Venous thrombosis in the elderly: risk factors and consequences

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CHAPTER 5

Association of remote history of venous thrombosis with risk of venous thrombosis after age 70 years

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ABSTRACT

Background

Previous venous thrombosis is associated with risk of future venous thrombosis, but quantification of risk over the life-course is poorly understood. More information is needed for clinicians to understand the association of remote history of venous thrombosis with the risk of venous thrombosis in older patients.

Objectives

To assess the association between a remote history of venous thrombosis and the development of venous thrombosis in older age.

Methods

The AT-AGE case-control study enrolled patients aged ≥70 years with venous thrombosis and controls aged ≥70 years without venous thrombosis between June 2008 and August 2011. Controls were identified in the same geographical areas as the patients and were randomly selected. The main outcome was the risk of venous thrombosis at older age. We calculated the crude and adjusted association of self-reported history of remote venous thrombosis with venous thrombosis at older age by calculating odds ratios (OR) as estimates of relative risk with 95% confidence intervals (CI).

Results

460 venous thrombosis patients and 456 control subjects were included. There were slightly more women than men and the mean age of patients and controls was 78 years. Compared with those without remote venous thrombosis, individuals with remote history of venous thrombosis had a 2.54-fold (95% CI: 1.56-4.13) increased risk of venous thrombosis. The crude risk estimate was robust to adjustment and time since remote venous thrombosis. The population attributable fraction of a remote history of venous thrombosis was 7.7%.

Conclusions

A remote history of venous thrombosis is associated with risk of venous thrombosis in the elderly. This quantification could assist clinicians in advising patients on venous thrombosis prevention.

INTRODUCTION

Venous thrombosis (VT) is the third most common cardiovascular disease, after myocardial infarction and stroke. VT includes deep vein thrombosis (DVT) and pulmonary embolism (PE). The risk of VT increases strongly with age [1]; 60% of all events occur after the age of 60 years. The incidence of VT is less than 5 per 100,000 individuals per year in people aged under 15 years but is approximately 500 patients per 100,000 individuals per year at the age 80 years [2].

VT has a strong tendency to recur, with a recurrence rate approximately 5% per year [3], and recurrent VT may occur even in the presence of adequate therapy [4]. Very few studies that focus on the risk of recurrence of VT have information over decades of follow-up. Among the studies with longer duration of follow-up, the cumulative recurrence was reported to be ~10% after 1-2 years and increased to 44-56% after 20 years since the initial event [5,6]. A 2019 meta-analysis showed that the cumulative recurrence risk of VT was 10% in the first year after anticoagulant treatment, 16% at two years, 25% at 5 years, and 36% at 10 years after a first VT [7]. The recurrence rate is not stable over time. In the available studies with follow-up time more than 10 years, the recurrence rate was high during the first year after a first VT, i.e., 7.8 per 100 person years, after which the rate attenuated (1-18 years) [5].

Considering that VT is common, that aging is the most important risk factor for VT, that the risk of VT diminishes over time, and that the longest follow-up available in most observational studies after VT is approximately 10 years, more information is needed for clinicians to understand the impact of remote history of VT on risk of future VT in older individuals.

Currently, there are no prediction models for the risk of VT specifically in the elderly. Our aim is to assess whether a remote history of VT, i.e., a VT more than 10 years ago, is associated with the risk of future VT in older patients.

METHODS

Study design

The Age and Thrombosis, Acquired and Genetic risk factors in the Elderly (AT-AGE) Study, is a two-center, population-based case-control study carried out in Leiden, the Netherlands and Burlington, Vermont, US. The design has been described previously [6]. In brief, consecutive patients were included from June 2008 to August 2011 in Leiden and

from December 2008 to July 2011 in Vermont. All participants were 70 years or older. Patients with an objectively diagnosed, proven episode of VT, i.e., deep vein thrombosis of the leg or a pulmonary embolism (DVT or PE (with or without DVT)) were included. These consecutively diagnosis patients were recruited based on identifying all imaging tests that were positive. Diagnostic tests included compression ultrasonography, Doppler ultrasound, impedance plethysmography and contrast venography for diagnosis of deep vein thrombosis and perfusion and ventilation lung scanning, spiral computer tomography and pulmonary angiography for pulmonary embolism. Neither patients nor controls were excluded due to the use of anticoagulation. In Leiden, patients were identified from two anticoagulation clinics in a defined area in the western part of the Netherlands. In Vermont, sequential patients were identified through testing in all imaging centers in the area. Control subjects were identified in the same geographical areas as the patients and were randomly selected from five primary care practices in Leiden and four in Vermont. Both patients and controls were invited by letter, followed by a phone call to discuss participation. Exclusion criteria were a diagnosis of cancer, receiving chemotherapy or radiotherapy six months prior to entry, and a recent episode of venous thrombosis (within ten years previously). Participants with severe psychiatric or cognitive disorder, as judged during telephone contact, were also excluded. In total, of 1187 patients and 723 controls identified, 498 patients and 92 controls were excluded based on the exclusion criteria, and 216 eligible patients and 170 controls refused to participate due to time constraints or illness. This left 473 patients and 461 controls who were visited. Due to 13 patients and 5 controls having incomplete interview data, 460 patients and 456 controls were included in the study.

Participation

All participants were visited by a trained research assistant at their homes for an interview and a venipuncture. All participants provided written informed consent. The study was approved by the Medical Ethical Committee of the Leiden University Medical Center (protocol number: P08.066) and by the Committee of Human Research of the University of Vermont (protocol number: CHRMS M09-008).

Data collection and definitions

During the home visit, an interview was conducted to ascertain details about the VT (for patients), medical history, family history of VT, and lifestyle habits. Weight, height, and blood pressure were measured. Furthermore, all participants provided information regarding the exposure, i.e., a remote VT history. Remote VT history was defined as self-reported VT occurring >10 years prior to the index date. A venipuncture was performed by a trained research assistant using standard methods.

The index date was defined as the date of diagnosis of the current thrombosis for the patients and the date of the home visit for the control subjects.

VT was classified as provoked if it occurred after hospitalization (including recent surgery), fracture, plaster cast, splint, minor injuries of lower extremities (such as a sprained ankle or contusion of the lower leg), or transient immobilization at home ≥4 successive days in the three months before the index date.

Statistical analysis

Firstly, descriptive statistics for all participants were presented as frequencies and percentages for categorical variables and as mean and range for continuous variables. Secondly, we calculated the crude relative risk of VT associated with a remote history of VT (i.e., any VT >10 years prior to the index date) compared with not having a history of VT to assess the crude value of a remote history of VT on the development of VT after the age of 70 years. This was calculated both overall and separately for the risk of DVT and PE and for provoked and unprovoked events. Thirdly, participants who reported a remote VT were divided into two groups based on the time between the prior and the current VT, i.e., prior event 10-30 years prior to the index date and prior event more than 30 years prior to the index date. Fourthly, we adjusted the risk estimates for available VT risk factors. Two models were used, one with study center and standard available risk factors of a VT at older age (age, sex, body mass index(BMI), and family history of VT) and one also including genetic markers of VT, factor V Leiden, prothrombin G20210A mutation, and non-O blood group.

The relative risk of VT was estimated by calculating odds ratios (ORs) with corresponding 95% confidence intervals (CIs), using multivariable logistic regression models. This study is a case-control study sampled from a dynamic population. In this study setting, the odds ratio is a perfect estimation of the rate ratio (relative risk), and can be interpreted as such [8]. The population attributable risk (PAR) was calculated as: proportion of cases exposed to the risk factor of interest*(OR-1)/(OR). The PAR indicates the proportion of the total incidence of venous thrombosis in those ≥70 years old who were eligible for this study that can be attributed to a remote history of venous thrombosis. Lastly, to determine if the association of remote VT with the risk of VT was consistent across key groups, we assessed VT risk after dichotomization by age (dichotomized at the mean age of the whole study population, i.e., 78.1 years), sex and BMI (dichotomized at 25 kg/m^2). All analyses were performed in SPSS 23.0 for Windows (SPSS Inc, Chicago, Ill).

RESULTS

In total, 460 patients and 456 controls were reported in our study (Table 1). The mean age of patients was 78.7 years (range: 70-100.9), which was similar to that of the controls (mean age: 77.5, range: 70.3-96.3). There were slightly more women than men (60.2% of the patients and 52.4% of the controls). The majority of study participants were Caucasians. BMI was similar for patients and controls. Of the patients, 196 (42.6%) had DVT only, while 263 (57.2%) were diagnosed with PE (with or without DVT). Roughly half of patients had provoked VT. Remote history of VT was present in 59 (12.8%) patients and 25 (5.5%) controls. All provoking VT risk factors and genetic risk factors were more common in patients than in control subjects.

Table 2 shows the risk of VT associated with a remote history of VT (crude estimate). Compared with individuals without a history of VT, those with a remote history of VT had a relative risk of VT that was 2.54-fold (95% CI, 1.56-4.13) increased. The population attributable risk (PAR) of a remote history of VT was 7.7%. The risk of VT was similar for a history of VT that occurred 10-30 years and a history that occurred more than 30 years prior to the index date. The risk of VT associated with a remote history of VT was only mildly attenuated after adjustment for standard available risk factors and after further adjustment for genetic factors (table 2).

Table 3 shows the risk of DVT, PE±DVT, provoked, and unprovoked events separately. The association between a remote history of VT and a VT at older age, was stronger for DVT than PE±DVT, i.e., the OR was 3.12 (95%CI, 1.78-5.46) for DVT and 2.05 (95%CI, 1.17-3.60) for PE±DVT. The risk estimates were also more pronounced for unprovoked than for provoked events; risk of unprovoked VT was 3.54-fold increased (95%CI, 2.09-5.99) and risk of provoked VT was 1.50-fold (0.79-2.83) increased. Similar risk patterns were seen after adjustment for standard available risk factors and after further adjustment for genetic risk factors (table 3).

Table 4 shows the risk of VT associated with a remote history of VT in subgroups after dichotomization on the mean age at the index date (78.1 years), BMI, or sex. The association of a remote history of VT was increased in all subgroups, however, point estimates were numerically greater in participants below 78.1 years of age compared with older participants. In those with a BMI<25 kg/m^2 compared with a BMI>25 kg/m^2, and in men compared with women. This remained after full adjustment, and across categories of time since VTE. We performed subgroup analysis merely to assess the robustness of the estimates and for descriptive purposes, not to find important differences between groups. Therefore, we did not perform formal interaction testing.

Table 1. Population characteristics

Participant Characteristics [a]	Patients N=460	Controls N=456
Age, mean in years(range)	78.7 (70-100.9)	77.5 (70.3-96.3)
Sex, female n (%)	277 (60.2)	239 (52.4)
Sex, male n (%)	183 (39.8)	217 (47.6)
Ethnicity (Caucasians), n (%)	412 (89.6)	379 (83.1)
BMI, mean in kg/m^2 (range)	27.3 (14.4-52)	27 (17-49.7)
VT >10 years ago, n (%)	59 (12.8)	25 (5.5)
Mean time since prior VT (range)	31.2 (11-56)	33.6 (14-56)
Type of current VT, n (%)		
Deep vein thrombosis (DVT)	196 (42.6)	-
Pulmonary embolism +/- deep vein thrombosis (PE ± DVT)	263 (57.2)	-
Provoked VT	213 (46.3)	-
Unprovoked VT	235 (51.1)	-
Provoking factors, n (%)		
Hospital admission	143 (31.1)	31 (6.8)
Surgery	79 (17.2)	16 (3.5)
Fracture	30 (6.5)	3 (0.7)
Plaster cast	22 (4.8)	4 (8.8)
Immobilization	41 (8.9)	8 (1.8)
Minor injury	54 (11.7)	35 (7.7)
Genetic factors, n (%)		
Factor V Leiden	47 (10.2)	19 (4.2)
Prothrombin G20210A	11 (2.4)	8 (1.8)
Non-O blood group	278(60.4)	247(54.1)
Family history of venous thrombosis	124(30.0)	61(13.4)

Abbreviation: N, number; BMI, body mass index; VT, venous thrombosis.

[a] Missing in patients: 24 for BMI; 4 for mean time since prior VT; 11 for ethnicity; 12 for immobilization; 7 for minor injury; 1 for DVT/PE±DVT; 12 for provoked or unprovoked VT; 8 for factor V Leiden; 8 for prothrombin G20210A; 28 for non-O blood group.

[a] Missing in controls: 10 for BMI; 2 for mean time since prior VT; 8 for ethnicity; 1 for fracture; 2 for immobilization; 1 for minor injury; 6 for factor V Leiden; 4 for prothrombin G20210A; 16 for non-O blood group; 1 for family history of VT.

Table 2. The risk of VT associated with a remote history of VT

	Patients N=460	Controls N=456	OR crude (95%CI)	Adjusted OR[a] (95%CI)	Adjusted OR[b] (95%CI)
No prior VT	401	431	1(ref)	1(ref)	1(ref)
Remote VT	59	25	2.54 (1.56-4.13)	2.37 (1.39-4.04)	2.21 (1.26-3.86)
VT 10-30y ago[c]	28	11	2.74 (1.34-5.57)	2.54 (1.19-5.41)	2.05 (0.93-4.51)
VT>30y ago[c]	27	12	2.42 (1.21-4.84)	2.05 (0.96-4.38)	2.21 (0.99-4.94)

Abbreviation: N, number; OR, odds ratio; CI, confidence interval; y, years; VT, venous thrombosis.

[a] Adjusted for age, sex, body mass index (BMI), study center and family history of VT(standard factors).

[b] Adjusted for age, sex, BMI, study center, family history of VT, factor V Leiden, prothrombin G20210A mutation and non-O blood group (extensive factors).

[c] Exact time between former VT and index date is missing for 4 patients and 2 controls.

Table 3. The risk of DVT, PE±DVT, provoked, and unprovoked VT associated with a remote history of VT

	Patients N=460	Controls N=456	OR DVT (95%CI)	OR PE±DVT (95%CI)	OR provoked (95%CI)	OR unprovoked (95%CI)
Crude						
No prior VT	401	431	1(ref)	1(ref)	1(ref)	1(ref)
Remote VT	59	25	3.12 (1.78-5.46)	2.05 (1.17-3.60)	1.50 (0.79-2.83)	3.54 (2.09-5.99)
VT 10-30y ago[a]	28	11	3.07 (1.35-6.99)	2.33 (1.04-5.22)	2 (0.84-4.79)	3.22 (1.47-7.06)
VT>30y ago[a]	27	12	2.81 (1.26-6.29)	2.14 (0.97-4.70)	1.28 (0.50-3.31)	3.68 (1.77-7.69)
Standard factors[b]						
No prior VT	401	431	1(ref)	1(ref)	1(ref)	1(ref)
Remote VT	59	25	2.83 (1.52-5.27)	1.93 (1.03-3.60)	1.23 (0.59-2.53)	3.37 (1.89-6.02)
VT 10-30y ago[a]	28	11	2.60 (1.08-6.23)	2.30 (0.94-5.58)	1.87 (0.73-4.80)	2.82 (1.21-6.57)
VT>30y ago[a]	27	12	2.44 (0.98-6.09)	1.76 (0.74-4.18)	0.78 (0.25-2.42)	3.42 (1.53-7.64)
Genetic factors[c]						
No prior VT	401	431	1(ref)	1(ref)	1(ref)	1(ref)
Remote VT	59	25	2.43 (1.24-4.76)	1.95 (1.02-3.72)	1.21 (0.57-2.58)	3 (1.62-5.53)
VT 10-30y ago[a]	28	11	1.71 (0.64-4.52)	2.12 (0.86-5.25)	1.66 (0.62-4.45)	1.96 (0.80-4.84)
VT>30y ago[a]	27	12	2.63 (0.98-7.03)	1.93 (0.78-4.79)	0.88 (0.27-2.84)	3.65 (1.55-8.59)

Abbreviation: N, number; OR, odds ratio; CI, confidence interval; y, years; VT, venous thrombosis; DVT, deep vein thrombosis; PE±DVT, pulmonary embolism.

[a] Exact time between former VT and index date is missing for 4 patients and 2 controls.

[b] Adjusted for age, sex, BMI, study center and family history of VT (standard factors).

[c] Adjusted for age, sex, BMI, study center, family history of VT, factor V Leiden, prothrombin G20210A mutation and non-O blood group (extensive factors).

Table 4. Risk of VT associated with a remote history of VT after stratification by age, sex and BMI

	Patients N=460	Controls N=456	OR crude (95%CI)	Adjusted OR[a] (95%CI)	Adjusted OR[b] (95%CI)
Age at index ≤78.1[c]					
No prior VT	204	261	1(ref)	1(ref)	1(ref)
Remote VT	31	14	2.83 (1.47-5.47)	2.83 (1.39-5.78)	2.69 (1.25-5.76)
VT 10-30y ago[d]	10	5	2.56 (0.86-7.60)	2.60 (0.83-8.20)	1.75 (0.50-6.17)
VT >30y ago[d]	19	8	3.04 (1.30-7.08)	2.95 (1.16-7.52)	3.48 (1.27-9.54)
Age at index >78.1[c]					
No prior VT	197	170	1(ref)	1(ref)	1(ref)
Remote VT	28	11	2.20 (1.06-4.54)	2.03 (0.90-4.59)	1.94 (0.83-4.51)
VT 10-30y ago[d]	18	6	2.59 (1-6.67)	2.51 (0.90-6.97)	2.33 (0.81-6.67)
VT >30y ago[d]	8	4	1.73 (0.51-5.83)	1.03 (0.27-3.96)	0.98 (0.24-3.95)
Men					
No prior VT	166	209	1(ref)	1(ref)	1(ref)
Remote VT	17	8	2.68 (1.13-6.35)	3.86 (1.36-10.97)	3.51 (1.19-10.35)
VT 10-30y ago[d]	13	5	3.27 (1.14-9.37)	3.80 (1.20-11.99)	3.17 (0.96-10.47)
VT >30y ago[d]	2	2	1.26 (0.18-9.03)	2.10 (0.14-30.74)	2.10 (0.11-40.52)
Women					
No prior VT	235	222	1(ref)	1(ref)	1(ref)
Remote VT	42	17	2.33 (1.29-4.22)	2.06 (1.10-3.86)	1.87 (0.96-3.64)
VT 10-30y ago[d]	15	6	2.36 (0.90-6.20)	1.77 (0.64-4.94)	1.35 (0.45-4.02)
VT >30y ago[d]	25	10	2.36 (1.11-5.03)	2.21 (1-4.93)	2.28 (0.98-5.31)
BMI<25 kg/m^2[e]					
No prior VT	127	154	1(ref)	1(ref)	1(ref)
Remote VT	22	6	4.45 (1.75-11.30)	4.15 (1.57-10.97)	4.88 (1.64-14.56)
VT 10-30y ago[d]	11	3	4.45 (1.21-16.28)	3.86 (0.98-15.23)	3.45 (0.82-14.51)
VT >30y ago[d]	11	3	4.45 (1.21-16.28)	4.43 (1.15-17.02)	7.28 (1.36-39.06)
BMI≥25 kg/m^2[e]					
No prior VT	254	269	1(ref)	1(ref)	1(ref)
Remote VT	33	17	2.06 (1.12-3.78)	1.84 (0.96-3.52)	1.59 (0.81-3.14)
VT 10-30y ago[d]	16	8	2.12 (0.89-5.04)	2.10 (0.84-5.29)	1.56 (0.58-4.16)
VT >30y ago[d]	13	8	1.72 (0.70-4.22)	1.34 (0.52-3.45)	1.35 (0.51-3.54)

Abbreviation: N, number; OR, odds ratio; CI, confidence interval; y, years; VT, venous thrombosis; BMI, body mass index.

[a] Adjusted for age, sex, body mass index (BMI), study center and family history of VT(standard factors).

[b] Adjusted for age, sex, BMI, study center, family history of VT, factor V Leiden, prothrombin G20210A mutation and non-O blood group (extensive factors).

[c] Mean age of the total study population

[d] Exact time between former VT and index date is missing for 4 patients and 2 control.

[e] Mean BMI in patients and controls

DISCUSSION

In this population aged 70 and older, a remote history of VT was associated with an increased risk of VT, independent of other factors, including common gene variants. Similar risk patterns were observed for VT types, albeit the relative risks were more pronounced for DVT than for PE±DVT, and more pronounced for provoked events than unprovoked events. Associations were robust in various important subgroups, and similar for remote VT that occurred 20-30 years previous, or 10-20 years previous. Since the OR was modest and the proportion of cases with a remote history of VT relatively low (12%), the PAR of a remote history of VT alone was only 7.7%. Nevertheless, findings highlight the importance of considering lifetime history of VT in older people.

Several cohort studies showed that a previous history of VT was associated with recurrence of VT in the population younger than 70 years and a previous history of VT was an independent predictor of VT recurrence [9-14]. However, these studies generally had short follow up of less than 10 years, so evaluation of the impact of prior VT on health and VT risk in older people could not be determined. The current findings are important as they provide clinicians with quantitative information that might allow them to be aware of a future VT in people presenting for primary care or with impending provoking VT risk settings like surgery. Consideration of risk models for VT in this age group requires further study, and such studies should consider remote as well as recent history of VT (for which there is more information).

Limitations:

Our study had some limitations that may have led to underestimation of the true risk associated with remote history of VT. Since we use self-reported information on remote history of VT, we do not have data on VT characteristics or treatments for the remote VT, however, in the time frame of study, VT was usually treated with time-limited vitamin K antagonists. For three out of the 84 remote VT events, it was unclear whether they had suffered from DVT/PE or only superficial VT. Excluding these individuals did not materially change the results. Self-report of remote VT may be affected by recall bias, as patients may better recall a history of VT than controls. However, for both patients and controls, the time since a previous event was more than 10 years so it is likely for both groups that it was equally difficult to remember. Thus, recall bias should not have a major effect on observed risk estimates. Potentially, if older people in general have difficulties remembering distant events, non-differential misclassification would only lead to underestimation of the risk.

Individuals who had a thrombotic event more than 10 years ago, had to survive until at least the age of 70 in order to be considered as participant in our study which would lead to biases in estimating the strength for a study of VT etiology. However, we did not aim to infer causality. Our study participants are predominately Caucasian, so results cannot be generalized to other ethnicities. Confidence intervals for risk estimates in subgroups became wide, so differences between subgroups should be interpreted with caution. Due to the case- control study design, absolute risk cannot be determined, but we were able to determine the risks of developing VT according to exposures of interest. It is likely that the relationship between remote VT and provoked VT was lower than that of unprovoked VT due to the routine use of prophylaxis in high-risk settings reducing provoked VT.

Strengths

The main strength of our study is that it is one of the largest studies on VT risk in the elderly. We were able to recruit older individuals by performing home visits and achieved a high participation rate. Furthermore, we had a sufficient number of individuals with a history of remote VT, enabling us to assess the association between this history and the risk of VT. We also had detailed information on other risk factors of VT, both standard available risk factors and genetic markers. This allowed us to further assess the adjusted association of a remote history of VT.

Conclusions

A remote history of VT is associated with an increased risk of VT at older age. Information on a remote history of VT may help to identify older people who are at increased risk of venous thrombosis. To fully incorporate this finding in clinical practice, study of the added value of this factor to prediction models in this age group requires investigation.

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