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Do hospital doctors test for thrombophilia in patients with venous thromboembolism?

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Abstract
The predictive value of factor V Leiden and the G20210A prothrombin mutation regarding recurrent venous thromboembolism (VTE) is limited and does not influence subsequent patient management. Systematic testing for such genetic thrombophilia should be avoided, but to which extent such testing is practiced in a Swiss Hospital is unknown. To examine the current practice of factor V Leiden and/or G20210A prothrombin mutation testing in a University Hospital, and to assess the clinical consequences of testing on patients. 1388 adult patients (48.7% women) with a main diagnosis of VTE hospitalized at the Lausanne university hospital between January 2013 and December 2015. FV Leiden and/or prothrombin G20210A mutation testing was performed in 61 (4.4%) patients with VTE, an average of 20 patients/year. On multivariable analysis, age <65 years [odds ratio and (95% confidence interval) 5.91 (3.12–11.19)], being admitted in a medical ward [5.71 (2.02–16.16)] and staying in the intensive care unit [0.34 (0.12–0.97)] were associated with thrombophilia testing. No differences were found between patients with and without testing regarding in-hospital mortality [OR and 95% CI for tested vs. non-tested: 0.23 (0.03–1.73), $p=0.153$] and length of stay (multivariable adjusted average $\pm$ standard error: 16.9 ± 3.3 vs. 20.0 ± 0.7 days for tested and non-tested patients, respectively, $p=0.875$). Thrombophilia testing in hospitalized patients with a main diagnosis of VTE is seldom performed. FV Leiden and/or prothrombin G20210A mutation should not be routinely assessed in patients with acute VTE.

Keywords Venous thromboembolism · Thrombophilia testing · Hospital data · Length of stay · In-hospital mortality

Highlights

- The frequency of testing for the two most common heritable causes of thrombophilia (FV Leiden and/or prothrombin G20210A) in patients with history of VTE admitted to a Swiss University Hospital is 4.4%
- Testing is seldom prescribed and does not impact length of stay or initial (in-hospital) management of VTE
- FV Leiden and/or prothrombin G20210A mutation should not be routinely assessed in patients with acute VTE

Introduction

Genetic thrombophilia, such as factor V (FV) Leiden and prothrombin G20210A mutations, are associated with an increased risk for a first venous thromboembolism (VTE)

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[1, 2]. Whether such mutations also carry a higher risk of recurrent VTE remains controversial.

Thus, testing for genetic thrombophilia in patients with VTE is debated, and data supporting the clinical benefits of testing are limited [3, 4]. No randomized trial has ever assessed the benefit of testing for thrombophilic risk factors to prevent a recurrent VTE [5]. Several studies have shown that VTE recurrence risk does not differ between tested and non-tested patients [6, 7], and between patients with and without thrombophilia [6]. A recent review article concluded that only a minority of patients with VTE should be tested for thrombophilia [8]. Current guidelines also recommend that duration of anticoagulant therapy in patients with VTE should not be based on the results of thrombophilia testing [9, 10]. Furthermore, testing results are often misinterpreted, as adequate conditions for testing are often not met [8]. Patients tested positive are regularly over-anticoagulated, even when a causal condition is present [8]. Conversely, patients tested negative may be falsely reassured that they have a low risk of recurrent VTE [11, 12].

Because the predictive value of factor V Leiden and the G20210A prothrombin mutation regarding recurrent VTE is limited and does not influence subsequent patient management, in-hospital testing should be avoided. Still, to which extent Swiss Hospital doctors prescribe such tests is currently unknown. In this study, we aimed to examine the current practice of factor V Leiden and/or G20210A prothrombin mutation testing in a Swiss University Hospital, and to assess the clinical consequences of testing on patients.

Methods

Setting and sampling

The study was conducted in the Lausanne University Hospital (CHUV), one of the five medical teaching hospitals in Switzerland. The CHUV has over 1400 beds and performs over 45,000 hospitalizations per year (http://www.chuv.ch). The CHUV has no practice guidelines regarding thrombophilia testing.

For this study, the target population was all adult (≥ 18 years) patients hospitalized between January 2013 and December 2015. If a patient was hospitalized several times for VTE, only the first hospitalization was included. Patients were eligible if they had a main *International Statistical Classification of Disease, 10th revision* (ICD-10) code of deep vein thrombosis or pulmonary embolism at discharge, in accordance with previous studies [13]. ICD-10 codes related to thrombosis (I80.1, I80.2, I80.20, I80.28, I80.3, I82.2, O22.3, O87.1) and embolism (I26.0, I26.9, O88.2, O88.20, O88.28) were considered.

Patients were excluded if (1) they had a thrombosis at a different site than lower limb and (2) did not provide informed consent to use their medical data (40% in 2014). Reasons for exclusion are summarized in Fig. 1. Data was extracted from hospital electronic files by a dedicated team using the inclusion criteria defined previously and was anonymized before being provided to the investigators. Due to regulatory constraints, it was not possible to assess how many patients were excluded.

Covariates

Socio-demographic data included age; gender; marital status (single/married or cohabitating/divorced/widowed); nationality (Swiss/non-Swiss); coming from home (versus nursing home); type of ward (medical, surgical, intensive care unit) and private health insurance (yes/no). We hypothesized that there may be implicit bias in doctors' decision making depending on socio-demographic factors.

Previous studies reported an association between thrombophilia and stroke [14–16]. Also, pulmonary hypertension is a potential complication of pulmonary embolism [17, 18] and thrombophilia has been associated with higher risk of miscarriage [19]. Thus, we also considered the following secondary diagnoses: stroke (ICD-10 codes I63, I67.82, I65, I66); pulmonary hypertension (ICD-10 code I27.2) and miscarriage (ICD-10 code 003).

Clinical outcomes

To assess the clinical consequences of thrombophilia testing, we collected the length of hospital stay for the patients discharged alive and in-hospital mortality. Data regarding a

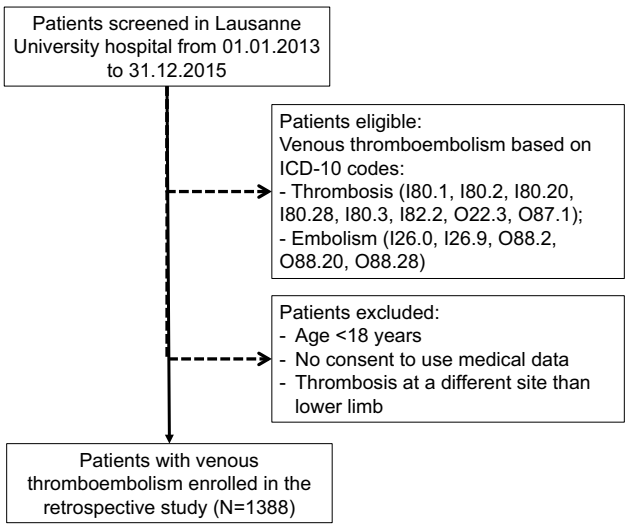

Fig. 1 Selection procedure

stay in the intensive care unit (yes/no) was also collected, regardless of the type of ward at admission.

Ethical statement

This study was approved by the Ethics Commission of Canton Vaud (http://www.cer-vd.ch) on 28th of June 2016 (reference 2016-01024). The study was performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. Only information from participants who consented that their medical data be used for medical research was used.

Statistical analysis

Statistical analyses were performed using Stata version 15.0 for windows (Stata Corp, College Station, Texas, USA). Descriptive results were expressed as number of participants (percentage) for categorical variables and as average ± standard deviation or median and [interquartile range] for continuous variables. Bivariate analyses were performed using Chi square or Fisher's exact test for qualitative variables and student's *t* test, analysis of variance or Kruskall–Wallis test for quantitative variables. Multivariable analysis for categorical variables was performed using logistic regression and the results were expressed as multivariable-adjusted odd ratio (OR) and 95% confidence interval (CI). Multivariable analysis for continuous variables was performed by analysis of variance and the results were expressed as multivariable-adjusted average ± standard error. Given the skewed distribution of length of stay, values were log-transformed prior to analysis. Multivariable models were adjusted on age (< 65/≥65 years); gender; marital status (single/married or cohabitating/divorced/widowed); nationality (Swiss/non-Swiss); coming from home (vs. nursing home); private health insurance (yes/no); ICU stay (yes/no) and type of ward (medical/surgical). Due to the strong association between ICU stay and intensive care ward, multivariable analyses had to be conducted after excluding participants admitted in the intensive care ward (n = 38). Due to the fact that factors associated with the presence of an inherited thrombophilia include VTE at a young age, often considered to be < 40–50 years of age, we performed a second multivariable analysis by age group (< 45, 45–64, ≥ 65). Statistical significance was assessed for a two-sided test with $p < 0.05$.

Results

Overall, 1388 adults with a main diagnosis of VTE were included (mean age 67.4 ± 17.2 years, 48.7% female), 122 (8.8%) died during hospital stay and the median length of stay was 11.9 days (interquartile range [4.8–24.0]).

Prevalence and determinants of FV Leiden and/or prothrombin G20210A testing

During the study period, FV Leiden and/or prothrombin G20210A mutation testing was performed in 61 (4.4%) patients. Among the 61 tested patients, 6 (9.8%) had a positive test (simple heterozygous status). Bivariate comparisons between tested and untested patients are summarized in Table 1. Tested patients were 12 years younger on average than untested ones and were more often hospitalized in a medical ward at admission. In our sample of patients with VTE, testing was not performed among patients with a secondary diagnosis of stroke, pulmonary hypertension, or miscarriage.

Multivariable analysis showed younger age and being admitted in a medical ward to be positively associated and staying in the intensive care unit to be negatively associated with thrombophilia testing (Table 2a). A second multivariable analysis by age group (< 45, 45–64, ≥ 65) confirmed the positive association between younger age and thrombophilia testing (Table 2b). The younger the patient was, the more likely he was to be tested.

Table 1 Characteristics of hospitalizations according to testing for FV Leiden and/or prothrombin G20210A mutation, Lausanne University Hospital, 2013–2014

	No (N = 1327)	Yes (N = 61)	P-value
Age (years)	67.9 ± 17.1	56.4 ± 16.3	< 0.001
Age < 65 years (%)	483 (36.4)	42 (68.9)	< 0.001
Female gender (%)	643 (48.5)	33 (54.1)	0.389
Living alone (%)	705 (53.1)	29 (47.5)	0.393
Swiss national (%)	1011 (76.2)	49 (80.3)	0.457
Coming from home (%)	1085 (81.2)	44 (72.1)	0.059
Private insurance (%)	135 (10.2)	10 (16.4)	0.120
Ward at admission			< 0.001
Medical (%)	892 (67.2)	47 (77.0)	
Surgical (%)	407 (30.7)	4 (6.6)	
Intensive care (%)	28 (2.1)	10 (16.4)	
Secondary diagnosis of			
Stroke (%)	42 (3.2)	0	0.158 §
Pulmonary hypertension (%)	20 (1.5)	0	0.334 §
Miscarriage (%)	1 (0.1)	0	0.830 §
Intensive care unit stay (%)	265 (20.0)	14 (23.0)	0.570

Results are expressed as number of participants (percentage) for categorical data or as average ± standard deviation for continuous variables. Between-group comparisons using Chi square or Fisher's exact test (§) for qualitative variables and student's test for continuous variables

Table 2 Multivariable analysis of the factors associated with testing for FV Leiden and/or prothrombin G20210A mutation, Lausanne University Hospital, 2013–2014

	Odd ratio and (95% CI)	P-value
(a)		
Age < 65 versus ≥ 65 years	5.91 [3.12–11.19]	< 0.001
Female versus male gender	0.96 [0.54–1.73]	0.903
Living alone versus in couple	0.83 [0.46–1.49]	0.530
Swiss national versus other	1.79 [0.85–3.76]	0.123
Coming from home versus other locations	0.51 [0.25–1.01]	0.054
Private insurance versus other	2.10 [0.92–4.82]	0.080
Medical ward at admission versus surgical	5.71 [2.02–16.16]	0.001
Intensive care unit stay (yes vs. no)	0.34 [0.12–0.97]	0.043
(b)		
Age group		
≥ 65	1 (reference)	
45–64	4.65 (2.32–9.32)	< 0.001
< 45	10.33 (4.61–23.15)	< 0.001
Female versus male gender	0.90 (0.50–1.63)	0.740
Living alone versus in couple	0.75 (0.41–1.37)	0.354
Swiss national versus other	2.12 (0.98–4.59)	0.055
Coming from home versus other locations	0.50 (0.25–1.02)	0.056
Private insurance versus other	2.09 (0.91–4.79)	0.080
Medical ward at admission versus surgical	6.30 (2.21–17.94)	0.001
Intensive care unit stay (yes vs. no)	0.32 (0.11–0.94)	0.037

Results are expressed as odd ratio (95% CI). Statistical analysis performed using logistic regression including all variables of the table in the model. Due to the strong association between intensive care unit stay and intensive care ward, analysis was conducted after excluding participants admitted in the intensive care ward (n = 38)

CI confidence interval

Clinical consequences of in-hospital testing

In the bivariate analysis, in-hospital mortality was significantly lower for patients with testing compared to those without testing (1.6 vs. 9.0%, respectively, p = 0.044), while no differences were found regarding length of stay [median and (interquartile range) 8.1 (4.5–14.7) vs. 12.2 (4.8–24.4) days, p = 0.096].

Multivariable analysis confirmed the lack of association for length of stay (multivariable adjusted average ± standard error: 16.9 ± 3.3 vs. 20.0 ± 0.7 days for tested and non-tested patients, respectively, p = 0.875). Also, no association was found with mortality [OR and 95% CI for tested vs. non-tested: 0.23 (0.03–1.73), p = 0.153].

Discussion

This study established the frequency of testing for the two most common heritable causes of thrombophilia in patients with VTE. Our results show that testing is seldom prescribed and does not impact length of stay or initial (in-hospital) management of VTE.

Current evidence indicates that testing for FV Leiden and/or prothrombin G20210A mutation is generally *not* recommended in patients after VTE [6], unless specific risk factors being identified [20]. An algorithm for selecting patients for thrombophilia testing has been proposed [8], it has not been yet included in the latest US [9] or British [21] guidelines. Also, the American Society of Hematology recommended not to test for thrombophilia in adults with VTE who have major transient risk factors [22].

In this study, only 20 FV Leiden and/or prothrombin G20210A mutation tests were performed per year, corresponding to approximately 1.5% of the patients with VTE admitted to the Lausanne University hospital. In most cases, thrombophilia testing seemed to comply with guidelines, which recommend to test only a minority of patients [9, 10, 20]. Our findings differ from results from previous retrospective studies [3, 23], which reported that testing for thrombophilia is widespread and that only few tested patients have an indication for testing. However, study methods were different, making comparison difficult.

Factors associated with thrombophilia testing

Genetic testing was more prescribed to younger patients, a finding in agreement with a systematic review [24]. Possible explanations include the fact that factors associated with the presence of an inherited thrombophilia include VTE at a young age [8] and a trend for more aggressive care for younger people [24].

Being admitted in a medical ward was positively associated with thrombophilia testing. This finding agrees with a previous study showing that testing is most commonly requested by internists [3]. A possible explanation is that patients hospitalized in medical wards present more often with idiopathic VTE events, whereas VTE events in surgical wards are more frequently attributed to the surgery.

Staying in the intensive care unit was negatively associated with thrombophilia testing. A possible explanation is that management of critically ill patients focuses on support of vital functions rather to detailed investigations.

Clinical consequence of in-hospital testing

No significant differences were found between patients tested or non-tested regarding length of stay or mortality. Our findings are in agreement with the literature [3, 4, 8], highlighting the importance of selecting the appropriate patients to test (i.e., younger patients).

Strengths and limitations

As far as we know, this is one of the few European studies examining the current hospital practice regarding FV Leiden and/or prothrombin G20210A mutation.

This study also has some limitations. Firstly, as we had no information regarding the aetiology of the VTE, we could not confirm the hypothesis that patients hospitalized in the medical ward were more often tested because they had more often idiopathic VTE events. Secondly, we could not investigate the rate of patients with anticoagulant treatment at discharge because ICD-10 code Z79.01 were not reported on our hospital electronic files. Thirdly, as our findings are based on data from a University hospital, they do not forcibly reflect testing practice in non-academic hospitals or in private practice. Finally, VTE patients were selected retrospectively based on ICD-10 codes rather than on clinical assessment using a prospective approach. Hence, some unreported VTE cases might have been missed. Still, it has been shown that ICD-10 codes yield a satisfactory sensitivity for identifying venous thromboembolism [13].

Conclusion

At our teaching hospital, thrombophilia testing in hospitalized patients with a main diagnosis of VTE is seldom performed. FV Leiden and/or prothrombin G20210A mutation should not be routinely assessed in patients after VTE, unless specific risk factors being identified.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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