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Adherence to thrombophilia testing guidelines and its influence on anticoagulation therapy: A single-center cross-sectional study

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ABSTRACT

Introduction: The collected evidence on thrombophilia guidelines is scarce and data about their impact on clinical decisions are unknown. We aimed to investigate the adherence to thrombophilia testing guidelines, its therapeutic impact in patients with guideline-adherent and non-adherent testing and identify the patients' clinical characteristics mostly associated with treatment decisions.

Materials and methods: We conducted a single-center cross-sectional study of patients referred for thrombophilia testing at the outpatient clinic of a tertiary hospital between 01/2010–10/2020. We systematically evaluated the adherence of thrombophilia testing to internal guidelines and the influence of test results on anticoagulation therapy. Using multivariable logistic regression, we evaluated the association between clinical characteristics and influence of thrombophilia tests on anticoagulation therapy in the entire cohort and by indication for referral.

Results: Of 3686 included patients, mostly referred for venous thromboembolism (2407, 65 %) or arterial thrombosis (591, 16 %), 3550 patients (96 %) underwent thrombophilia testing. Indication for testing was according to guidelines in 1208 patients (33 %). Test results influenced treatment decisions in 56 of 1102 work-ups (5.1 %) that were adherent to guidelines, and in 237 of 2448 (9.7 %) non-adherent work-ups (absolute difference, 4.3 %; 95 % confidence interval, 2.9–6.3 %). Age < 50 years, female sex, absence of risk factors and comorbidities, weakly provoked venous thromboembolism and referral indication other than venous thromboembolism were associated with influence on anticoagulation therapy.

Conclusions: Adherence to guidelines for thrombophilia testing was poor and did not have an impact on treatment decisions. Refinement of selection criteria is needed to increase the therapeutic impact of thrombophilia testing.

1. Introduction

The clinical utility of testing for hereditary and acquired thrombophilia and the best selection criteria for testing remain uncertain. Because confirmation of high-risk thrombophilia influences treatment decisions to a bigger extent than confirmation of low-risk thrombophilia, identification of these patients is essential to obtain a high therapeutic yield of thrombophilia testing [1]. Due to changing practice over time and inconsistent recommendations in current guidelines [2,3], the adherence to guidelines in clinical practice is variable [4,5].

Baglin et al. reported the first clinical guidelines to test for thrombophilia, suggesting no role of unselected thrombophilia testing and discussing the role of testing in patients with a strong positive family history for venous thromboembolism (VTE) or recurrent VTE [6].

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Subsequent guidelines proposed even more restrictive selection criteria suggesting a very limited role of testing in persons without prior VTE and in patients with pregnancy-related morbidity [7–15]. Guidance for thrombophilia in patients with arterial thrombosis is even more sparse [12,16].

The adherence to thrombophilia testing guidelines is low in acute hospital care and disciplines other than hematology [4,17–19]. Better adherence was shown for hematologists in a small retrospective study [20]. Previous studies mainly focus on adherence for thrombophilia testing in patients with VTE [4,17], whereas studies of patients with arterial thrombosis or pregnancy-related morbidity, and asymptomatic persons with a family history of VTE are lacking.

Therefore, we aimed to evaluate the adherence to thrombophilia testing guidelines for any type of indications, the influence of test results on subsequent guideline-recommended treatment decisions according to guideline adherence and investigate the patients' characteristics mostly associated with further anticoagulation treatment after the thrombophilia work-up in a cross-sectional study of patients referred to a tertiary thrombophilia center.

2. Materials and methods

2.1. Study design

This cross-sectional study was conducted at the Department of Hematology of the Bern University Hospital in Switzerland. We included consecutive patients who were referred for testing of hereditary and/or acquired thrombophilia by general practitioners or non-hematologist medical specialists between January 2010 and October 2020. Patients medical records were systematically queried in the hospital database system with the support of the hospital data management service using specific internal codes for thrombophilia work-up. Patients were included if they had provided a general consent and a documented history of objectively confirmed VTE and/or arterial thrombosis in any location, a history of pregnancy-related morbidity or were referred for thrombophilia testing due to a positive family history for VTE or hereditary thrombophilia. The study was approved by the Ethics Commission of the Canton of Bern (ID 2019-02102).

Standard imaging techniques were applied to diagnose a venous or arterial event [21–28]. Pregnancy-related morbidities were defined as pregnancy loss at all gestational ages, placenta failure, preeclampsia [28] and HELLP syndrome (hemolysis, elevated liver enzyme levels, low platelet count) according to diagnostic criteria of obstetricians and gynecologists [29]. Categorization as minor and major provoking risk factors of VTE was based on criteria provided by the International Society on Thrombosis and Haemostasis (ISTH) [30]. In addition to the ISTH based criteria, the presence of intravenous catheter [31] or May-Thurner syndrome (>70 % iliofemoral compression) [32] were categorized as major risk factors, whereas immobilization >4 h [33] and heavy smoking (>20 pack years) [34] as minor risk factors. VTE in the presence of merely an environmental risk factor (male sex and older age) was categorized as unprovoked thromboembolism.

Objective clinical data were retrospectively collected from structured electronic forms using a standardized case report form and entered in a computerized database (REDCap software) by two persons. In case of a disagreement, a third person was included to reconcile. Data comprised demographic characteristics of patients (age, sex) and their family history for VTE in first- and second-degree relative, details of all previous thrombotic events or pregnancy-related morbidity (date and location), risk factors of most recent VTE and arterial thrombosis (heavy smoking [>20 pack years], immobilization >4 h, infections requiring bedrest >3 days, estrogen-based medications, pregnancy and peripartum period, intravenous catheters, active cancer, obesity [body mass index (BMI) > 30 kg m^{-2}], trauma, surgery, cancer medication, presence of extensive varicose veins, patent foramen ovale or other septal defect) and co-morbidities (diabetes mellitus, arterial hypertension, liver cirrhosis, kidney failure, rheumatic disease, depression, chronic inflammatory disease, dyslipidemia, cardiovascular diseases, pulmonary diseases, neurological diseases).

2.2. Thrombophilia testing

Thrombophilia testing was performed standardly between 3 and 6 months following the index event after the evaluation of the patient by a hematologist taking into consideration age, risk factors, family history of VTE, co-morbidities and type of thromboembolism or pregnancy-related morbidity. A thrombophilia work-up was considered as "performed", if one or more of the following thrombophilia parameters were tested: factor V Leiden (FVL) mutation status, prothrombin gene G20210A polymorphism status, protein C (PC) and S (PS) as well as antithrombin (AT) levels, lupus anticoagulant (LA), anticardiolipin antibodies, or anti-β2-glycoprotein I antibodies, which were usually ordered as a standard panel.

Testing for PC (Protein C Berichrom®, Siemens; Protein C COAG, Siemens), PS (Free protein S, Asserachrom®, Diagnostica Stago from 2010 to 2015; Free Protein S Antigen, Innovance®, Siemens from 2015 to 2020), AT activity (LR Antithrombin, Coamatic®, Diapharma from 2010 to 2013; LRT Antithrombin, Biophen®, Endotell from 2013 to 2014 and Antithrombin Innovance®, Siemens from 2014 to 2020) was performed in the routine hemostasis laboratory (Bern University Hospital) and values below 70 %, 59 % and 69 % were considered as AT, PC and PS deficiencies, respectively. Antiphospholipid antibodies were tested using Varelisa diagnostic kits (Phadia®, ThermoFisher) from 2010 to 2014, fluorescence enzyme immunoassay (Phadia® 250, ThermoFisher) from 2014 to 2015 and automated chemiluminescence assay (Bio-flash®, Inova Diagnostics) from 2015 to 2020 and dilute Russell's viper venom time (Cryocheck®, Endotell). The diagnosis of an antiphospholipid antibody syndrome was established by persistent laboratory evidence of antiphospholipid antibodies at least 12 weeks later and presence of VTE, arterial thrombosis or criteria pregnancy-related morbidity [35]. Genetic mutations were detected by polymerase chain reaction method (FVL and Prothrombin, RealFast Assay®, Vienna Lab Diagnostics).

2.3. Adherence to guidelines and accuracy

Two persons working in the field of hematology evaluated the adherence to testing guidelines separately in all study participants in accordance to institutional recommendations, which were implemented at the center in 2014 and are fully or partially based on international guidance of British Society for Hematology [6,36,39], American Society of Hematology [9], International Consensus Statement [15], The National Institute for Health and Care Excellence (NICE) [7], Anticoagulation Forum of North America [11], European Society of Cardiology [14] and American College of Obstetricians and Gynecologists (ACOG) [37] (Table 1). The 2020 NICE guidelines for VTE [38] were not considered in determining the selection criteria, because they were published after initiation of the study. If study criteria in Table 1 were not met, thrombophilia testing was considered as not adherent to guidelines.

Measurement of PC and PS whilst on vitamin K antagonists or liver disease (Child-Pugh-Score B and C), PS in puerperium time or during estrogen-based treatment or thrombophilia work-up for PC, PS and AT in the acute phase (within 3 months of index event) was considered inaccurate [11] and classified as a negative result.

2.4. Influence of thrombophilia testing on treatment decisions

For the entire study period, the thrombophilia center at the Bern University Hospital used a structured report form to document thrombophilia testing and subsequent treatment decisions including a description of diagnosis, thrombophilia test results, risk factors, therapy

Table 1
Comparison of international thrombophilia testing guidelines and criteria used in this study.

Guidance / Testing indication	BCSH 2010 [6] and 2012 [37, 40]	ASH 2013 [9] and 2021 [16]	NICE 2012 [7]	ISC 2013 [15]	ACF 2016 [11]	ESC 2019 [14]	ACOG 2018 [38]	Study criteria
Hereditary thrombophilia								
VTE in common locations	All patients with strong family history in first-degree relative for unprovoked and recurrent VTE	All patients with strong family history in first-degree relative VTE or VTE provoked by estrogen-based treatment	Patients with unprovoked VTE and positive family history for VTE in first-degree relative	Patients <60 y. with unprovoked or weakly provoked VTE (estrogen-based treatment), and recurrent VTE	All patients with unprovoked VTE, if a patient wants to stop anticoagulation treatment or has a high-bleeding risk	Patients <50 y. with unprovoked VTE, especially with a strong family history for VTE	All woman with weakly or strongly provoked VTE, if estrogen-based treatment or pregnancy is planned	Patients <50 y. with unprovoked VTE or provoked with minor persistent risk factor (obesity, smoking) or co-morbidity (chronic inflammatory disease)
VTE in uncommon locations	No testing	-	-	All patients <50 y.	-	-	-	No testing
Unexplained arterial thromboembolism	-	Patients <50 y., especially with positive family history for thromboembolism in first-degree relative	-	-	-	-	-	Patients < 50 y. in presence of a cardiac septal defect
Pregnancy-related morbidity	-	-	-	-	-	-	No testing	No testing
Asymptomatic patients	-	-	No testing	Woman <50 y. with a family history for VTE in first-degree relative	Women <40 y. with a family history for VTE and thrombophilia in a first-degree relative	-	Women with a family history for high-risk inherited thrombophilia in a first-degree relative	Women <40 y. with a family history for VTE or hereditary thrombophilia in a first-degree relative
Antiphospholipid antibody syndrome								
VTE in common locations	All unprovoked VTE	-	All patients	-	-	-	-	All patients with unprovoked or minor risk factor provoked VTE
VTE in uncommon locations	All patients	-	-	-	-	-	-	All patients
Unexplained arterial thromboembolism	All patients <50 y.	-	-	-	-	-	-	All patients
Pregnancy-related morbidity	All patients	-	-	-	-	-	All patients	All patients
Asymptomatic patients	-	-	-	-	-	-	-	No testing

Red indicates no role of thrombophilia testing; green indicates unselective testing; blue indicates only selective testing; grey indicates no statement. Abbreviations: ACF, Anticoagulation Forum; ACOG, The American College of Obstetricians and Gynecologists; ASH, The American Society of Hematology; BCSH, The British Society of Hematology; ESC, The European Society of Cardiology; ISC, International Consensus Statement; NICE, The National Institute for Health and Care Excellence; y., years; VTE, venous thromboembolism.

decision, and discussion. Based on this report, an experienced hematologist determined for each patient whether decision on the length of anticoagulation treatment and initiation or stopping the prophylactic or therapeutic anticoagulation were based on the thrombophilia test results or merely on clinical aspects. This decision was based on international guidelines, discussing both aspects of clinical-decision making [11,16,37,40] (Table 2). For the purpose of this study, exclusively thrombophilia testing-based treatment decisions regarding prophylactic and therapeutic anticoagulation treatment were considered, excluding other related advices, such as avoidance of estrogen-based treatment, the change of the type of anticoagulant or life style modification.

2.5. Statistical analysis

Continuous and categorical variables were compared using unpaired ANOVA test and χ^2 test, respectively. The associations between clinical characteristics and treatment influence was evaluated using univariable and multivariable logistic regression models in the entire cohort and in subgroup analysis by indication for referral (i.e., patients with VTE, arterial thrombosis, or pregnancy-related morbidity, or asymptomatic persons with family history of VTE). We adjusted the logistic regression models for recurrent VTE and arterial thrombosis in the analysis including the entire study cohort; recurrent and unprovoked VTE in the analysis including only patients with VTE; age $>$ 50 years and presence of $\geq$2 thrombotic risk factors in the analysis including only patients with arterial thrombosis; family history of VTE in a first-degree relative and female sex in the analysis including only asymptomatic patients; and family history of VTE in a first-degree relative and presence of $\geq$2 thrombotic risk factors in the analysis including only pregnancy-related morbidity. Only complete case analysis was performed, without an attempt to replace missing values with imputation methods. A p-value $<$ 0.05 was considered statistically significant. All analyses were performed with R, version 4.1.1, and figures were edited with GraphPad Prism, version 9.1.2.

Table 2
Classification of thrombophilia result influence on treatment decisions.

No influence on management	Anticoagulation therapy or prophylaxis should have been initiated or stopped, continued or discontinued irrespective of thrombophilia testing result based on: • Type of thromboembolic event (i.e., extended anticoagulation in unprovoked or recurrent venous thromboembolism, short-term anticoagulation in provoked venous thromboembolism). • Family or personal history for venous thromboembolism (i.e., prophylactic anticoagulation in risk situations).
Influence on management	Decision to continue, stop or initiate prophylactic or therapeutic anticoagulation was based/should have been based on a thrombophilia testing result • Prolonged anticoagulation in provoked venous thromboembolism or arterial thrombosis due to high-risk thrombophilia. • Prophylactic anticoagulation in risk situations in asymptomatic family members or pregnancy-related morbidity merely due to a positive thrombophilia result. • Termination of anticoagulation in case of a negative thrombophilia work-up result

3. Results

3.1. Study population and prevalence of thrombophilia

A total of 5064 patients were screened for eligibility, of which we excluded 1356 patients due to lack of general consent and 22 persons because VTE, arterial thrombosis or pregnancy-related morbidity was not objectively confirmed, leaving a final study sample of 3686 participants.

Patient characteristics at the time of thrombophilia work-up are shown in Table 3. Overall, 2218 patients (60 %) were women and median age was 44 years (standard deviation, ±16). Most patients were referred for VTE (2407 patients, 65 %), mainly DVT and/or PE (1840/2407 patients, 76 %), or unexplained arterial thrombosis (591 patients, 16 %), mainly stroke (446/591 patients, 75 %) (Supplementary Table 1). A total of 567 participants (15 %) had no prior thromboembolic event or pregnancy-related morbidity, but a positive family history for VTE in first-degree (341/567 persons, 60 %) or second-degree (165/567 persons, 29 %) family members. Few referrals were for pregnancy-related morbidity (121 patients, 3.3 %). Most patients (56 %) had no documented co-morbidity and about a third of patients no documented risk factor for thromboembolism (Table 3).

A total of 1756 patients (48 %) were referred to the thrombophilia center up to 2014 and 1930 (52 %) from 2014 to 2020. In 3550 patients (96 %) a partial or full thrombophilia work-up was performed (in 97 % of referred patients before 2014 and 96 % from 2014 to 2020). Female patients, asymptomatic patients, or patients with VTE provoked by a major risk factor were less likely to be tested (Supplementary Table 2). A total of 1260 thrombophilias were found in 1192 (34 %) patients. The most common type of hereditary thrombophilia was heterozygous FVL mutation (714 patients, 20 %), followed by heterozygous prothrombin G20210A mutation (193 patients, 5 %) and antiphospholipid antibody syndrome (119 patients, 3 %) (Table 4).

3.2. Adherence to testing recommendations and accuracy of the work-up

In 1208 patients (33 %) the indication for thrombophilia testing was adherent to guidelines (32 % from 2010 to 2014, 34 % from 2014 to 2020). Adherence was more likely in younger patients, women, patients without risk factors or co-morbidities, and those with recurrent VTE or a positive family history of VTE in first-degree relatives (Table 3). Non-adherence was more likely in patients with arterial thrombosis or VTE in uncommon locations (Supplementary Table 1). Overall, patients with guideline-adherent testing were more likely to be tested positive for any thrombophilia (Table 3). However, this association was limited to patients with heterozygous and homozygous FVL mutation and PS deficiency (Table 4). A total of 3325/3550 thrombophilia work-ups (94 %) were accurate, whereas 79 (2 %) were performed, whilst on VKA and 59 (2 %) on estrogen-based treatment or in pregnancy. Accuracy could not be determined in 87 patients (2 %).

Table 3
Clinical characteristics of patients by adherence to thrombophilia testing guidelines.

Characteristics	Total N = 3686	No adherence to guidelines n = 2478 (67)	Adherence to guidelines n = 1208 (33)	P
Age at consultation, mean ± SD (years)	44 (16)	47 (16)	37 (13)	<0.001
Women, n (%)	2218 (60)	1443 (58)	775 (64)	<0.001
Indication for consultation, n (%)				<0.001
VTE	2407 (65)	1611 (65)	796 (66)	
Arterial thrombosis	591 (16)	449 (18)	142 (12)	
Asymptomatic patients	567 (15)	334 (13)	233 (19)	
Pregnancy-related morbidity	121 (3.3)	84 (3.4)	37 (3.1)	
Provoking factors of VTE§, n (%)				<0.001
Unprovoked	702 (19)	415 (17)	287 (24)	
Minor risk factor	1267 (34)	820 (33)	447 (37)	
Major risk factor	435 (12)	373 (15)	62 (5.1)	
Recurrent VTE§, n (%)	589 (16)	320 (13)	269 (22)	<0.001
Family history of VTE in first-degree relative§, n (%)	1159 (31)	598 (24)	561 (46)	<0.001
Number of co-morbidities*, n (%)				<0.001
0	2078 (56)	1287 (52)	791 (65)	
1	841 (23)	608 (25)	233 (19)	
≥2	767 (21)	583 (24)	184 (15)	
Number of risk factors*, n (%)				<0.001
0	1323 (36)	845 (34)	478 (40)	
1	1219 (33)	808 (33)	411 (34)	
≥2	1144 (31)	825 (33)	319 (26)	
Positive thrombophilia test result, n (%)	1192 (32)	768 (31)	424 (35)	<0.001

Categorical values are compared by x^2 test and continuous variables by ANOVA test. *At time of VTE, arterial thrombosis, pregnancy-related morbidity, or consultation in asymptomatic patients. Risk factors included smoking, immobilization >4 h, cancer, central intravenous catheter, infection, estrogen-based treatment, pregnancy, cancer, obesity, trauma, surgery, cancer, and its medication. Co-morbidities included diabetes, arterial hypertension, liver cirrhosis, kidney failure, rheumatic diseases, depression, dyslipidemia, lung diseases, neurological disorders, cardiovascular diseases, and chronic inflammatory diseases. §Values were missing for provoking factors of VTE (0.1 %), history of prior VTE at time of consultation (0.9 %), family history of VTE in first-degree relatives (1.3 %). Abbreviations: SD, standard deviation; VTE, venous thromboembolism.

3.3. Influence of thrombophilia testing on treatment decisions

A total of 293 test results (8.3 % of performed testing, 23 % of

Table 4
Positive results of thrombophilia in adherent and not adherent work-ups.

Type of thrombophilia, n (%)	Total tested patients $N = 3550$	No adherence to guidance $N = 2448$ (69)	Adherence to guidance $N = 1102$ (31)	P
Factor V Leiden heterozygous mutation	714 (20)	455 (19)	259 (23)	<0.001
Prothrombin G20210A heterozygous mutation	193 (5.4)	136 (5.6)	57 (5.2)	0.31
Antiphospholipid antibody syndrome	119 (3.3)	77 (3.1)	43 (3.6)	0.41
Protein S deficiency, <59 %	101 (2.8)	58 (2.4)	43 (3.9)	0.007
Antithrombin deficiency, <70 %	52 (1.5)	35 (1.4)	17 (1.5)	0.70
Factor V Leiden homozygous mutation	48 (1.4)	29 (1.2)	19 (1.7)	<0.001
Protein C deficiency, <69 %	28 (0.79)	19 (0.78)	9 (0.82)	0.85
Prothrombin G20210A homozygous mutation	5 (0.14)	2 (0.08)	3 (0.27)	0.31

Categorical values are compared by x^2 test. Testing was not performed or missing for factor V Leiden mutation (6 %), prothrombin G20210A mutation (13 %), antithrombin (20 %), protein C (30 %), protein S (29 %), antiphospholipid syndrome (11 %).

positive results for thrombophilia) influenced anticoagulation therapy (Supplemental Table 3). Test results influenced treatment in 56 of 1102 work-ups (5.1 %) that were adherent to guidelines, and in 237 of 2448 (9.7 %) non-adherent work-ups (absolute difference, 4.3 %; 95 % confidence interval, 2.9–6.3) (Fig. 1). Non-adherent testing was associated with influence on anticoagulation treatment compared to adherent testing (adjusted odds ratio 2.59, 95 % confidence interval, 1.89–3.56).

Age < 50 years, female sex, absence of co-morbidities and risk factors, and referral for arterial thrombosis, pregnancy-related morbidity or asymptomatic persons with family history of VTE were associated with influence on anticoagulation therapy (Table 5). However, most of these associations were absent in subgroup analyses by indication for referral. When stratified by indication for referral, VTE provoked by a minor risk factor and age < 50 years were associated with influence on treatment decisions in patients referred for VTE. None of the evaluated clinical characteristics was associated with influence on anticoagulation therapy in patients with arterial thrombosis or pregnancy related-morbidity, or in asymptomatic persons with a family history of VTE (Table 5).

4. Discussion

In this large single-center, cross-sectional cohort study of 3686 patients, the indication for thrombophilia testing was in accordance with guidelines in only 33 % of patients, which did not improve after implementation of internal guidelines. Adherence to guidelines partially improved the diagnostic, but not the therapeutic yield of testing. In contrast, test results in patients in whom testing was adherent to guidelines were less likely to influence treatment decisions than those in patients with non-adherent testing (absolute difference, 5.4 %). Whilst age < 50 years, female sex, absence of co-morbidities and risk factors, and referral for arterial thrombosis, pregnancy-related morbidity, or asymptomatic persons with family history of VTE were associated with influence on treatment decision in the entire cohort, these associations disappeared in subgroup analysis by indication for referral. The only clinical characteristics that were associated with treatment influence in subgroup analysis by indication for referral was VTE provoked by a minor risk factor and age < 50 years in patients that were referred for VTE.

Our cohort comprised mostly younger patients without comorbidities and more women than men, probably due to frequent referral for family planning and primary infertility. Most studies on adherence to thrombophilia guidelines were conducted in a primary care setting and

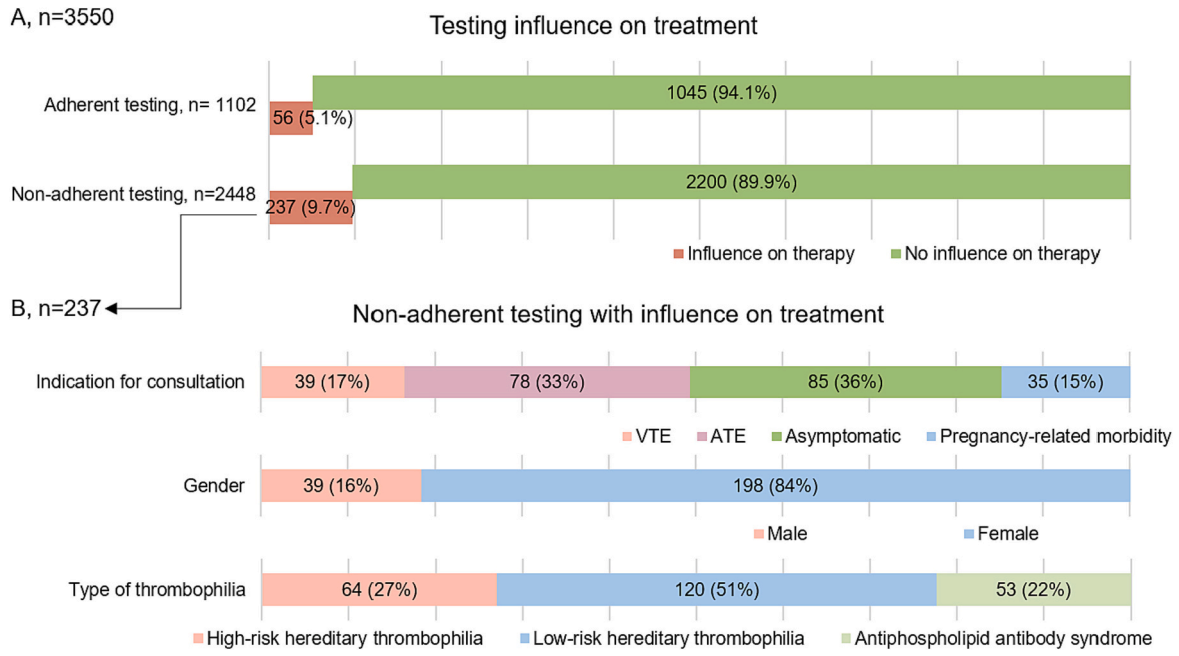

Fig. 1. Thrombophilia testing influence on therapy and adherence to guidance.
A. Thrombophilia testing influence on therapy decision. B. Clinical characteristics of patients with non-adherent work-up with clinical utility. A total 12 work-ups could not be categorized due to unclear statement on treatment decision in the clinical report. Low-risk hereditary thrombophilia is defined by the presence of heterozygous factor V Leiden, heterozygous prothrombin G20210A mutation; high-risk hereditary thrombophilia comprises homozygous factor V Leiden, homozygous prothrombin G20210A mutation, antithrombin < 70 %, protein C < 69 %, protein S < 59 %, and compound thrombophilias. Abbreviations: ATE, arterial thrombosis; VTE, venous thromboembolism.

Table 5
Association between clinical characteristics and influence of thrombophilia testing on anticoagulation treatment in the full study cohort and by indication for consultation.

Clinical characteristic	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Full cohort (n = 3686)		
Age < 50 years	2.20 (1.64–2.95)	2.20 (1.64–2.95)
Women	1.92 (1.47–2.51)	1.92 (1.47–2.51)
Indication for consultation		
VTE	1 (ref)	1 (ref)
Asymptomatic patients	7.09 (5.11–9.84)	7.12 (5.12–9.90)
Arterial thrombosis	6.60 (4.76–9.17)	6.60 (4.75–9.16)
Pregnancy-related morbidity	15.73 (9.95–24.86)	15.80 (9.98–24.99)
Number of co-morbidities		
≥2	1 (ref)	1 (ref)
1	1.33 (0.89–1.98)	1.32 (0.89–1.97)
0	1.61 (1.15–2.26)	1.61 (1.14–2.26)
Number of risk factors for thromboembolism		
≥2	1 (ref)	1 (ref)
1	2.10 (1.49–2.96)	2.10 (1.49–2.96)
0	2.42 (1.74–3.38)	2.42 (1.73–3.37)
Patients with VTE (*n* = 2407)		
Age < 50 years	1.93 (1.12–3.33)	1.73 (1.01–3.01)
Female	1.84 (1.08–3.12)	1.60 (0.93–2.76)
Risk factors for VTE		
Unprovoked	1 (ref)	1 (ref)
Minor risk factor	2.90 (1.46–5.75)	2.94 (1.48–5.84)
Major risk factor	0.97 (0.35–2.69)	0.97 (0.35–2.69)
Family history of VTE in first-degree relative	1.14 (0.67–1.92)	1.15 (0.68–1.94)
Recurrent VTE	0.45 (0.22–0.91)	0.49 (0.24–0.99)
Number of co-morbidities		
≥2	1 (ref)	1 (ref)
1	1.02 (0.43–2.43)	1.07 (0.45–2.54)
0	1.78 (0.89–3.56)	1.86 (0.93–3.72)
Patients with arterial thrombosis (*n* = 591)		
Age < 50 years	1.04 (0.66–1.63)	1.01 (0.64–1.60)
Female	1.17 (0.75–1.82)	1.31 (0.83–2.07)
Family history of VTE in first-degree relative	0.79 (0.44–1.44)	0.81 (0.44–1.48)
Recurrent arterial thrombosis	0.90 (0.50–1.61)	0.94 (0.51–1.73)
Number of risk factors for thromboembolism		
≥2	1 (ref)	1 (ref)
1	2.39 (1.33–4.29)	1.41 (0.83–2.40)
0	1.69 (0.87–3.28)	1.23 (0.71–2.13)
Number of co-morbidities		
≥2	1 (ref)	1 (ref)
1	1.34 (0.79–2.29)	1.24 (0.71–2.16)
0	1.14 (0.66–1.97)	1.01 (0.56–1.80)
Asymptomatic patients (*n* = 567)		
Age < 35 years	1.77 (1.04–3.02)	1.67 (0.93–2.99)
Women	2.06 (1.03–4.12)	1.81 (0.85–3.86)
Family history of VTE in first-degree relative	0.06 (0.03–0.11)	0.06 (0.03–0.11)
Number of risk factors for thromboembolism		
≥2	1 (ref)	1 (ref)
1	2.25 (0.64–7.92)	1.38 (0.35–5.43)
0	2.80 (0.84–9.34)	2.02 (0.55–7.47)
Number of co-morbidities		
≥2	1 (ref)	1 (ref)
1	5.97 (0.76–47.13)	6.79 (0.81–57.05)
0	5.46 (0.73–40.81)	6.16 (0.78–48.88)
Women with pregnancy-related morbidity (*n* = 121)		
Age < 30 years	0.75 (0.34–1.65)	0.76 (0.32–1.76)
Family history of VTE in first-degree relative	0.12 (0.03–0.52)	0.13 (0.03–0.61)
Number of risk factors for thromboembolism		
≥2	1 (ref)	1 (ref)
1	0.38 (0.06–2.29)	0.38 (0.06–2.29)
0	1.56 (0.39–6.32)	1.56 (0.39–6.32)
Number of co-morbidities		
≥2	1 (ref)	1 (ref)
1	0.23 (0.02–2.37)	0.89 (0.13–6.27)
0	0.75 (0.12–4.71)	0.21 (0.02–2.43)

Influence of clinical characteristics was calculated by logistic regression model. Models were adjusted for recurrent venous and arterial thromboembolism in the entire cohort; recurrent and unprovoked VTE in patients with VTE; age > 50 years and presence of ≥2 risk factors in patients with arterial thrombosis; family history for VTE in a first-degree relative and female sex in asymptomatic patients; family history of VTE in a first-degree relative and presence of ≥2 risk factors in pregnancy-related morbidity. Risk factors included smoking, immobilization >4 h, cancer, central intravenous catheter, infection, estrogen-based treatment, pregnancy, cancer, obesity, trauma, surgery, cancer, and its medication. Co-morbidities included diabetes, arterial hypertension, liver cirrhosis, kidney failure, rheumatic diseases, depression, dyslipidemia, lung diseases, neurological disorders, cardiovascular diseases, and chronic inflammatory diseases. Abbreviations: CI, confidence interval; OR, odds ratio; VTE, venous thromboembolism.

more frequently included patients with pre-existing co-morbidities or major risk factors than our study [5,17,41]. Differences between patient characteristics can likely be explained by different settings, because patients in our study were selected and referred by general practitioners or other specialists. Despite these differences and inclusion of patients with any reason for referral for thrombophilia testing, the prevalence of thrombophilia in our study (34 %) aligned well with that in other European and US studies, in which hereditary thrombophilia was confirmed in about a third of the patients with VTE [43,44].

Adherence to thrombophilia guidelines has been investigated in acute in hospital care and other departments than hematology [17,19,20,44–46] and was found to be poor. To our knowledge, this is the first study reporting data from a tertiary hematology center comprising all types of indications for consultation. Our study showed similar results with adherence to guidelines in only one-third of work-ups. Considering that 96 % of cohort patients were tested, our center did not carefully select patients that were referred by general practitioners or other specialists. Further, no significant effect on adherence was found after implementing the institutional selection criteria in 2014. Requests of patients themselves to be tested and expectations of referring physician may have likely contributed to this finding, in addition to physicians' preference and knowledge. Although better established local guidelines and implementation of clear selection criteria have been shown to improve adherence at other centers [47], it did not affect the testing practices in Bern. Therefore, not only the implementation, but also the continuous teaching regarding indications to thrombophilia work-up seems to be of high importance as well.

Because testing was performed in 96 % of patients, we were able to assess the influence of testing on treatment decision in a rather unselected population. Overall, only 8 % of thrombophilia tests and 25 % of positive results were relevant for determining further anticoagulation treatment. Surprisingly, the proportion of test with influence on treatment was higher in patients in whom testing was not adherent to current guidelines (absolute difference, 5.4 %), which highlights the limited clinical utility of current selection criteria, especially in women with pregnancy-related morbidity, asymptomatic patients and patients with arterial thrombosis, where only a very restricted testing is suggested [11,15,16,37]. Selection criteria for patients with VTE, such as age < 50 years, unprovoked venous event and positive family history for VTE have been proposed to increase the diagnostic yield of thrombophilia testing, whereas strongly provoked VTE should not be tested and weakly provoked VTE should be tested only to a limited extent [6,7,9,11,14,15].

In our study, only age < 50 years and presence of a minor risk factor in patients with VTE was associated with influence on treatment decision, which highlights the discordance between the selection criteria aiming at diagnostic or therapeutic yield of thrombophilia work-up. This finding corresponds with only few guidelines [9,15], suggesting testing in young patients with weakly provoked VTE, if discontinuation of anticoagulation at 3–6 months is planned, and highlights the importance of the therapy-related testing.

Our study has also limitations. First, we retrospectively determined treatment influence, which may be prone to information bias and possible misclassification of the influence of thrombophilia testing on treatment decisions. However, the structured reporting system and testing pattern during the entire study period and cross-validation of the data by two individuals likely limited missing values and random misclassification. Second, due to the inhomogeneous selection criteria worldwide and a large study time span, internal selection criteria were used as a reference to the status of adherence, limiting the generalizability of the study results. However, due to a large study population, comparable work-up rate and adherence over the years and clearly defined selection criteria, which are largely consistent with published guidelines, the study gives a comprehensive insight regarding the adherence to thrombophilia testing and its therapeutic yield. Third, we did not consider any other impact on treatment than anticoagulation therapy, such as the avoidance of estrogen-related medications, possible indication to substitution therapy in case of PC and AT deficiency, higher motivation to life style modification, and the change of type of anticoagulant, which would have resulted in higher impact and usefulness of thrombophilia testing. Nevertheless, the accumulated experience through this systematic analysis reflects most of the general influence and constitutes a solid basis of the next testing strategies to be discussed. Fourth, a very small proportion of patients with PS type II deficiency might have been missed, because no systematic measurement of PS activity was performed [48]. Moreover, some AT type II defects may be detected only by genetic testing (AT Dublin, AT Wibble, and AT Rouen VI) or detected more accurately with anti-IIa-based activity assays (AT Cambridge II, AT Denver, and AT Stockholm) [49], which was not performed in our center. However, the prevalence of these types of thrombophilias is generally very low, reducing the impact of this limitation.

In conclusion, adherence to thrombophilia testing guidelines was poor in our tertiary thrombophilia center. Since thrombophilia testing was less likely to influence the treatment decisions in patients in whom testing adhered to guidelines than in those in whom testing would not have been indicated, better criteria to improve the therapeutic yield of thrombophilia work-up are needed. A more comprehensive testing in patients <50 years old and in weakly provoked VTE should be further explored.

CRediT authorship contribution statement

K.V.B. and A.A.S.: Designed the protocol and the analysis plan. K.V.B., T.T. and A.A.S.: Interpreted the data and drafted the manuscript. A.H.: Performed the statistical analysis. H.B and F.S.: Under the supervision of K.V.B. collected the data. D.A, A.R, J.A.K.H., J.S.S. and K.A.J.: Intellectually reviewed the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: T. T. is an investigator of the CanVECTOR Network; the Network receives grant funding from the Canadian Institutes of Health Research (CDT-142654). The remaining authors declare no competing financial interests. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2022.12.001.

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