Universiteit
Leiden
The Netherlands

Procoagulant factor levels and risk of venous thrombosis in the elderly

Wang, H.J.; Rosendaal, F.R.; Cushman, M.; Vlieg, A.V.

Citation
Wang, H. J., Rosendaal, F. R., Cushman, M., & Vlieg, A. V. (2020). Procoagulant factor levels and risk of venous thrombosis in the elderly. *Journal Of Thrombosis And Haemostasis*, *19*(1), 186-193. doi:10.1111/jth.15127

Version:	Publisher's Version
License:	Creative Commons CC BY-NC 4.0 license
Downloaded from:	https://hdl.handle.net/1887/3277323

Note: To cite this publication please use the final published version (if applicable).

Check for updates

Received: 10 April 2020 | Accepted: 29 September 2020

DOI: 10.1111/jth.15127

ORIGINAL ARTICLE

Procoagulant factor levels and risk of venous thrombosis in the elderly

Huijie Wang[1] | Frits R. Rosendaal[1] | Mary Cushman[2] | Astrid van Hylckama Vlieg[1]

[1]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands

[2]Department of Medicine, Larner College of Medicine at the University of Vermont, Burlington, VT, USA

Correspondence
Astrid van Hylckama Vlieg, Department of Clinical Epidemiology, Leiden University Medical Center, C7-P, PO Box 9600, 2300 RC Leiden, the Netherlands.
Email: a.van_hylckama_vlieg@lumc.nl

Funding Information
The Netherlands Heart Foundation and the Foundation Leducq did not play a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or presentation, review, or approval of the manuscript.

Abstract

Background: Venous thrombosis (VT) incidence increases markedly with age. Coagulation factors are also positively associated with age.

Objective: To study whether higher levels of coagulation factors II (prothrombin), VIII, IX, and XI are associated with risk of a first VT in the elderly.

Methods: Four hundred and one patients and 431 control subjects aged 70 and older were included in the Age and Thrombosis, Acquired and Genetic risk factors in the Elderly (AT-AGE) study. Blood was collected 1 year after the event in patients and in all control subjects for measurement of coagulation factors. To assess the risk of VT, odds ratios (ORs) were calculated after stratification of coagulation factors in quartiles and at the 90th percentile, adjusting for potential confounders (age, sex, body mass index, and study center).

Results: Mean age was 78 years (range: 70-100 years). The ORs of VT for factors in the top quartile compared with the lowest quartile were 4.5 (95% confidence interval [CI]:2.7-7.3) for factor VIII, 2.4 (95% CI:1.1-5.2) for factor IX, and 1.7 (95% CI:1.0-2.9) for factor XI. High prothrombin was not associated with an increased VT risk. There was no dose-response association between the number of high coagulation factors and VT risk. The population attributable risk (PAR) of VT was 37.6%, 23.3%, and 12.4% for factor VIII, IX, and XI, respectively.

Conclusion: In this study of the elderly, higher factors VIII, IX, and XI but not prothrombin, were positively associated with the risk of VT.

KEYWORDS

aged, factor IX, factor VIII, factor XI, prothrombin, venous thrombosis

Manuscript handled by: Jean Connors

Final decision: Jean Connors, 07 October 2020

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2020 The Authors. *Journal of Thrombosis and Haemostasis* published by Wiley Periodicals LLC on behalf of International Society on Thrombosis and Haemostasis

1 | INTRODUCTION

The incidence of venous thrombosis (VT) in the general population is 1 to 2 per 1000 per year, rising sharply with age to 1 per 100 annually in the very old.[1] Increasing age is by far the most important risk factor for VT and the reasons for this are largely unknown. Because of the multi-causal character of VT, it is likely that multiple factors contribute to the risk of VT in the elderly.[2]

Some acquired risk factors for thrombosis, eg, immobilization, severe medical disorders, malignant disease, and heart failure, are more prevalent in the elderly than in younger populations,[3-5] which explains part of the increase in incidence with age. However, after adjustment for this increased prevalence and possible accumulation of risk factors in the elderly, the risk of VT is still positively associated with age.[3,4]

Because the levels of coagulation factors VIII, IX, and XI (FVIII, FIX, FXI) all increase with age[5-9] and are associated with VT risk,[10-15] they are candidates for consideration as age-specific VT risk factors. To date, associations between coagulation factors and VT risk have been mainly established in studies that included patients under 70 years of age, as the elderly are often excluded from clinical studies on etiology and management because of comorbidities, short life expectancies, and logistical difficulties.[16]

Few studies addressed the association between procoagulant factors and risk of VT in the elderly. The Cardiovascular Health Study (CHS), which is a population-based cohort study with people aged 65 years or older in the United States indicated FVIII and FXI were each positively associated with the risk of VT.[12,17] No association was observed between prothrombin and FIX and the risk of VT.[15,18] A hospital-based case-control study published by Oger et al, with patients 70 years and older, concluded that higher FVIII activity was associated with VT.[19] While the cohort of CHS contains a large sample of elderly individuals, the number of patients with VT in that study as well as in the case-control study by Oger et al was small. Therefore, replication of these findings in a larger sample is indicated. Knowledge regarding the associations between procoagulant factors and the risk of VT in the elderly may guide physicians in the identification of high-risk individuals and subsequent targeted prophylactic treatment in those at high risk.

The aim of this study was to assess whether high levels of coagulation factors previously reported in relation to VT risk in young and middle-aged populations were also associated with the risk of a first VT in the elderly. We evaluated coagulation factors II (FII; prothrombin), FVIII, FIX, and FXI in a large population-based case-control study including 401 patients and 431 controls aged 70 years and older.

Essentials

- Venous thrombosis (VT) risk and coagulation factor levels increase with age.
- We studied the association between levels of procoagulant factors and the risk of a first VT in the elderly.
- Higher levels of factors VIII, IX, and XI, but not prothrombin, were associated with the risk of VT.
- Similar risk patterns were observed for provoked and unprovoked VT and for deep vein thrombosis and pulmonary embolism separately.

2 | MATERIALS AND METHODS

2.1 | Study design

All analyses were performed in the Age and Thrombosis, Acquired and Genetic risk Factors in the Elderly (AT-AGE) Study, which is a two-center population-based case-control study in Leiden, the Netherlands and Burlington, Vermont, USA, designed to study risk factors for VT in older people. As previously reported,[20] patients aged 70 years and older with an objectively diagnosed, first episode of VT, ie, deep vein thrombosis of the leg or a pulmonary embolism (DVT or PE [with or without DVT]) were included from the files of the anticoagulation clinics in Leiden and Haarlem. Diagnostic tests included compression ultrasonography, Doppler ultrasound, impedance plethysmography, and contrast venography for diagnosis of DVT and perfusion and ventilation lung scanning, spiral computer tomography, and pulmonary angiography for PE. Patients with active malignancy, a history of VT, or severe cognitive impairment (measured with Mini-Mental State Exam [MMSE]) were excluded. Similarly, patients aged 70 years and older, with the same inclusion and exclusion criteria as in Leiden, were enrolled in Burlington, Vermont, USA. In Burlington, sequential patients were identified through testing in imaging centers. Both study locations cover large geographic areas. In total, 403 patients and 433 individuals without VT from primary care practices in the same geographic areas were included in this study. The same inclusion and exclusion criteria as for the patients were applied to controls. For this analysis we included 401 patients and 431 controls with complete interview data.

2.2 | Participation

All participants were visited by a trained research assistant at their homes for an interview and a venipuncture. Data collection was performed identically in Leiden and Burlington. Patients were visited twice, ie, as soon as possible after the VT event and again 1 year after the event; control subjects were visited only once. During the first home visit, an interview was conducted to ascertain VT event information, medical history, family history, and lifestyle habits. Weight, height, and blood pressure were also measured. Citrated blood was collected in Sarstedt tubes® using the aspiration method (citrate, pre-dosed with 0.106 molar solution [equivalent to 3.2% trisodium citrate] with a mixing ratio of 1:10 [sample 1]). During the second home visit in patients only, about 1 year after diagnosis of the VT, a second venipuncture was performed to collect citrated blood in the absence of anticoagulants or the acute phase response (sample 2).

Not all patients were available for the second home visit at 1 year after the VT as 21 of them had died after the first visit and 24 declined to participate in the second home visit. Furthermore, in 44 patients and 26 controls, blood collection failed or the coagulation assays were unsuccessful, leaving 312 patients and 405 controls for the analyses of the non-vitamin K dependent coagulation factors (FVIII and FXI). Vitamin K antagonists were still used by 149 patients at the time of the second home visit, and they were excluded from the analysis of vitamin K dependent coagulation factors, as were 36 controls who used these anticoagulants at their home visit. Thus, 163 patients and 369 controls could be included for the analyses of the vitamin K dependent coagulation factors (FII and FIX).

VT events were classified as provoked and unprovoked. Provoked VT was defined as thrombosis after hospitalization, (major) surgery, fracture, plaster cast, splint, minor injuries of the lower extremities (such as a sprained ankle or contusion of the lower leg), or transient immobility at home ≥4 successive days in the 3 months before the index date (defined as the date of VT diagnosis for the patients and the date of the home interview for the control subjects).

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).

2.3 | Blood collection and laboratory measurements

All blood was collected and processed within 4 hours. Blood tubes were centrifuged for 10 min 769 *g* at 18°C, aliquoted, and frozen at −80°C. Plasma samples that had not been previously thawed were retrieved for controls and at 1 year after the thrombotic event for the patients. The coagulation factor levels were measured as activity levels in one laboratory on the ACL TOP (Werfen).

In every run, two commercial controls, ie, a normal and a low control, and normal pooled plasma, were included. Using these three quality control (QC) samples, the coefficients of variation (CV) ranged between 5.8% and 7.3% for FII, 5.9% and 11.0% for FVIII, 3.9% and 4.9% for FIX, 3.7% and 4.3% for FXI.

2.4 | Statistical analysis

First, we assessed the risk of VT associated with the levels of all coagulation factors as continuous variables. Second, we categorized coagulation factor levels into quartiles based on the distribution in controls and also dichotomized levels at the 90th percentile. In addition to the assessment of the risk of VT associated with individual coagulation factors, we assessed the risk of VT associated with the combined effect of FIX and its co-factor FVIII because the formation of the intrinsic tenase complex is an essential event in the procoagulant reactions that lead to clot formation.[21]

We investigated the association between the number of coagulation factor levels that were high (defined as $>P_{75}$, and including only those factors individually associated with VT risk) and the risk of VT to assess whether the burden of elevated procoagulant factors adds to VT risk. We separately analyzed associations between coagulation factors and provoked and unprovoked VT, and between coagulation factors and the type of VT (DVT only or PE with or without DVT). This study is a case-control study sampled from a dynamic population. In this study setting, the odds ratio (OR) is a perfect estimation of the rate ratio (relative risk) and can be interpreted as such.[22]

Population attributable risks (PAR) were estimated as PAR = pd * (OR − 1)/(OR), in which pd refers to the proportion of patients exposed to the risk factor of interest. The PAR indicates the proportion of the total incidence of VT that can be attributed to the specific risk factor.

2.5 | Sensitivity analysis

Sensitivity analyses with imputed data for missing coagulation factor levels replicated all main analyses. We used multiple imputation for 89 patients and 26 controls with missing data on coagulation factor levels. For an additional 149 patients who were still using vitamin K antagonists at the time of both blood collections, the levels of vitamin K dependent FII and FIX were imputed. Controls (n = 36) who were using vitamin K antagonists for indications other than VT were excluded.

In the imputation model, missing coagulation factor levels of controls and patients were imputed separately. We imputed missing coagulation factors levels in controls using the information on age, sex, body mass index (BMI), study center, provoking factors (hospital admission, fracture, plaster cast, immobilization, and minor injury), and for the patients, in addition to all the parameters above, we also accounted for coagulation factor levels measured in samples obtained during the first visit. IBM SPSS 23.0 for Windows (SPSS Inc) was used for all data analysis.

3 | RESULTS

Table 1 shows the characteristics of patients and control subjects. The mean age in controls was 77.5 years (range: 70.2-96.3), which was similar to patients (mean age: 78.7; range: 70.0-100.9). In the patients, there were more women than men (58.5% versus 41.5%). Of all patients, 166 (41.4%) had DVT without PE, 213 (53.1%) were diagnosed with PE without a DVT diagnosis, and 22 (5.5%) had both PE and DVT. Of the patients, 131 (32.7%) had had a hospital admission within 3 months before the index date compared with 29 (6.7%) controls. Other acquired risk factors including fractures, plaster cast use, immobilization, and minor injuries within 3 months before the index date occurred more often in patients than controls. In our study population, 96.2% of the participants were White.

TABLE 1 Baseline characteristics

	Controls	Patients
N	431	401
Men, N (%)	209 (48.5)	166 (41.5)
Age, mean (range)	77.5 (70.2-96.3)	78.7 (70.0-100.9)
BMI, mean (kg/m^2)$^+$(range)	27.0 (17.0-49.7)	27.2 (14.5-45.4)
Type of VT, N (%)		
DVT	–	166 (41.4)
PE	–	213 (53.1)
PE + DVT	–	22 (5.5)
Hospital admission, N (%)	29 (6.7)	131 (32.7)
Surgery, N (%)	16 (3.7)	73 (18.2)
Fracture, N (%)	3 (0.7)	27 (6.7)
Plaster cast, N (%)	4 (0.9)	21 (5.2)
Immobilization, N (%)	8 (1.9)	39 (9.7)
Minor injury, N (%)	33 (7.7)	49 (12.2)

Note: Minor injury: defined as an injury of the lower extremities (hip, knee, ankle, or foot) such as a sprained ankle or contusion of the lower leg that started within the 3-month window.

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; N, number; VT, venous thrombosis; VTE, venous thromboembolism.

Table 2 shows the associations between coagulation factor levels and characteristics of controls. Mean coagulation levels in women were slightly higher than in men. Furthermore, the levels of all coagulation factors did not differ much between age subgroups. None of the coagulation factors showed a consistent trend across age or BMI categories.

In the analysis of the association between levels of coagulation factors as continuous variables and the risk of VT, the ORs of VT associated with an increase in 10 units of the coagulation factors were 0.74 (95% CI:0.66-0.90) for prothrombin, 1.22 (95% CI:1.10-1.22) for FVIII, 1.22 (95% CI:1.10-1.34) for FIX, and 1.10 (95% CI:1.01-1.22) for FXI. This model assumes a linear increase in the risk of VT associated with coagulation factor levels. As this model may not correctly describe the data, we also stratified the levels into quartiles using the lowest quartile as the reference category.

Using quartiles of the coagulation factor levels, all except FII were positively associated with the risk of VT. Compared with the lowest quartile, the ORs were 4.5 (95% CI:2.7-7.3), 2.4 (95% CI:1.1-5.2), and 1.7 (95% CI:0.9-2.9) in the highest quartiles of FVIII, FIX, and FXI, respectively. In contrast, FII was not associated with an increased risk of VT (OR 0.3, 95% CI:0.1-0.6; Table 3). The ORs were not substantially different when we dichotomized the coagulation factors at the 90th percentile (Table 4).

To assess whether the burden of elevated procoagulant factors added to VT risk, we considered the coagulation factors that were individually associated with VT risk, ie, FVIII, FIX, and FXI, as shown in Table 5. Using the 75th percentile as a cut-off as the risk of VT increased above 75th percentile for all the included factors, we compared individuals with one or more high coagulation factors with individuals without any high coagulation factor as a reference category. The OR was 1.8, 2.3, and 1.9 when one, two, or three coagulation factors were >75th percentile compared with none of the coagulation factors >75th percentile, indicating no clear trend for an increasing risk of VT associated with the number of high coagulation factors could be observed. Overall, similar risk patterns were observed for provoked and unprovoked VT and for DVT and PE ± DVT (Table 5).

In the combined analysis of co-factors FVIII and FIX, compared with individuals with FVIII and FIX below the 75th percentile, individuals with high FIX alone had no increased risk of VT (OR 1.0, 95% CI:0.5-1.7) and individuals with high FVIII alone had a 4.2-fold

TABLE 2 Associations between baseline characteristics and coagulation factors in controls

	N (%)	Factor II mean (SD) IU/dL	Factor VIII mean (SD) IU/dL	Factor IX mean (SD) IU/dL	Factor XI mean (SD) IU/dL
Sex					
Men	209 (49)	83 (26)	134 (37)	109 (35)	102 (23)
Women	222 (51)	95 (21)	135 (29)	118 (26)	115 (20)
Age (years)					
70-75	175 (40)	92 (22)	129 (31)	113 (26)	110 (21)
75-80	129 (30)	88 (25)	136 (35)	115 (36)	108 (26)
80-85	85 (20)	86 (27)	141 (36)	113 (32)	107 (22)
>85	42 (10)	86 (27)	140 (30)	115 (35)	104 (19)
BMI, kg/m^a					
17-27	240 (55.7)	89 (24)	132 (33)	111 (32)	107 (23)
27-37	169 (39.2)	89 (26)	137 (32)	116 (29)	110 (22)
37-47	12 (2.8)	94 (13)	150 (26)	141 (20)	120 (16)
>47	2 (0.5)	91 (5)	113 (20)	126 (4)	122 (36)

Abbreviations: BMI, body-mass index; N, number; SD, standard deviation.

[a]Number of missing is 8 (1.8%).

TABLE 3 Coagulation factor levels and risk of VT

Coagulation factor	Patients[a]	Controls[a]	Model 1 OR (95 CI)	Model 2 OR (95 CI)	Model 3 OR (95 CI)	Model 4 OR (95 CI)
Factor II						
$<P_{25}$	25	63	1 (ref)	1 (ref)	1 (ref)	1 (ref)
P_{25}-P_{50}	55	99	1.4 (0.8-2.4)	1.3 (0.7-2.3)	1.0 (0.6-1.9)	0.9 (0.5-1.7)
P_{50}-P_{75}	60	116	1.3 (0.7-2.4)	1.3 (0.7-2.3)	0.9 (0.5-1.7)	0.8 (0.4-1.6)
$>P_{75}$	23	91	0.6 (0.3-1.1)	0.5 (0.3-1.1)	0.3 (0.1-0.7)	0.3 (0.1-0.6)
Factor VIII						
$<P_{25}$	33	101	1 (ref)	1 (ref)	1 (ref)	1 (ref)
P_{25}-P_{50}	45	111	1.2 (0.7-2.1)	1.2 (0.7-2.0)	1.3 (0.7-2.2)	1.2 (0.7-2.1)
P_{50}-P_{75}	83	93	2.7 (1.7-4.4)	2.5 (1.5-4.0)	2.8 (1.7-4.6)	2.5 (1.5-4.2)
$>P_{75}$	151	101	4.4 (2.7-7.0)	4.2 (2.6-6.8)	4.7 (2.9-7.6)	4.5 (2.7-7.3)
Factor IX						
$<P_{25}$	14	63	1 (ref)	1 (ref)	1 (ref)	1 (ref)
P_{25}-P_{50}	31	96	1.5 (0.7-3.0)	1.6 (0.8-3.2)	1.3 (0.6-2.7)	1.3 (0.6-2.8)
P_{50}-P_{75}	53	113	2.1 (1.1-4.1)	2.5 (1.3-5.1)	1.7 (0.9-3.5)	2.1 (1.0-4.2)
$>P_{75}$	65	97	2.8 (1.5-5.5)	3.2 (1.5-6.6)	2.3 (1.2-4.6)	2.4 (1.1-5.2)
Factor XI						
$<P_{25}$	46	101	1 (ref)	1 (ref)	1 (ref)	1 (ref)
P_{25}-P_{50}	86	108	1.8 (1.2-2.9)	1.9 (1.2-3.0)	1.6 (1.0-2.6)	1.7 (1.0-2.7)
P_{50}-P_{75}	86	96	2.2 (1.4-3.6)	2.3 (1.4-3.7)	1.9 (1.1-3.2)	1.9 (1.1-3.1)
$>P_{75}$	94	100	2.1 (1.2-3.5)	2.0 (1.2-3.4)	1.8 (1.0-3.0)	1.7 (1.0-2.9)

Note: Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, and BMI.

Model 3: Adjusted for age, sex, and study center.

Model 4: Adjusted for age, sex, BMI, and study center.

Cut-off values for quartiles: Factor II- P_{25} 86 IU/dL, P_{50} 94 IU/dL, P_{75} 103 IU/dL. Factor VIII- P_{25} 112 IU/dL, P_{50} 132 IU/dL, P_{75} 152 IU/dL. Factor IX- P_{25} 104 IU/dL, P_{50} 117 IU/dL, P_{75} 132 IU/dL. Factor XI- P_{25} 93 IU/dL, P_{50} 108 IU/dL, P_{75} 123 IU/dL.

Abbreviations: BMI, body mass index; CI, confidence interval; N, number; OR, odds ratio; ref, reference group; VT, venous thrombosis.

[a]Three hundred and twelve patients and 406 controls for non-vitamin K dependent factor VIII; 312 patients and 405 controls for non-vitamin K dependent factor XI; 311 patients, 163 patients, and 369 controls for vitamin K dependent factors (factor II and IX).

increased risk of VT (OR 4.2, 95% CI:2.7-6.4). Participants with both FVIII and FIX above the 75th percentile were not at further increased risk compared to those with either high FVIII alone or high FIX alone (Table 6).

The PAR of VT was 37.6% for FVIII ($>P_{75}$), 23.3% for FIX ($>P_{75}$), and 12.4% for FXI ($>P_{75}$).

Results of the sensitivity analyses using multiple imputation of missing levels of coagulation factors were similar to the main analysis except for the analysis of the burden of elevated coagulation factors where, in the sensitivity analysis, a trend for an increasing risk of VT associated with the number of high coagulation factors was observed (see Tables S1-S4 in supporting information).

4 | DISCUSSION

In this study, high levels of coagulation factors FVIII, FIX, and FXI, but not prothrombin, were associated with the risk of VT in elderly individuals. The risks were increased, with adjusted ORs of VT between 2 and 4 for levels in the top quartile compared with the lowest quartile. In the main analysis, there was no clear dose-response association between the number of elevated coagulation factors and the risk of VT. Similar risk patterns were observed for provoked and unprovoked VT and for DVT and PE separately. Unexpectedly, we found no association between high prothrombin levels and risk of VT.

The CHS study reported similar results in those aged ≥ 65, with an association between procoagulant factors FVIII and FXI and VT during an average 7.8 years of follow-up,[17] whereas no association was observed between prothrombin level and the risk of VT.[18] We previously reported the frequency of carriers of prothrombin G20210A in the patients and controls included in this study, which was 2.3% and 1.6%, respectively.[23] The risk of VT was a 1.4-fold (95% CI:0.5-3.9) increase in carriers of the prothrombin mutation compared with non-carriers,[23] indicating also that the prothrombin 20210A mutation is, at most, weakly associated with the risk of VT in the elderly. Furthermore, FIX was associated with the risk of VT in univariate and multivariate analysis in CHS, but not after

TABLE 4 Associations of coagulation factor levels in the top decile with VT

Coagulation factor	Patients[a]	Controls[a]	Model 1 OR (95 CI)	Model 2 OR (95 CI)	Model 3 OR (95 CI)	Model 4 OR (95 CI)
Factor II						
$<P_{90}$	154	331	1 (ref)	1 (ref)	1 (ref)	1 (ref)
$>P_{90}$	9	38	0.5 (0.2-1.1)	0.5 (0.3-1.2)	0.4 (0.2-0.9)	0.4 (0.2-1.0)
Factor VIII						
$<P_{90}$	240	364	1 (ref)	1 (ref)	1 (ref)	1 (ref)
$>P_{90}$	72	42	2.5 (1.7-3.9)	2.6 (1.7-4.0)	2.9 (1.9-4.5)	2.9 (1.9-4.5)
Factor IX						
$<P_{90}$	122	325	1 (ref)	1 (ref)	1 (ref)	1 (ref)
$>P_{90}$	41	44	2.3 (1.4-3.8)	2.4 (1.5-4.0)	2.1 (1.3-3.4)	2.1 (1.2-3.5)
Factor XI						
$<P_{90}$	259	365	1 (ref)	1 (ref)	1 (ref)	1 (ref)
$>P_{90}$	53	40	1.9 (1.2-3.0)	1.8 (1.2-2.9)	1.9 (1.2-3.0)	1.8 (1.1-2.9)

Note: Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, and BMI.

Model 3: Adjusted for age, sex, and study center.

Model 4: Adjusted for age, sex, BMI, and study center.

Cut-off values for 90th percentile of coagulation factors: Factor II, P_{90} 110 IU/dL. Factor VIII, P_{90} 176 IU/dL. Factor IX, P_{90} 143 IU/dL. Factor XI, P_{90} 135 IU/dL.

Abbreviations: BMI, body mass index; CI, confidence interval; N, number; OR, odds ratio; ref, reference group; VT, venous thrombosis.

[a]Three hundred and twelve patients and 406 controls for non-vitamin K dependent factor VIII, 312 patients and 405 controls for non-vitamin K dependent factor XI, 163 patients and 369 controls for vitamin K dependent factors (factor II and IX).

TABLE 5 The risk of VT associated with increasing number of coagulation factors (factor VIII, factor IX, and factor XI, all coagulation factors dichotomized at P_{75})

Number of elevated factors	Controls N	Patients N	OR overall[a] (CI 95)	OR provoked[a] (CI 95)	OR unprovoked[a] (CI 95)	OR DVT[a] (CI 95)	OR PE ± DVT[a] (CI 95)
0	118	219	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1	97	105	1.8 (1.2-2.6)	1.4 (0.9-2.3)	2.1 (1.3-3.5)	1.9 (1.2-3.2)	1.7 (1.1--2.7)
2	64	52	2.3 (1.4-3.6)	1.6 (0.9-2.9)	3.1 (1.8-5.5)	2.6 (1.4-4.9)	2.0 (1.1-3.5)
3	33	28	1.9 (1.0-3.5)	1.8 (0.9-3.8)	2.0 (0.9-4.3)	1.8 (0.8-4.1)	1.9 (0.9-3.8)

Abbreviations: BMI, body mass index; CI, confidence interval; DVT, deep vein thrombosis; N, number; OR, odds ratio; PE, pulmonary embolism; ref, reference group; VT, venous thrombosis.

[a]OR adjusted for age, sex, BMI, and study center.

adjustment for BMI and diabetes.[15] Similar results were reported in the Atherosclerosis Risk In Communities (ARIC) study, which examined adults aged 45 to 64 years.[15,17,18]

In our study, we included a higher proportion of women than men. Previous research shows that incidence rates are higher in women during childbearing years, while incidence rates after 45 years are generally higher in men. However, at old age, this difference appears much less pronounced. In a paper by Naess et al, describing a population from central Norway (the HUNT2-study),[1] it was shown that after the age of 70, the incidence of DVT and PE is similar or even higher in women than in men (eg, the incidence DVT for mean aged 85+: 4.05 [2.59-6.36], for women: 4.73 [3.54-6.31]; the incidence PE for mean aged 85+: 1.49 [0.71-3.13], for women: 2.67 [1.82-3.93]). In line with these numbers, in our study population, we included consecutive patients with VT, which included a slightly larger percentage of women than men.

Our results showed that the levels of all coagulation factors did not differ much between age subgroups, and none of the coagulation factors showed a consistent trend across age in control groups. Most studies describing the age trend in coagulation factor levels consider the age range from 18 to 70 years old. In our data set, we included people aged 70 years and older, and, therefore, we were interested in whether this trend also continued at old age. We did not see a further increase in coagulation factor levels when comparing individuals aged 70 to 75 with those >85, indicating a threshold effect after 70.[24] Nonetheless, the mean coagulation factor levels in controls of our study population are high, which is in accordance with the previously described age increase in younger individuals.

TABLE 6 Association with high coagulation factors FVIII and FIX (coagulation factors dichotomized at P_{75})

Factor VIII	Factor IX	Controls N	Patients N	OR overall[a] (CI 95)
–	–	136	260	1 (ref)
–	+	25	45	1.0 (0.5-1.7)
+	–	97	50	4.2 (2.7-6.4)
+	+	54	51	1.9 (1.1-3.1)

Abbreviations: BMI, body mass index; N, number; OR, odds ratio; ref, reference group; VT, venous thrombosis.

[a]OR adjusted for age, sex, BMI, and study center.

Inherent to a study design in which analyses are restricted to elderly individuals, a potential limitation may be the presence of index event bias. Due to index event bias, some risk factors may seem unrelated to the outcome or risk estimates may even reverse, ie, risk factors may seem protective.[25] This bias could therefore explain the absence of an association between high prothrombin levels and the risk of VT or even the seemingly protective effect. For index event bias to affect the risk estimates, the risk factor of interest should be associated with survival until the age of 70. Furthermore, there should be other risk factors associated with survival until the age of 70, which in turn are also associated with the outcome, ie, VT. The latter is possible, ie, comorbidities associated with mortality as well as the risk of VT. However, the association between high coagulation factors and survival until old age is, if anything, weak, which suggests that index event bias in this study is unlikely. Moreover, the risk estimates for the other procoagulant factors were in the expected direction. As elevated levels of prothrombin have been associated with an increased venous thrombosis risk multiple times, the seemingly protective effect of prothrombin levels in our study is most likely due to chance. In the CHS study, prothrombin levels did not play a role in thrombosis in the elderly, and we therefore come to a similar conclusion, ie, that prothrombin levels were not associated with an increased risk of VT in elderly.

While our observed associations were modest with ORs slightly lower than those reported in young and middle-aged populations, in this age group, the PARs associated with high levels of coagulation factors were not trivial. This is because the absolute risk of VT increases sharply with age, which emphasizes the importance of these risk factors in the elderly population.

Our study has several other limitations. First, 96.2% of the participants were White, so we cannot generalize our findings to other ethnicities. Second, blood samples were obtained after the VT, so it remains a theoretical possibility that coagulation factors were high as a consequence of thrombosis. However, because the blood samples were obtained a year after the VT event, observed associations are unlikely to be due to acute-phase effects. Due to the fact that some patients were using oral anticoagulants during the second home visit, sample size for the analysis of the vitamin K dependent coagulation factors was limited in some subgroup analyses. However, this is unlikely to have affected the results as sensitivity analysis after multiple imputation led to similar results.

The main strength of our study is that it is one of the largest studies on VT risk in the elderly (individuals aged 70 years and older). Recruiting elderly patients can be difficult, but the use of home visits here facilitated participation. Furthermore, we measured multiple coagulation factors, enabling us to directly compare risk estimates and assess the risk of VT associated with multiple high coagulation factors.

Knowledge of the associations between procoagulant factors and the risk of VT in the elderly may guide physicians in identifying high-risk individuals and subsequent targeted prophylactic treatment in those at high risk. It remains difficult to draw conclusions on the causality of the association. Future studies could focus on a broader range of genetic variants that have been associated with levels of coagulation factors in young and middle-aged populations.

In conclusion, this study demonstrates that elevated levels of FVIII, FIX, and FXI, but not prothrombin, are associated with the risk of VT in the elderly.

ACKNOWLEDGMENTS

The authors wish to thank the directors of the anticoagulation clinics of Leiden (F. J. M. van der Meer) and Haarlem (E. van Meegen) who made the recruitment of patients in Leiden and Haarlem possible. We thank the director of the Ultrasound Unit of the Radiology Department at University of Vermont Medical Center (N. Sturtevant) and the study examiner and project coordinator, R. Marin. We thank all the individuals who participated in the AT-AGE study. We thank Saskia le Cessie for her contribution to the statistical analysis. This study was supported by grants from the Netherlands Heart Foundation (grant no: 2009B50) and the Leducq Foundation, Paris, France, for the development of Transatlantic Networks of Excellence in Cardiovascular Research.

CONFLICTS OF INTEREST

The authors state that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

A. van Hylckama Vlieg, F. R. Rosendaal, and M. Cushman contributed to the concept and design of the study. A. van Hylckama Vlieg, M. Cushman, and M. J. Engbers contributed to the data collection. H. Wang, M. Cushman, and A. van Hylckama Vlieg contributed to the analysis and interpretation of data. H. Wang, A. van Hylckama Vlieg, and S. le Cessie contributed to the statistical analysis of the draft. H. Wang and A. van Hylckama Vlieg contributed to the drafting of the manuscript. The manuscript has been read and approved for submission by all authors.

ORCID

Mary Cushman https://orcid.org/0000-0002-7871-6143

TWITTER

Huijie Wang @wang_huijie

REFERENCES

1. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost*. 2007;5(4):692-699.
2. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet*. 1999;353(9159):1167-1173.
3. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. 1998;158(6):585-593.
4. Gillum RF. Pulmonary embolism and thrombophlebitis in the United States, 1970–1985. *Am Heart J*. 1987;114(5):1262-1264.
5. Balleisen L, Bailey J, Epping PH, Schulte H, van de Loo J. Epidemiological study on factor VII, factor VIII and fibrinogen in an industrial population: I. Baseline data on the relation to age, gender, body-weight, smoking, alcohol, pill-using, and menopause. *Thromb Haemost*. 1985;54(2):475-479.
6. Lowe GD, Rumley A, Woodward M, et al. Epidemiology of coagulation factors, inhibitors and activation markers: the Third Glasgow MONICA Survey. I. Illustrative reference ranges by age, sex and hormone use. *Br J Haematol*. 1997;97(4):775-784.
7. Conlan MG, Folsom AR, Finch A, et al. Associations of factor VIII and von Willebrand factor with age, race, sex, and risk factors for atherosclerosis. The Atherosclerosis Risk in Communities (ARIC) Study. *Thromb Haemost*. 1993;70(3):380-385.
8. Sweeney JD, Hoernig LA. Age-dependent effect on the level of factor IX. *Am J Clin Pathol*. 1993;99(6):687-688.
9. Folsom AR, Tang W, Roetker NS, Heckbert SR, Cushman MA, Pankow JS. Prospective study of circulating factor XI and incident venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology (LITE). *Am J Hematol*. 2015;90(11):1047-1051.
10. Cushman M. Epidemiology and risk factors for venous thrombosis. *Semin Hematol*. 2007;44(2):62-69.
11. Debeij J, van Zaane B, Dekkers OM, et al. High levels of procoagulant factors mediate the association between free thyroxine and the risk of venous thrombosis: the MEGA study. *J Thromb Haemost*. 2014;12(6):839-846.
12. Koster T, Vandenbroucke JP, Rosendaal FR, Briët E, Rosendaal FR, Blann AD. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. *Lancet*. 1995;345(8943):152-155.
13. Meijers JC, Tekelenburg WLH, Bouma BN, Bertina RM, Rosendaal FR. High levels of coagulation factor XI as a risk factor for venous thrombosis. *N Engl J Med*. 2000;342(10):696-701.
14. Rosendaal FR. Risk factors for venous thrombotic disease. *Thromb Haemost*. 1999;82(2):610-619.
15. Cushman M, O'Meara ES, Folsom AR, Heckbert SR. Coagulation factors IX through XIII and the risk of future venous thrombosis: the Longitudinal Investigation of Thromboembolism Etiology. *Blood*. 2009;114(14):2878-2883.
16. McMurdo ME, Witham MD, Gillespie ND. Including older people in clinical research. *BMJ*. 2005;331(7524):1036-1037.
17. Tsai AW, Cushman M, Rosamond WD, et al. Coagulation factors, inflammation markers, and venous thromboembolism: the longitudinal investigation of thromboembolism etiology (LITE). *Am J Med*. 2002;113(8):636-642.
18. Folsom AR, Cushman M, Tsai MY, Heckbert SR, Aleksic N. Prospective study of the G20210A polymorphism in the prothrombin gene, plasma prothrombin concentration, and incidence of venous thromboembolism. *Am J Hematol*. 2002;71(4):285-290.
19. Oger E, Lacut K, Van Dreden P, et al. High plasma concentration of factor VIII coagulant is also a risk factor for venous thromboembolism in the elderly. *Haematologica*. 2003;88(4):465-469.
20. Engbers MJ, Blom JW, Cushman M, Rosendaal FR, van Hylckama Vlieg A. The contribution of immobility risk factors to the incidence of venous thrombosis in an older population. *J Thromb Haemost*. 2014;12(3):290-296.
21. Autin L, Miteva MA, Lee WH, Mertens K, Radtke K-P, Villoutreix BO. Molecular models of the procoagulant factor VIIIa-factor IXa complex. *J Thromb Haemost*. 2005;3(9):2044-2056.
22. Vandenbroucke JP, Pearce N. Case–control studies: basic concepts. *Int J Epidemiol*. 2012;41(5):1480-1489.
23. Karasu A, Engbers MJ, Cushman M, Rosendaal FR, van Hylckama Vlieg A. Genetic risk factors for venous thrombosis in the elderly in a case-control study. *J Thromb Haemost*. 2016;14(9):1759-1764.
24. Lijfering WM, Rosendaal FR, Cannegieter SC. Risk factors for venous thrombosis - current understanding from an epidemiological point of view. *Br J Haematol*. 2010;149(6):824-833.
25. Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. *JAMA*. 2011;305(8):822-823.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Wang H, Rosendaal FR, Cushman M, van Hylckama Vlieg A. Procoagulant factor levels and risk of venous thrombosis in the elderly. *J Thromb Haemost*. 2021;19:186–193. https://doi.org/10.1111/jth.15127