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Do factor V Leiden and prothrombin G20210A mutations predict recurrent venous thromboembolism in older patients?

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Running head: Genetic thrombophilia in the elderly with venous thromboembolism

ABSTRACT

Background: The value of genetic thrombophilia testing in elderly patients with an unprovoked venous thromboembolism (VTE) is unclear. We assessed whether the factor V (FV)-Leiden and the prothrombin G20210A mutation are associated with recurrent VTE in elderly patients in a prospective multicenter cohort study.

Methods: We genotyped the factor V Leiden and the prothrombin G20210A mutation in 354 consecutive in- and outpatients aged ≥ 65 years with a first unprovoked venous thromboembolism from nine Swiss hospitals. Patients and managing physicians were blinded to testing results. The outcome was recurrent symptomatic venous thromboembolism during follow-up. We examined the association between the factor V Leiden and the prothrombin G20210A mutation and venous thromboembolism recurrence using competing risk regression, adjusting for age, sex, and periods of anticoagulation as a time-varying covariate.

Results: Overall, 9.0% of patients had a factor V Leiden and 3.7% a prothrombin G20210A mutation. At 36 months of follow-up, patients with a factor V Leiden and a prothrombin G20210A mutation had a cumulative incidence of recurrent venous thromboembolism of 12.9% (95% confidence interval [CI] 5.1-30.8%) and 18.5% (95% CI 4.9-56.5%), respectively, compared to 16.7% (95% CI 12.5-22.1%) of patients without mutation ($P=0.91$ by the log-rank test). After adjustment, neither the factor V Leiden (sub-hazard ratio [SHR] 0.98; 95% CI 0.35-2.77) nor the prothrombin G20210A mutation (SHR 1.15; 95% CI 0.25-5.19) was associated with recurrent venous thromboembolism.

Conclusion: In elderly patients with a first unprovoked VTE, thrombophilic mutations were not associated with an increased risk of recurrent VTE. Our results suggest that testing for genetic thrombophilia may not be beneficial in elderly patients with a first unprovoked venous thromboembolism

BACKGROUND

Genetic thrombophilia, such as the factor V (FV) Leiden and the prothrombin G20210A mutation, are associated with an increased risk for a first venous thromboembolism (VTE) [1, 2]. However, while the association between these mutations and a first VTE is well accepted, it remains controversial whether such mutations also carry a higher risk of recurrent venous thromboembolism. A meta-analysis of prospective studies demonstrated a slightly increased risk of recurrent venous thromboembolism in patients who had a heterozygous FV factor V Leiden (relative risk 1.4, 95% CI 1.1-1.8) or prothrombin G20210A mutation (relative risk 1.7, 95% CI 1.3-2.3) [3].

Although the incidence of venous thromboembolism rises with age and venous thromboembolism carries a worse prognosis in older patients, including a potential 17% increase in recurrent venous thromboembolism per decade [4, 5], prior studies that examined the risk of recurrent venous thromboembolism related to genetic thrombophilia either explicitly excluded elderly patients or enrolled mainly younger individuals (mean age 50-67 years) [3]. Thus, the relationship between genetic thrombophilia and the risk of recurrent venous thromboembolism in elderly patients with unprovoked venous thromboembolism remains unknown. To fill this gap of knowledge, we aimed to evaluate whether the factor V Leiden and prothrombin G20210A mutations are associated with recurrent venous thromboembolism in a prospective multicenter cohort study of elderly patients with a first unprovoked venous thromboembolism.

METHODS

Study design, setting, and participants

This study was conducted between September 2, 2009 and December 6, 2013 as part of the Swiss Venous Thromboembolism Cohort (SWITCO65+), a prospective multicenter cohort study that assessed long-term medical outcomes in elderly patients with acute venous thromboembolism from five university and four high-volume non-university hospitals in Switzerland [6]. Consecutive patients aged ≥ 65 years with an acute, objectively confirmed, symptomatic venous thromboembolism were prospectively identified in the in- and outpatient services of all participating study sites. Symptomatic pulmonary embolism (PE) was defined as a positive spiral computed tomography or pulmonary angiography, a high probability ventilation-perfusion scan, or proximal deep vein thrombosis (DVT) documented by compression ultrasonography or contrast venography in patients with acute chest pain, new or worsening dyspnea, hemoptysis, or syncope. Symptomatic deep vein thrombosis was defined as an acute onset of leg pain or swelling plus incomplete compressibility of a venous segment on ultrasonography or an intraluminal filling defect on contrast venography. The detailed study methods were previously published [6]. The study was approved by the Institutional Review Board at each participating center.

For this study, we included only patients with a first unprovoked venous thromboembolism, defined as venous thromboembolism occurring in the absence of immobilization (fracture or cast of the lower extremity, bed rest >72 hours, or voyage in sitting position for >6 hours), major surgery, oral estrogen therapy, or active cancer (surgery, chemotherapy, radiotherapy, or palliative care) during the last three months.

Baseline data collection and thrombophilia testing

Trained study nurses prospectively collected baseline demographics (age and

sex), comorbid conditions (history of prior venous thromboembolism, major surgery, immobilization, and active cancer), estrogen therapy, and venous thromboembolism - related treatments (low-molecular-weight heparin, unfractionated heparin, fondaparinux, vitamin K antagonists) from all enrolled patients using standardized data collection forms.

DNA was extracted from frozen EDTA whole blood shortly after the index venous thromboembolism event and used for polymerase chain reaction assays of the factor V Leiden (QIAamp DNA Blood Mini QIAcube kit, Qiagen AG®, Switzerland) and prothrombin G20210A mutation (Roche Diagnostics AG®, Switzerland) in a core laboratory. Patients and managing physicians were blinded to the test results.

Outcome

The outcome was the recurrence of an objectively confirmed, symptomatic venous thromboembolism, defined as a fatal or new non-fatal pulmonary embolism or new proximal or distal deep vein thrombosis based on predefined imaging criteria or autopsy findings, as previously described [6]. Follow-up included semi-annual contacts, alternating between face-to-face evaluations (clinic visits or home visits in house-bound patients) and telephone calls as well as periodic reviews of the patient's hospital chart. During each visit/contact, study nurses interviewed patients to obtain information about the date and type of clinical events (recurrent venous thromboembolism, death). If a clinical event had occurred, this information was complemented by reviewing medical charts and interviewing patients' primary care physicians and family members. We also collected international normalized ratio (INR) values throughout follow-up.

An independent committee of three clinical experts blinded to the testing results adjudicated the outcomes and classified the cause of all deaths as definitely

due to pulmonary embolism, possibly due to pulmonary embolism (e.g., sudden death without obvious cause), or due to another cause. Fatal PE was defined as death due to definite or possible PE. Death was judged to be pulmonary embolism-related if confirmed by autopsy, or if death followed a clinically severe pulmonary embolism, either initially or after an objectively confirmed recurrent event. Pulmonary embolism unrelated deaths were the result of an obvious cause other than pulmonary embolism, such as an initially unknown cancer, bleeding, acute coronary syndrome, left ventricular failure, stroke, or other causes (e.g., sepsis, suicide, or accident). Final classification was made on the basis of the full consensus of this committee.

Statistical analyses

We calculated the incidence rates of a first recurrent venous thromboembolism in patients with a factor V Leiden mutation, a prothrombin G20210A mutation, and those without mutations. We compared cumulative incidences of recurrent venous thromboembolism in patients with thrombophilic mutations to those without mutations using Kaplan-Meier curves and the log-rank test. In patients receiving vitamin K antagonists, we also compared the quality of anticoagulation, expressed as the percentage of time within the therapeutic INR range (2.0-3.0), between patients with and without mutations [7]. We examined associations between thrombophilic mutations and the time to a first venous thromboembolism recurrence using competing risk regression according to Fine and Grey, accounting for non-pulmonary embolism-related death as a competing event [8]. The strength of the association is reflected by the sub-hazard ratio (SHR), which is the ratio of hazards associated with the cumulative incidence function in the presence of a competing risk. We adjusted the model for age, sex, and periods of anticoagulation as a time-varying covariate. In our primary analysis, we included the entire follow-up period, regardless of whether

patients were under anticoagulants or not. In a sensitivity analysis, we considered only the observation period after completion of the initial anticoagulant treatment. All analyses were done using Stata 14 (Stata Corporation, College Station, Texas).

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RESULTS

Study sample

Overall, 1003 patients were enrolled in our cohort. We excluded 215 patients with provoked venous thromboembolism, 204 with a history of prior venous thromboembolism, 181 with cancer-related venous thromboembolism, and 8 denying use of their data, leaving 395 patients with a first unprovoked venous thromboembolism. After the exclusion of another 41 patients (40 without genotyping and 1 with early consent withdrawal), our final study sample comprised 354 elderly patients with a first acute unprovoked symptomatic venous thromboembolism. Overall, there was no statistically significant difference in age and sex between analyzed and excluded patients with a first unprovoked venous thromboembolism (data not shown).

Analyzed patients had a median age of 75 years, 46% were women, 257 (73%) had pulmonary embolism ± deep vein thrombosis, 79 (22%) proximal ±distal DVT, and 18 (5%) isolated distal DVT as the initial VTE event. Overall, 32 patients (9.0%) had a factor V Leiden (31 heterozygous, 1 homozygous), 13 (3.7%) a prothrombin G20210A (all heterozygous), and 1 (0.3%) both mutations (both heterozygous). Patients with a prothrombin G20210A mutation were older than patients with a factor V Leiden or no mutation, but otherwise, groups did not differ in terms of patient baseline characteristics (Table 1).

Comparison of recurrent VTE

The median follow-up period was 30 months (interquartile range 24-41 months). Overall, 29 (91%) of patients with a factor V Leiden mutation, 12 (100%) of patients with a prothrombin G20210A mutation, and 273 (88%) of patients without mutations received anticoagulants for >3 months ($P=0.41$). The median duration of

initial anticoagulation was 7.1 months in patients with a factor V Leiden, 20.2 months in patients with a prothrombin G20210A, and 8.2 months in patients without mutations, but the differences did not reach statistical significance ($P=0.07$). In the 342 of 354 patients who received vitamin K antagonists, the percentage of time within the therapeutic INR range (2.0-3.0) did not differ in patients with a factor V Leiden (59%), prothrombin G20210A (67%), and no mutation (67%) ($P=0.23$).

Overall, 54 of 354 patients (15.3%) had recurrent venous thromboembolism during follow-up, resulting in an overall incidence of recurrent VTE of 7.0 (95% confidence interval [CI] 5.3-9.1) events per 100 patient-years. Fifty-six patients (16%) died during follow-up. Of these, 14 (25%) died from pulmonary embolism. No patient with a thrombophilic factor died from pulmonary embolism. At 36 months, the cumulative incidence of VTE was 12.9% (95% CI 5.1-30.8%) in patients with a factor V Leiden, 18.5% (95% CI 4.9-56.5%) in patients with a prothrombin G20210A, and 16.7% (95% CI 12.5-22.1%) in patients without a mutation ($P=0.91$; by the logrank test, see Figure).

Association between thrombophilic mutations and recurrent VTE

After adjustment for age, sex, and periods of anticoagulation as a time-varying covariate, thrombophilic mutations were not associated with recurrent venous thromboembolism, with a SHR of 0.98 (95% CI 0.35-2.77) for the factor V Leiden and 1.15 (95% CI 0.25-5.19) for the prothrombin G20210A mutation (Table 2). When we considered only observation periods after the completion of the initial anticoagulation, the results were similar (Table 2).

DISCUSSION

In this prospective multicenter cohort of elderly patients with a first unprovoked venous thromboembolism, the factor V Leiden and the prothrombin G20210A mutation were not associated with venous thromboembolism recurrence. Prior prospective studies demonstrated that genetic thrombophilia is only a very modest predictor of recurrence (relative risk 1.4 to 1.8) in younger patients with unprovoked venous thromboembolism [3]. Our results confirm that the prognostic impact of genetic thrombophilia is even less relevant in the elderly, possibly, because clinical factors, such as comorbid conditions, may be stronger drivers of venous thromboembolism recurrence than genetic thrombophilic factors [5].

Given the absence of randomized trials, high-quality evidence on the usefulness of genetic thrombophilia testing following unprovoked venous thromboembolism is lacking. In a case-control study, testing for factor V Leiden and prothrombin G20210A mutations in patients with a first venous thromboembolism was not associated with a reduced incidence of recurrent venous thromboembolism [9]. Similarly, testing for genetic thrombophilia did not influence medical management in 77% of tested patients [10]. Evidence suggests that even combined heterozygous or single homozygous factor V Leiden or prothrombin G20210A mutations do not appear to carry a relevant venous thromboembolism recurrence risk [11] and that the venous thromboembolism risk becomes substantial only among the very rare individuals with compound homozygous mutations of these polymorphisms [12].

Given the high costs of testing (approximately \$300) [13] and its presumed lack of benefit, genetic thrombophilia testing is not useful in elderly patients with a first unprovoked venous thromboembolism [14, 15]. Although current guidelines do not support genetic thrombophilia testing for predicting recurrent venous

thromboembolism [14, 16, 17], testing continues to be done in one out of five patients aged more than 50 years with a first unprovoked venous thromboembolism [18].

Our study, to our knowledge the only existing prospective cohort study examining the usefulness of genetic thrombophilia testing in the elderly with unprovoked venous thromboembolism, has several strengths. First, we enrolled patients from university and non-university hospitals, increasing the generalizability of our results. Second, patients and managing physicians were blinded to testing results, which makes a performance bias unlikely. While we cannot entirely rule out the possibility that managing physicians ordered thrombophilia testing outside the study protocol, the comparable anticoagulation durations (with the exception of a somewhat longer anticoagulation duration in patients with a prothrombin G20210A mutation) and quality in patients with and without thrombophilia do not support this possibility. Finally, outcomes were adjudicated by an independent committee blinded to the testing results, decreasing the risk of a detection bias (i.e., higher venous thromboembolism observation rates in patients with thrombophilia).

Our study has also potential limitations. First, our analysis is based on a subsample of a prospective cohort study and we did not perform a formal sample size calculation to answer our research question. While our study may not have sufficient power to detect small associations between thrombophilic mutations and recurrent venous thromboembolism, the point estimates around 1 indicate that even a much larger sample would not have allowed for the detection of a significant association. Besides, our sample size of 354 elderly patients compares well with the sample sizes of similar prospective studies conducted in younger patients with a first unprovoked venous thromboembolism [19, 20]. Second, because the observation period in our primary analysis included also the initial anticoagulation period, the risk of venous thromboembolism recurrence may have been lower than expected.

However, when we considered only observation periods after the completion of the initial anticoagulation in a sensitivity analysis, our results remained similar, confirming the robustness of our findings. Finally, we could not examine whether patients who had completed their initial course of anticoagulation subsequently received aspirin, which could potentially lead to a performance bias.

In conclusion, our results demonstrate that in elderly patients with a first unprovoked venous thromboembolism, genetic thrombophilia is not associated with an increased risk of venous thromboembolism recurrence. Although additional study is needed, our data suggest that testing for genetic thrombophilia may not be beneficial in elderly patients with a first unprovoked VTE.

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Figure Legend**Cumulative incidence of recurrent venous thromboembolism**

The cumulative 36-month incidence of venous thromboembolism was 12.9% (95% confidence interval [CI] 5.1-30.8%) in patients with a factor V Leiden, 18.5% (95% CI 4.9-56.5%) in patients with a prothrombin G20210A, and 16.7% (95% CI 12.5-22.1%) in patients without mutation ($P=0.91$ by the logrank test).

Table 1. Patient baseline characteristics

Characteristic	Factor V Leiden mutation* (N=32)	Prothrombin 20210A mutation (N=12)	No mutation (N=310)	P-value
	Median (IQR) or n (%)			
Age, years	72 (68-77)	78 (72-81)	76 (70-83)	0.04
Age ≥80 years	4 (13)	6 (50)	106 (34)	0.02
Female sex	12 (38)	4 (33)	148 (48)	0.36
Clinical manifestation of venous thromboembolism				
Pulmonary embolism ±deep vein thrombosis	20 (63)	8 (67)	229 (74)	0.51
Proximal ±distal deep vein thrombosis	10 (31)	4 (33)	65 (21)	
Isolated distal deep vein thrombosis	2 (6)	0 (0)	16 (5)	
Initial parenteral anticoagulation†				0.57
Low-molecular-weight heparin	15 (47)	5 (42)	154 (50)	
Unfractionated heparin	6 (19)	4 (33)	89 (29)	
Fondaparinux	10 (31)	3 (25)	55 (18)	
None	1 (3)	0 (0)	12 (4)	
Vitamin K antagonist treatment	31 (97)	12 (100)	299 (96)	0.80

Abbreviations: IQR= interquartile range; VTE= venous thromboembolism; PE= pulmonary embolism; DVT= deep vein thrombosis; AC= anticoagulation.

*1 patient had both a heterozygous FV Leiden and a prothrombin G20210A mutation.

†Percentages may not add up to 100% due to rounding.

Table 2. Association between thrombophilic mutations and recurrent venous thromboembolism

Thrombophilic mutation	Number of events/patients	Unadjusted SHR (95% CI)	Adjusted* SHR (95% CI)
Full observation period			
No mutation	48/310	1 (reference)	1 (reference)
Factor V Leiden†	4/32	0.80 (0.29-2.24)	0.98 (0.35-2.77)
Prothrombin G20210A	2/12	1.21 (0.27-5.47)	1.15 (0.25-5.19)
After initial anticoagulation only			
No mutation	41/190	1 (reference)	1 (reference)
Factor V Leiden†	3/24	0.51 (0.15-1.71)	0.62 (0.19-2.10)
Prothrombin G20210A	0/3	‡	‡

Abbreviations: SHR= sub-hazard ratio; CI= confidence interval.

*Adjusted for age, sex, and periods of anticoagulation as a time-varying covariate.

†Including 1 patient with both a heterozygous FV Leiden and prothrombin G20210A mutation.

‡Not estimable because no patient with a prothrombin G20210A mutation had recurrent VTE after stopping initial anticoagulation.

Figure

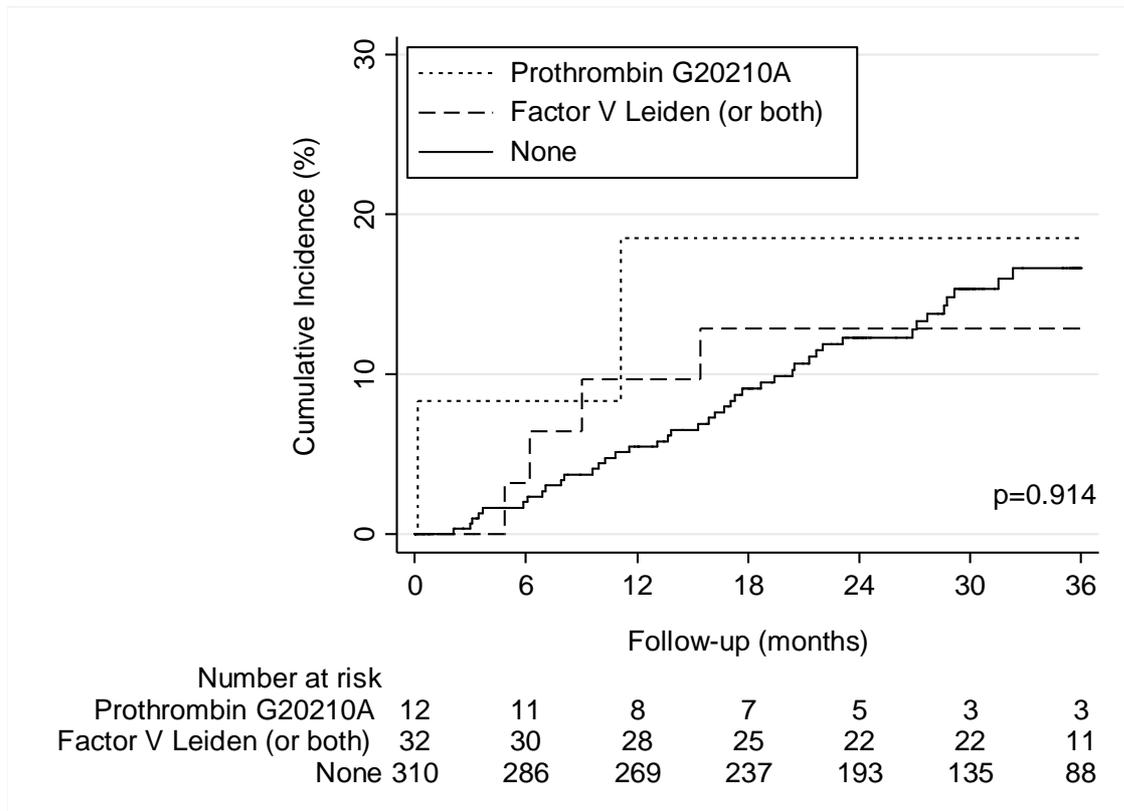


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Isolated distal deep vein thrombosis	2 (6)	0 (0)	16 (5)	
Initial parenteral anticoagulation†				0.57
Low-molecular-weight heparin	15 (47)	5 (42)	154 (50)	
Unfractionated heparin	6 (19)	4 (33)	89 (29)	
Fondaparinux	10 (31)	3 (25)	55 (18)	
None	1 (3)	0 (0)	12 (4)	
Vitamin K antagonist treatment	31 (97)	12 (100)	299 (96)	0.80

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Abbreviations: SHR= sub-hazard ratio; CI= confidence interval.

*Adjusted for age, sex, and periods of anticoagulation as a time-varying covariate.

†Including 1 patient with both a heterozygous FACTOR V Leiden and prothrombin G20210A mutation.

‡Not estimable because no patient with a prothrombin G20210A mutation had recurrent venous thromboembolism after stopping initial anticoagulation.

Clinical significance

- In elderly patients with a first unprovoked venous thromboembolism, the prevalence of Factor V Leiden and prothrombin G20210A mutations was 9.0% and 3.7%, respectively
- These mutations were not associated with long-term venous thromboembolism recurrence
- Costly testing for genetic thrombophilia may not be beneficial in elderly patients with a first unprovoked venous thromboembolism

Clinical significance

- ~~The value of genetic thrombophilia testing in elderly with a first unprovoked venous thromboembolism is unclear~~
- In our prospective cohort of elderly patients with a first unprovoked venous thromboembolism, the prevalence of Factor V Leiden and prothrombin G20210A mutations was 9.0% and 3.7%, respectively
- ~~We found no association between~~ These mutations were not associated with long-term venous thromboembolism recurrence
- ~~and~~ long-term venous thromboembolism recurrence
- Costly testing for genetic thrombophilia is unlikely to carry any benefit in elderly patients with a first unprovoked VTE may not be beneficial in elderly patients with a first unprovoked venous thromboembolism

FIGURE**Cumulative incidence of recurrent venous thromboembolism**

The cumulative 36-month incidence of venous thromboembolism was 12.9% (95% confidence interval [CI] 5.1-30.8%) in patients with a factor V Leiden, 18.5% (95% CI 4.9-56.5%) in patients with a prothrombin G20210A, and 16.7% (95% CI 12.5-22.1%) in patients without mutation ($P=0.91$ by the logrank test).

