cannot be ruled out. If misclassification is present, we would expect that the misclassification would be non-differential in the cases and the control subjects. This may have led to an underestimation of the risks. Ideally, clinical examination of the legs before the thrombotic event should have been performed. The AT-AGE study is a predominantly Caucasian study, thus we were not able to address racial differences in the associations.

In conclusion, clinical features of venous insufficiency were risk factors for venous thrombosis in this older population. This gives further insight into the aetiology of venous thrombosis in older people. Physicians may be more alert on thrombosis when one of the clinical features of venous insufficiency is present as these contribute to the burden of venous thrombosis in this older patient group.

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