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ORIGINAL ARTICLE

Role of factor VIII, IX, and XI in venous thrombosis recurrence risk in adults and children: A systematic review

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Abstract

Background: Predicting recurrent venous thromboembolic events (VTEs) is challenging in clinical practice for both adults and children, but it is relevant for clinical management. Identifying laboratory risk factors for VTE recurrence may aid in clinical decision-making.

Objective: The goal of this systematic review is to investigate the predictive role of FVIII, IX, or XI in recurrent VTE in adult and pediatric patients with a first VTE.

Methods: A systematic review of the published literature was conducted in databases MEDLINE In-Process, Other Nonindexed Citations, MEDLINE Epub Ahead of Print, EMBASE Classic + EMBASE (OvidSP), and Cochrane (Wiley). We included observational and interventional studies that comprised adults or children with a first VTE, FVIII, FIX, and/or FXI and objectively confirmed VTE recurrence. The quality in prognosis studies tool was used to assess the risk of bias.

Results: We identified 2177 unique studies, of which 19 were included (18 for adults and 1 for children). The risk of bias was overall low to moderate. The studies were heterogenous with regards to population (provoked/unprovoked primary VTE), exposure (type of assay and cut-off values), and statistical analysis results (measures of association and modeling strategy). In adults, contradictory evidence was found for FVIII and FXI as outcome predictors, while no research could establish if FIX predicts VTE recurrence. Data in pediatrics were limited. Given the extensive heterogeneity of the literature, a meta-analysis was not performed.

Conclusions: Overall, there is contradictory evidence that FVIII, FIX, or FXI predict recurrent VTE in adults and children. Addressing heterogeneity is a relevant aspect to consider in future studies investigating prognostic factors for VTE recurrence.

KEYWORDS
adult, pediatrics, prognosis, risk factors, venous thromboembolism

New systematic review: No evidence that FVIII, IX, and XI are useful risk factors for VTE recurrence in children & adults. To overcome data heterogeneity: Is it time for prospective meta-analyses? #VTE #recurrence #riskfactors #predictors

Essentials

- Venous thromboembolic events (VTEs) recurrence causes morbidity and mortality.
- Our systematic review explores if factors VIII/IX/XI predict VTE recurrence in adults and children.
- Contradictory evidence exists for factors VIII and XI, but there is no evidence for factor IX, and data for children is scarce.
- Factors VIII/IX/XI may not be useful risk factors for VTE recurrence in children and adults.

1 | INTRODUCTION

After a first venous thromboembolic event (VTE), including deep vein thrombosis and pulmonary embolism (PE), it is uncertain which patient is at risk for recurrent events [1]. Recurrent VTE is associated with significant morbidity and mortality in adult patients [2]. Therefore, patients at risk may benefit from extended treatment or secondary prevention with anticoagulation to prevent recurrent events. However, anticoagulation therapy is also associated with clinically relevant bleeding risk [3]. Given the balance of risks and benefits, it is relevant to identify which individuals are at increased risk of recurrence that would benefit from extended-phase treatment.

The triggering event of a VTE is a relevant consideration when evaluating the risk of recurrence. Unprovoked VTE, defined as a VTE that occurs without a transient or persistent risk factor, comprises half of all first VTEs in adult patients [4]. The reported risk of VTE recurrence for unprovoked VTE is approximately 25%, with 4% of recurrent VTE leading to death [5]. It has been shown that extended-phase anticoagulation treatment in patients with unprovoked VTE reduces the risk of recurrence by a factor of 5 while bleeding rates are 2.6 times higher in patients not using anticoagulation, with a case fatality rate of 5% [6,7]. Risk of recurrent VTE, bleeding risks, and patient preferences regarding the cost and inconvenience of treatment play a role in decision-making around extended or indefinite anticoagulation in these patients. In contrast, patients with a provoked first VTE are at a lower risk of recurrence. Hence, anticoagulation is suggested to be discontinued after 3-6 months of treatment or when the provoking factor has subsided [8–10].

In pediatric patients, VTE is an increasing clinical phenomenon [11,12]. Pediatric VTE differs from adult VTE due to different physiology, hemostatic system differences, and underlying conditions in children compared to adults [13]. Pediatric VTE recurrence rate has been reported as 2% to 21%, and the median time to recurrence is 0.5-3.5 years [14–19]. To date, recurrent VTE cannot reliably be predicted or prevented in pediatrics. It is expected that these complications have a negative impact on young patients who have decades to live [20].

Though previous studies have suggested that elevated baseline coagulation factor VIII (FVIII), factor IX (FIX), and factor XI (FXI) play a predictive role in primary VTEs [21–25] in adult patients, there is conflicting published data as to whether these factors can predict recurrent VTE in adults and children. The goal of this systematic review is to investigate the predictive role of FVIII, IX, or XI in recurrent VTE in adult and pediatric patients with a first VTE.

2 | METHODS

A systematic search of published literature was conducted with the assistance of a professional librarian (EU) in databases MEDLINE In-Process, Other NonIndexed Citations, MEDLINE Epub Ahead of Print (OvidSP, 1946 to November 8, 2022), Embase Classic + Embase (OvidSP, 1947 to November 7, 2022), and Cochrane (Wiley, until issue 11 of December 2022) to identify studies that investigated the role of FVIII, IX, or XI to predict recurrent VTE in adults and children. Detailed search strategies are listed in the Supplementary Methods. For this systematic review, studies were included that met the following eligibility criteria: (1) interventional and observational studies that included adults or children with a first objectively confirmed provoked or unprovoked VTE; VTE included deep vein thrombosis and PE. (2) The exposure was defined as coagulation FVIII, FIX, or FXI, and (3) the outcome was defined as objectively confirmed VTE recurrence. Studies were excluded for (1) unusual site VTE and (2) studies publishing on the same or overlapping cohorts (only one study was included based on completeness of reporting).

Titles and abstracts of identified studies were screened by 2 authors (A.B. and L.A.), then a full-text review was conducted by both authors (A.B. and L.A.). Studies were included based on the eligibility criteria listed above and on a simple agreement, while disagreement was resolved with discussion. The reference lists of included studies were scanned to identify further eligible studies.

Study data were extracted by 1 reviewer (A.B.) and included the study design, patient and VTE characteristics, FVIII/FIX/FXI testing (time point of measurement, assay type, and cut-offs), recurrent events, and measures of association according to each study. If any relevant data was missing, the study authors were contacted. The data were summarized by coagulation factor (FVIII, IX, and XI) and age group (adult and pediatric studies). In addition, results were displayed according to the incorporation of provoked and unprovoked VTE into the analysis (eg, stratified and adjusted analysis).

The quality in prognosis studies (QUIPS) tool for prognostic factor studies was used to assess the risk of bias [26]. The areas of study participation, attrition, prognostic factor and outcome measurements, study confounders, and statistical analysis and reporting were assessed by authors A.B. and L.A. based on a simple agreement, while disagreement was resolved with discussion. The bias assessment was visualized in a traffic plot, generated with an online tool [27].

No Ethics Review Board approval was needed, as the included papers have already been published. The review protocol was not registered prior to conduction.

3 | RESULTS

A total of 2815 references were retrieved. All references were saved in an EndNote library to identify 642 duplicates [28]. Four additional studies were identified by manual review of the reference lists. Subsequently, 2177 unique references were reviewed against our inclusion criteria using Covidence [29]. After title and abstract screening, 64 studies were retrieved in full and reviewed, and 45 further studies were excluded due to duplicate study cohorts or ineligibility due to study design, study population, exposure, or outcome. Nineteen published studies were included in this review [30–48]. The study selection flow diagram is shown in Figure 1 [49].

Table 1 shows the study design, patient and VTE characteristics, and recurrent events of each of the 19 included studies; the incidence rate is included where reported. The data for each study about the time point of laboratory measurements, laboratory techniques, results of univariable and multivariable analysis on the association between predictors (factor levels) and the outcome (VTE recurrence), and covariates adjusted for models are summarized in Table 2.

The measures of association (odds ratio [OR], risk ratio [RR], and hazard ratio [HR] with their 95% CI), where available, are displayed in 4 subgroups in Figure 2, according to the analytical approach of the respective studies for each factor in the stratified analysis, adjusted analysis, or no stratification or adjustment. Due to the heterogeneity of the studies, a meta-analysis was deemed inappropriate, and hence, data were synthesized narratively.

The risk of bias assessment with the QUIPS tool is shown in a traffic plot in Figure 3. In general, most studies adequately defined and measured the prognostic factors and outcome, limiting potential misclassification bias. Attrition contributed to a risk of bias in half of the included studies due to mostly not accounting for the loss to follow-up. In most studies, potential confounders were considered for the statistical analysis. However, most studies had limited descriptions of model development and variable selection in statistical analysis and reporting. Major concerns for the risk of bias are addressed below.

3.1 | Studies in adult patients investigating FVIII

The following studies (3 case-control [30,36,41] and 4 prospective cohort studies [33,34,42,48]) reported that FVIII was an independent risk factor for VTE recurrence.

Kraaijenhagen et al. [30] identified FVIII as a risk factor for recurrent VTE in their case-control study, which included 185 adults. Most first events were unprovoked, but no specific proportion was documented. Sixty (32%) participants had recurrent VTE. FVIII was dichotomized at 175 U/dL, which was the 90th percentile of the control population. Univariable analysis showed that for every 10 U/dL increase of FVIII, the risk of recurrent VTE increased by 24% (95% CI, 11%-38%). Compared to controls, the unadjusted OR for a recurrent VTE was 45 (95% CI, 6-370) for FVIII >200 U/dL. The authors commented that the OR did not change after multivariable adjustment, but the data were not reported. The covariates of the model are shown in Table 2.

Kyrle et al. [33] studied the risk of recurrence in a prospective cohort that included 826 patients with unprovoked VTE. Twelve percent (102/826) of participants had a VTE recurrence. FVIII was studied as a binary variable using 234 U/dL as the cut-off (90th percentile of cohort population). FVIII >234 U/dL was associated with a RR of 3.4 (95% CI, 2.1-5.6) for recurrent VTE in univariable analysis and a RR of 2.9 (95% CI, 1.6-5.1) in multivariable analysis (Figure 2). The covariates of the model are shown in Table 2.

Legnani et al. [34] showed that elevated FVIII was associated with an increased risk of recurrent VTE in a prospective cohort of 564 adults. After a first provoked or unprovoked VTE, the frequency of recurrent VTE was 9% (53/564). The cut-off value for chromogenic FVIII used in this study was the 90th percentile of the cohort (2.98 U/mL). The RR for VTE recurrence of provoked first VTE in the univariable analysis was 3.4 (95% CI, 0.5-24) and 2.6 (95% CI, 0.3-19.9) in the multivariable analysis for FVIII >90th percentile. In contrast, the RR for VTE recurrence of the first unprovoked VTE in the univariable analysis was 4.4 (95% CI, 1.5-13.2) and 5.4 (95% CI, 1.8-16.8) in multivariable analysis for elevated FVIII (Figure 2). The covariates of the model are shown in Table 2.

Tirado et al. [36] investigated FVIII as a risk factor for VTE recurrence in their case-control study that included 250 patients with a first provoked unproved VTE. Sixty-five (26%) patients experienced recurrent VTE. The unadjusted OR for recurrent VTE was 2.3 (95% CI, 1.3-4.1) for FVIII levels higher than 232% (90th percentile of cohort) compared to lower FVIII levels, and in multivariable analysis, the OR was 2.6 (95% CI, 1.4-4.8, Figure 2). The covariates of the model are shown in Table 2.

Franco Moreno et al. [48] developed a risk score for VTE recurrence, including FVIII, in a prospective cohort study. A total of 398 patients with a primary unprovoked VTE were included, of which 16% (65/398) had a VTE recurrence. However, the median FVIII level in the recurrent VTE group was reportedly higher than in the nonrecurrent VTE group (134 vs 122, $P < .01$), but no units were available. In multivariable Cox regression analysis, the adjusted HR for predicting recurrent VTE was 1.01 (95% CI, 1.00-1.02, $P = .03$, Figure 2) for elevated FVIII. The covariates of the model are shown in Table 2. Of note, no measurement method for FVIII is described in this study, and the cut-off for elevated FVIII used to measure HR was not defined. Attrition is not mentioned in this study.

Kooiman et al. [41] identified FVIII as a risk factor in recurrent VTE in their retrospective case-control study, including 349 patients with provoked and unprovoked PE. Of these patients, 72 (21%) had a previous VTE; therefore, their PE was a recurrent event (cases). For the remaining patients (277/349, 79%), PE was their index event (controls). For FVIII >2.02 U/mL (fifth quintile of cohort), the univariable OR for VTE recurrence was 5.4 (95% CI, 1.9-15.1) compared to the lowest quintile; the adjusted OR was 4.2 (95% CI, 1.4-12.2, Figure 2). The covariates of the model are shown in Table 2.

Nagler et al. [42] studied risk factors of VTE recurrence in a prospective cohort study that included 479 patients with both provoked and unprovoked VTE. Twenty-one percent (101/479) of patients had a VTE recurrence. FVIII was studied as a binary variable at a

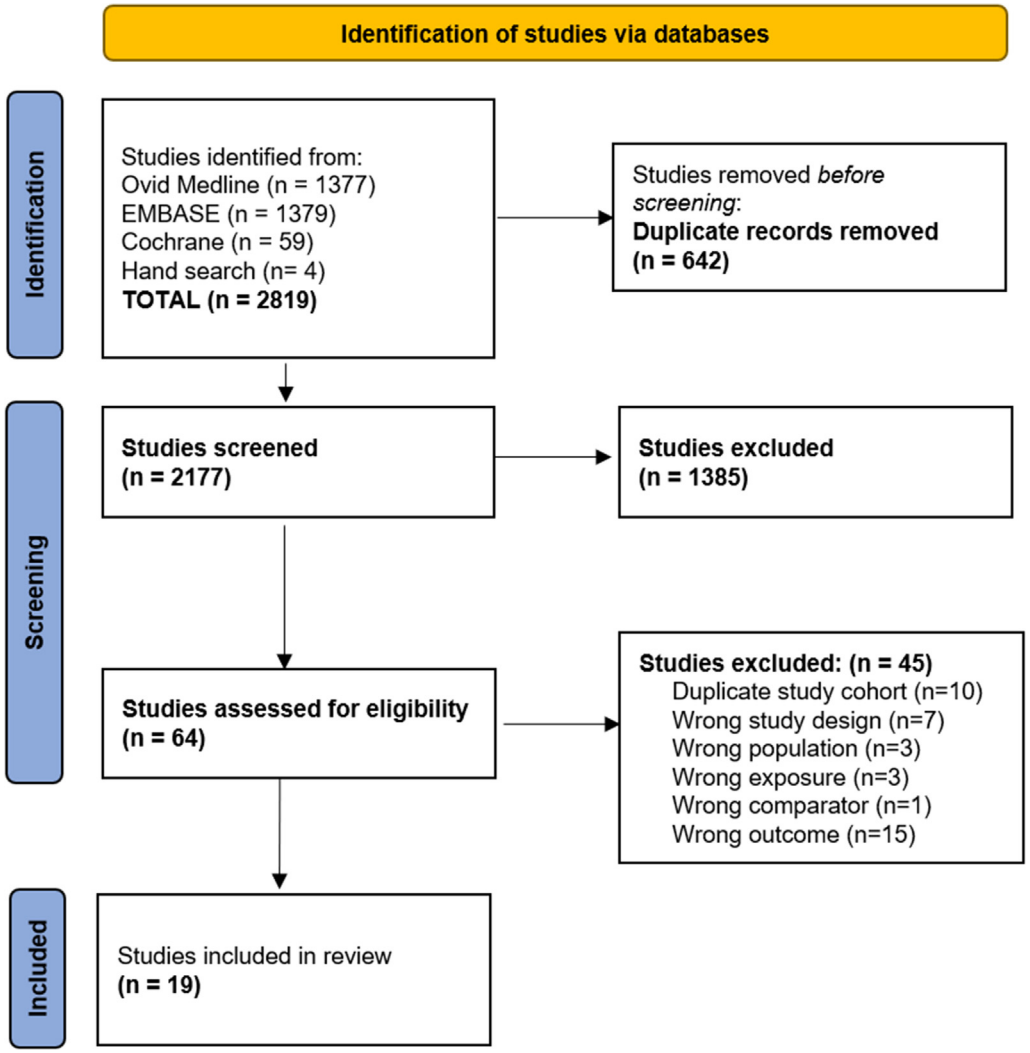

FIGURE 1 Flow diagram of the study selection process. *Source*: [49]

cut-off of 213% (80th percentile of cohort). In univariable analysis, the HR for FVIII >213% and VTE recurrence was 2.3 (95% CI, 1.0-3.2), and in multivariable analysis, the HR was 2.2 (95% CI, 1.2-4.0, Figure 2). The covariates of the model are shown in Table 2.

While FVIII was reported as an independent risk factor for VTE recurrence in the studies above, the following studies (one case-control [31] and 3 prospective cohort studies [39,44,45]) did not find evidence of FVIII to be a risk factor for recurrent thrombosis in multivariable analysis.

Meinardi et al. [31] investigated the risk of recurrent VTE in Factor V Leiden carriers in a case-control study. A total of 329 patients were included with both provoked and unprovoked primary VT, of which 115 patients (35%) had a recurrent VTE. Fifty-five percent of patients with recurrent VTE had an elevated FVIII >150%, whereas 40% had an elevated FVIII with no recurrent VTE. The adjusted OR for VTE recurrence was 1.8 (95% CI, 0.7-4.9, Figure 2) for FVIII levels >122% (first quartile of the sample). The covariates of the model are shown in Table 2.

Rodger et al. [39] studied predictors of VTE recurrence in a prospective cohort study. This study included 646 patients with primary unprovoked VTE, and 14% (91/646) of patients had a recurrence. The annual risk of recurrent VTE was 9.3% (95% CI, 7.7%-11.3%). The mean FVIII level was 1.83 U/mL for patients with recurrent VTE and 1.70 U/mL for patients without recurrent VTE (P = .005). In univariable analysis, men with an FVIII level >1.55 U/mL had a RR of 1.6 (95% CI, 1.0-2.5, P < .1) for VTE recurrence, while women with an FVIII level >2.0 U/mL had a RR 2.3 (95% CI, 1.3-5.4), P = .005. However, in multivariable analysis, FVIII was not an independent predictor for VTE recurrence in either sex (data not reported). The covariates of the model are shown in Table 2.

Timp et al. [44] developed and validated a model to predict recurrent venous thrombosis after a first VTE in a prospective cohort study. In the population cohort for model development, 3750 patients were included with a first provoked and unprovoked VTE; 14% (507) of patients had a recurrent event. The predictor was log-transformed. For every one unit increase of the natural logarithm of FVIII, the adjusted HR for recurrence was 1.6 (95% CI, 0.9-2.9, Figure 2) for a model that included 15 predictors, and 2.3 (95% CI, 1.5-3.3, Figure 2) for a model that had 12 predictors. The covariates of the model are shown in Table 2. Importantly, only 56% of the patients had blood

TABLE 1 Characteristics of included studies, patients, and frequency of outcome.

Study	Study design	Total no. of participants	Age (y)	Males (%)	Provoked first VTE (%)	Duration of follow-up (y)	Incidence proportion (No. of recurrent VTEs [%])	Incidence rate (/100 patient-years)	Definition provoked VTE
Kraaijenhagen et al. [30]	Case-control	185	55 (mean)	54	The majority had unprovoked VTE; no numbers documented	N/A	N/A	N/A	Thrombophilias (PC, PS, and AT deficiency)
Meinardi et al. [31]	Case-control	329	36 (median)	35	55	N/A	115 (35%)	2.3	<3 Months from surgery, trauma, immobilization for >7 d, oral contraceptives, pregnancy, and malignancy
Goldenberg et al. [32]	Prospective cohort	82	12 (median)	46	94	1 (median)	6 (7%)	N/A	Catheter-related, acute infection, lupus anticoagulant positive, and chronic inflammatory state
Kyrle et al. [33]	Prospective cohort	826	48 (mean)	45	0	2.2 (median)	102 (12%)	N/A	<3 Months from surgery, trauma, pregnancy, malignancy, thrombophilias (PC, PS, and AT deficiency), lupus anticoagulant, and hyperhomocysteinemia
Legnani et al. [34]	Prospective cohort	564	67 (median)	50	45	1.6 (median)	53 (9%)	5.7	Recent surgery, trauma, fracture, immobilization, oral contraceptives, pregnancy, puerperium, and hormone replacement therapy
Christiansen et al. [35]	Prospective cohort	474	45 (mean)	43	45	7.3 (mean)	90 (19%)	2.59	Surgery, immobilization, trauma, use of a plaster cast <3 mo, oral contraceptive use within 30 d, pregnancy, and the puerperium
Shrivastava et al. [46]	Randomized controlled trial (post hoc)	508	52 (median; FVIII <150) 56 (median; FVIII >150 U/dL)	57 (FVIII <150) 40 (FVIII >150 U/dL)	0	2.1 (median)	52 (10.2%)	2.1 (FVIII <150, on warfarin); 3.9 (FVIII >150, on warfarin)	Surgery, trauma, and active malignancy

(Continues)

TABLE 1 (Continued)

Study	Study design	Total no. of participants	Age (y)	Males (%)	Provoked first VTE (%)	Duration of follow-up (y)	Incidence proportion (No. of recurrent VTEs [%])	Incidence rate (/100 patient-years)	Definition provoked VTE
Tirado et al. [36]	Case-control	250	42 (mean)	45	52	N/A	65 (26%)	N/A	Surgery, immobilization, paralyzed legs, oral contraceptives, pregnancy, indwelling catheters, and autoimmune disease
Legnani et al. [37]	Prospective cohort	628	67 (median)	53	0	1.8 (median)	71 (11%)	N/A	<3 Months surgery, trauma, immobilization, fracture, pregnancy, and the puerperium
Laczkovics et al. [38]	Retrospective cohort	361	30 (median)	0	50	11.3 (median)	141 (39%)	N/A	Surgery, trauma, immobility, oral contraceptive use, pregnancy, puerperium, cesarian section, abortion, FVL, prothrombin mutation, AT/PC/PS deficiency, elevated FVIII, and hyperhomocysteinemia
Kearon et al. [47]	Randomized controlled trial (post hoc)	661	57 (mean)	46	0	2.3 (mean)	14 (2%)	0.9	Hospitalization >3 d, fracture or cast of leg, surgery with >30 min anesthesia within 3 mo, and malignancy within 2 y
Rodger et al. [39]	Prospective cohort	646	53 (mean)	51	0	1.5 (mean)	91 (14%)	N/A	<3 Months from leg fracture, lower-extremity plaster cast, immobilization, surgery, and malignancy within 5 y
Mello et al. [40]	Prospective cohort	343	36 (median)	34	60	6.1 (median)	69 (20%)	N/A	<3 Months from surgery, trauma, immobilization, plaster cast, oral contraceptives, <30 d from pregnancy, puerperium, and hormonal replacement therapy

(Continues)

TABLE 1 (Continued)

Study	Study design	Total no. of participants	Age (y)	Males (%)	Provoked first VTE (%)	Duration of follow-up (y)	Incidence proportion (No. of recurrent VTEs [%])	Incidence rate (/100 patient-years)	Definition provoked VTE
Franco Moreno et al. [48]	Prospective cohort	398	61 (median)	55	0	1.8 (median)	65 (16%)	N/A	Surgery, trauma, immobility, previous hospitalization, hormonal therapy, pregnancy, puerperium, active malignancy, thrombophilia (PC, PS, and AT deficiency) homozygous FVL, homozygous prothrombin mutation, and anticardiolipin antibodies or lupus anticoagulant
Kooiman et al. [41]	Case-control	349	54 (mean)	50	64	N/A	72 (21%)	N/A	Not reported
Nagler et al. [42]	Prospective cohort	479	58 (median)	50	45	4.6 (median)	101 (21%)	N/A	<3 Months from surgery, immobilization, long-distance travel, contraceptives, and pregnancy
Kyrle et al. [43]	Prospective cohort	815	53 (mean)	66	0	8.5 (median)	265 (31%)	N/A	<3 Months from surgery, trauma, pregnancy, malignancy, thrombophilias (PC, PS, and AT deficiency), lupus anticoagulant, and hyperhomocysteinemia
Timp et al. [44]	Prospective cohort	3750	48 (mean)	45	69	5.7 (median)	507 (14%)	2.64	Surgery, trauma, immobilization, plaster cast, prolonged travel, oral contraceptives, pregnancy, puerperium, hormone replacement therapy, and malignancy
Otero et al. [45]	Prospective cohort	166	64 (median)	54	100	0.5 (trial design)	16 (10%)	N/A	Cancer-associated thrombosis

AT, antithrombin; CVC, central venous catheter; FVIII, factor VIII; FVL, factor V Leiden; PC, protein C; PS, protein S; VTE, venous thromboembolic event.

TABLE 2 Characteristics of factor measurements and statistical analysis performed for the included studies.

Study	Timepoint of laboratory measurement	Assay type	Cut-off for analysis	Factor level distribution	Univariable statistical analysis performed in study	Multivariable statistical analysis performed in study	Covariates adjusted for in multivariable analysis where available
FVIII							
Kraaijenhagen et al. [30]	Unspecified	One-stage clotting assay	>175 U/dL (90th percentile of the control population)	33% of patients in the recurrent VTE group had FVIII >175 U/dL	OR for FVIII above 200 U/dL and VTE recurrence: 45 (95% CI, 6-370) OR for every 10 U/dL increase of FVIII: 1.24 (95% CI, 1.11-1.38)	OR for FVIII above 200 U/dL and VTE recurrence: unchanged to univariable OR (data not reported)	Adjusted for fibrinogen, C-reactive protein, fasting homocysteine concentrations, FVL, and prothrombin mutation
Meinardi et al. [31]	After discontinuation of anticoagulants	One-stage clotting assay	>150%; >122% (first quartile of the cohort)	40% had a FVIII >150%, with a median FVIII of 140% (no recurrence). 55% had a FVIII >150% (P = .06), with a median FVIII of 158% (recurrence); P = .008	Not reported	OR for FVIII >122% and VTE recurrence (in FVL patients): 1.8 (95% CI, 0.7-4.9)	Adjusted for sex, age, observation time, proband state, unprovoked first event, prothrombin mutation, homozygous FVL, hyperhomo-cysteinemia, and deficiency of antithrombin, protein C, and protein S
Kyrle et al. [33]	After discontinuation of anticoagulants	One-stage clotting assay	>234 U/dL (90th percentile of the cohort)	N/A	RR for FVIII >234 U/dL and VTE recurrence: 3.4 (95% CI, 2.1-5.6)	RR for FVIII >234 U/dL and VTE recurrence: 2.9 (95% CI, 1.6-5.1)	Adjusted for age, the presence or absence of a first symptomatic pulmonary embolism, factor V Leiden, factor II G20210A, FIX levels >138 U/dL, and duration of anticoagulation

(Continues)

TABLE 2 (Continued)

Study	Timepoint of laboratory measurement	Assay type	Cut-off for analysis	Factor level distribution	Univariable statistical analysis performed in study	Multivariable statistical analysis performed in study	Covariates adjusted for in multivariable analysis where available
Legnani et al. [34]	After discontinuation of anticoagulants, except in 48 patients' anticoagulation could not be stopped	One-stage clotting assay; chromogenic method	2.98 U/mL for the chromogenic FVIII (90th percentile of the cohort)	Unprovoked VTE group had a FVIII of 1.75 U/mL (0.65-5.41) Provoked VTE group had a FVIII of 1.47 U/mL (0.53-4.14); $P < .0001$	RR for FVIII >2.98 U/dL and VTE recurrence (unprovoked): 4.4 (95% CI, 1.5-13.2) RR for FVIII >2.98 U/dL and VTE recurrence (provoked): 3.4 (0.5-24.0).	RR for FVIII >2.98 U/dL and VTE recurrence (unprovoked): 5.4 (95% CI, 1.8-16.8) RR for FVIII >2.98 U/dL and VTE recurrence (provoked): 2.6 (0.3-19.9).	Adjusted for age, sex, duration of anticoagulation, prothrombin mutation, FVL, and deficiency of antithrombin, protein C, and protein S
Christiansen et al. [35]	After discontinuation of anticoagulants	One-stage clotting assay	166 U/dL	23% of all patients had a FVIII >166 U/dL	HR for FVIII >166 U/dL and VTE recurrence: 1.1 (95% CI, 0.7-1.8)	HR for FVIII >166 U/dL and VTE recurrence: 1.3 (95% CI, 0.8-2.1)	Adjusted for age, sex, and anticoagulation
Shrivastava et al. [46]	After discontinuation of anticoagulants	One-stage clotting assay	150 U/dL (75th percentile of the study population)	116 U/dL (median no recurrence); 122 U/dL (median recurrence); $P = .55$	HR for FVIII >150 U/dL and VTE recurrence: 1.5 (95% CI, 0.8-2.7)	HR for FVIII >150 U/dL and VTE recurrence: 1.5 (95% CI, 0.8-2.7)	Adjusted for age, sex, time from first VTE, number of prior VTEs, and treatment assignment
Tirado et al. [36]	6 Months after VTE. Vitamin K antagonists were withdrawn for 20 d	FVIII clotting activity	232% (90th percentile of the cohort)	N/A	OR for FVIII >232% and VTE recurrence: OR 2.3 (95% CI, 1.3-4.1);	OR for FVIII >232% and VTE recurrence: OR 2.6 (95% CI, 1.4-4.8).	Adjusted for sex, age, hyperhomo-cysteinemia, antiphospholipid antibodies, FVL, PT20210A, FXII46C→T and activated protein C resistance, and deficiencies in antithrombin, protein C, and protein S

(Continues)

TABLE 2 (Continued)

Study	Timepoint of laboratory measurement	Assay type	Cut-off for analysis	Factor level distribution	Univariable statistical analysis performed in study	Multivariable statistical analysis performed in study	Covariates adjusted for in multivariable analysis where available
Laczkovics et al. [38]	After discontinuation of anticoagulants	One-stage clotting assay	248% used as cut-off (95th percentile of 307 healthy individuals)	10.5% of all patients had a FVIII >248%	HR for FVIII >248% and VTE recurrence: 1.0 (95%I, 1.0-1.0, *P* = .33)	HR for FVIII >248% and VTE recurrence: 1.0 (95% CI, 0.1-1.0, *P* = .47) for all VTE; 1.0 (95% CI, 1.0-1.0, *P* = .68) for unprovoked VTE	Adjusted for FVL, prothrombin G20210A variation, hyperhomo-cysteinemia, and deficiencies in antithrombin, protein C, and protein S
Kearon et al. [47]	On anticoagulation, 3 mo after a VTE event	One-stage clotting assay	>2.59 U/mL (90th percentile of the study population)	N/A	HR for elevated FVIII (>2.59 U/mL) and recurrent VTE: 0.7 (95% CI, 0.0-4.0)	Not reported	Not reported
Rodger et al. [39]	On anticoagulation, 5-7 mo after a VTE event	One-stage clotting assay	>1.55 U/mL for men. >2.0 U/mL for women	1.70 U/mL (mean, no recurrence); 1.83 U/mL (mean, recurrence); *P* = .005	RR for elevated FVIII (>1.55 U/mL for men; >2.0 U/mL for women) and recurrent VTE: men, RR of 1.6 (95% CI, 1.0-2.5, *P* < .06, significant in this study); women, RR of 2.3 (95% CI, 1.3-5.4, *P* = .005)	RR for elevated FVIII (>1.55 U/mL for men; >2.0 U/mL for women) and recurrent VTE: RR for men and women statistically not significant (data not reported)	Adjusted for sex, age, weight, height, BMI, abnormal baseline imaging, D-dimer, homocysteine, hemoglobin, prothrombin gene mutation, FVL, ventilation-perfusion scan result, post-thrombotic signs, history or family history of chronic obstructive pulmonary disease, previous provoked

(Continues)

TABLE 2 (Continued)

Study	Timepoint of laboratory measurement	Assay type	Cut-off for analysis	Factor level distribution	Univariable statistical analysis performed in study	Multivariable statistical analysis performed in study	Covariates adjusted for in multivariable analysis where available
							VTE, and oral contraceptive pill or hormone replacement therapy
Mello et al. [40]	After discontinuation of anticoagulants	One-stage clotting assay	90th percentile	180 mg/dL (no recurrence); 188 mg/dL (recurrence)	Univariable Cox model showed no significant association (data not reported)	Not reported	
Franco Moreno et al. [48]	After discontinuation of anticoagulants	Not mentioned	Not reported	122 (no recurrence); 134 (recurrence); $P < .01$ (No unit identified in the paper)	Not reported	HR for elevated FVIII and recurrence: 1.01 (95% CI, 1.00-1.02)	Adjusted for sex, age, obesity, varicose veins, abnormal D-dimer, prothrombin mutation, and FVL
Kooiman et al. [41]	Various time points during follow-up	One-stage clotting assay	>2.02 U/mL (fifth quintile of the cohort)	1.6 U/mL (median, no recurrence); 1.8 U/mL (median, recurrence)	OR for elevated FVIII (>2.02 U/mL) and VTE recurrence: 5.4 (95% CI, 1.9-15.1)	OR for elevated FVIII (>2.02 U/mL) and VTE recurrence: 4.2 (95% CI, 1.4-12.2)	Adjusted for sex, age, and malignancy
Nagler et al. [42]	One mo after discontinuation of anticoagulants	One-stage clotting assay	>213% (80th percentile of the cohort)	N/A	HR for FVIII> 213% and VTE recurrence: 2.3 (95% CI, 1.0-3.2)	HR for FVIII >213% and VTE recurrence: 2.2 (95% CI, 1.2-4.0)	Adjusted for anticoagulation, age, surgery, pregnancy, contraceptive use at the time of thrombosis, travel, inflammation, sex, previous VTE, and D-dimer

(Continues)

TABLE 2 (Continued)

Study	Timepoint of laboratory measurement	Assay type	Cut-off for analysis	Factor level distribution	Univariable statistical analysis performed in study	Multivariable statistical analysis performed in study	Covariates adjusted for in multivariable analysis where available
Timp et al. [44]	After discontinuation of anticoagulants	ELISA	Continuous variables used	N/A	Not reported	HR for every unit increase of ln FVIII: 1.6 (95% CI, 0.9-2.9) for model A and 2.3 (95% CI, 1.5-3.3) for model B	Model A adjusted for sex, site of VTE, surgery, pregnancy/ puerperium, hormone use, plaster cast, immobility in bed, history of cardiovascular disease, D-dimer, von Willebrand factor, C-reactive protein, factor V, factor X, fibrinogen, and activated protein C ratio Model B adjusted for sex, site of VTE, surgery, pregnancy/ puerperium, hormone use, plaster cast, immobility in bed, history of cardiovascular disease, FVL mutation, D-dimer, and C-reactive protein
Otero et al. [45]	After discontinuation of anticoagulants	One-stage clotting assay	Continuous variables used	N/A	Significant increase in FVIII levels with VTE recurrence, compared to no recurrence (P = .01)	N/A	N/A

(Continues)

TABLE 2 (Continued)

Study	Timepoint of laboratory measurement	Assay type	Cut-off for analysis	Factor level distribution	Univariable statistical analysis performed in study	Multivariable statistical analysis performed in study	Covariates adjusted for in multivariable analysis where available
FIX							
Kyrle et al. [33]	After discontinuation of anticoagulants	One-stage clotting assay	>138 U/dL (75th percentile of the cohort)	N/A	RR for FIX >138 U/dL and VTE recurrence: 1.8 (95% CI, 1.2-2.7)	RR for FIX >138 U/dL and VTE recurrence: 1.3 (95% CI, 0.8-2.0)	Adjusted for age, the presence or absence of a first symptomatic pulmonary embolism, factor V Leiden, factor II G20210A, FIX levels >138 U/dL, and duration of anticoagulation
Christiansen et al. [35]	After discontinuation of anticoagulants	ELISA	129 U/dL	18% of all patients had a FIX >129 U/dL	HR for FIX >129 U/dL and VTE recurrence: 0.9 (95% CI, 0.5-1.7)	HR for FIX >129 U/dL and VTE recurrence: 1.2 (95% CI, 0.6-2.1)	Adjusted for age, sex, and anticoagulation
Legnani et al. [37]	After discontinuation of anticoagulants	Chromogenic assay	>1.51 U/mL (75th percentile of the cohort)	N/A	RR for FIX >1.51 U/dL and VTE recurrence: 3.1 (95% CI, 1.3-7.3)	Not reported	
Mello et al. [40]	After discontinuation of anticoagulants	One-stage clotting assay	90th percentile	127 mg/dL (no recurrence); 133 mg/dL (recurrence)	Univariable Cox model showed no significant association (data not reported)	Not reported	
FXI							
Christiansen et al. [35]	After discontinuation of anticoagulants	Monoclonal antifactor XI capture antibody and polyclonal antifactor XI	121 U/dL	19% of all patients had a FXI >121 U/dL	HR for FXI >121 U/dL and VTE	HR for FXI >121 U/dL and VTE	Adjusted for age, sex, and anticoagulation

(Continues)

TABLE 2 (Continued)

Study	Timepoint of laboratory measurement	Assay type	Cut-off for analysis	Factor level distribution	Univariable statistical analysis performed in study	Multivariable statistical analysis performed in study	Covariates adjusted for in multivariable analysis where available
		tagging antibody			recurrence: 0.6 (95% CI, 0.3-1.1)	recurrence: 0.6 (95% CI, 0.3-1.1)	
Legnani et al. [37]	After discontinuation of anticoagulants	Chromogenic assay	>1.4 U/mL (75th percentile of the cohort)	N/A	RR for FXI >1.4 U/dL and VTE recurrence: 2.14 (95% CI, 1.01-4.58)	Not reported	
Kearon et al. [47]	On anticoagulation, 3 mo after a VTE event	One-stage clotting assay	1.93 U/mL (90th percentile of the study population)	N/A	HR for elevated FXI (>1.93 U/mL) and recurrent VTE: 0.6 (95% CI, 0.0-3.5)	Not reported	Not reported
Mello et al. [40]	After discontinuation of anticoagulants	One-stage clotting assay	90th percentile	126 mg/dL (no recurrence); 124 mg/dL (recurrence)	Univariable Cox model showed no significant association (data not reported)	Not reported	
Kyrle et al. [43]	After discontinuation of anticoagulants	One-stage clotting assay	>115 U/dL (third tertile of the cohort)	N/A	N/A	HR for recurrence (FXI >115 U/dL was the comparator): 0.7 (95% CI, 0.5-0.99) for FXI <96 U/dL; 1.1 (95% CI, 0.8-1.4) for FXI 96-115 U/dL; adjusted HR of 0.9 (95% CI, 0.9-0.99)	Adjusted for age and sex

(Continues)

TABLE 2 (Continued)

Study	Timepoint of laboratory measurement	Assay type	Cut-off for analysis	Factor level distribution	Univariable statistical analysis performed in study	Multivariable statistical analysis performed in study	Covariates adjusted for in multivariable analysis where available
						for every 10 U/dL decrease in FXI	
Pediatric							
Goldenberg et al. [32]	At the time of the first VTE and after discontinuation of anticoagulation	One-stage clotting assay	150 U/dL	Time of acute event: median level of FVIII: poor-outcome group 180 U/dL[a]; good-outcome group 117 U/dL ($P < .001$); control group 108 U/dL ($P < .001$). Timepoint after 3-6 mo: median level of FVIII: poor-outcome group 168 U/dL[a]; control group 108 U/dL ($P < .001$).	No statistical analysis performed	Not reported	

FVIII, factor VIII; FVL, factor V Leiden; FIX, factor IX; FXI, factor XI; HR, hazard ratio; OR, odds ratio; RR, relative risk; VTE, venous thromboembolic event

[a]Results are for composite outcomes and not only for recurrence.

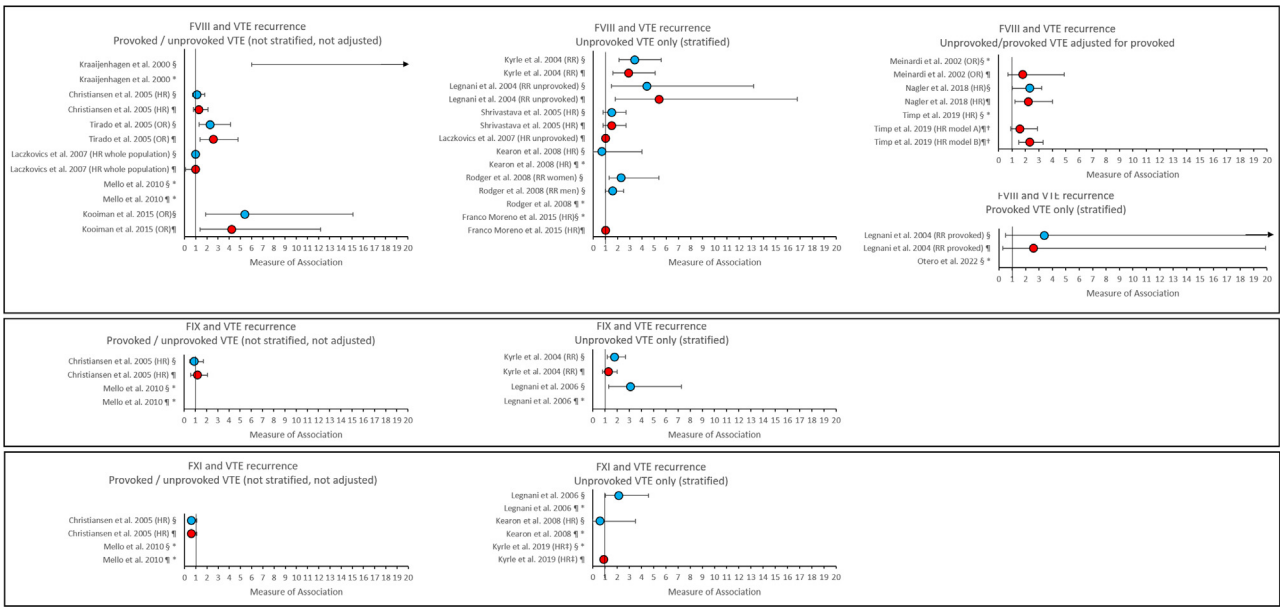

FIGURE 2 Forest plots of measures of association in uni- and multivariable analysis (OR, RR, and HR with their 95% CI) between VTE recurrence and FVIII, IX, and XI. Note: No overall pooled estimate is shown due to different measures of association (OR, RR, and HR). This forest plot is not intended for comparison but to show the heterogeneity of studies. FVIII, factor VIII; FIX, factor IX; FXI, factor XI; HR, hazard ratio; OR, odds ratio; RR, risk ratio; VTE, venous thromboembolic event. * Results not reported; † HR for every unit increase of ln FVIII; ‡ Adjusted HR for every 10 U/dL decrease of FXI; § Unadjusted measure of association (blue); ¶ Adjusted measure of association (red). *Source*: [56].

samples available, and though missing data was imputed for this study, there were no details reported on imputation techniques.

Otero et al. [45] investigated risk factors of VTE recurrence in cancer-associated thrombosis in a prospective cohort study. One hundred sixty-six patients were enrolled for this study with a first cancer-associated thrombotic event; 16 (10%) patients had a recurrent thrombotic event. FVIII was significantly increased in the VTE recurrence group compared to the nonrecurrence group (P = .01; no FVIII levels mentioned). No multivariable analysis was conducted.

Lastly, the following 3 prospective cohort studies [35,38,40] and 2 randomized controlled trials [46,47] did not find evidence of FVIII as a risk factor for VTE recurrence in either univariable or multivariable analysis.

Christiansen et al. [35] studied prothrombotic laboratory abnormalities (including FVIII, IX, and XI) in recurrent VTE in a prospective cohort study. For this study, 474 patients were included with a first provoked or unprovoked VTE; VTE recurred in 90/474 (19%) patients. The FVIII cut-off for the statistical analysis was 166 U/dL. The authors reported no increased risk of recurrence for elevated FVIII where the unadjusted HR was 1.1 (95% CI, 0.7-1.8), and the adjusted HR was 1.3 (95% CI, 0.8-2.1, Figure 2). The covariates of the model are shown in Table 2.

Shrivastava et al. [46] studied predictors (D-dimer and FVIII) for VTE recurrence in the study population of a randomized controlled clinical trial. Five hundred-eight patients were included with a first unprovoked VTE; 52 (10%) had a VTE recurrence. FVIII cut-off was 150 U/dL, which was the 75th percentile of the study population. No significant association between elevated FVIII and VTE recurrence was reported in univariable analysis (HR, 1.5; 95% CI, 0.8-2.7) or multivariable analysis (HR, 1.5; 95% CI, 0.8-2.7). The covariates of the model are shown in Table 2.

Laczkovics et al. [38] investigated the risk of VTE recurrence in young women in a prospective cohort study. A total of 361 patients with a primary VTE (provoked and unprovoked) were included; 141 (39%) had a recurrent VTE. FVIII was dichotomized at the 95th percentile of healthy individuals (248% FVIII clotting activity). No significant association between recurrence and FVIII was identified in univariable (HR, 1.0; 95% CI, 1.0-1.0) or multivariable analysis (HR, 1.0; 95% CI, 0.1-1.0 all first VTE; and HR, 1.0; 95% CI, 1.0-1.0 unprovoked first VTE, Figure 2). The covariates of the model are shown in Table 2.

Kearon et al. [47] investigated thrombophilic defects and their role in predicting VTE recurrence for patients during warfarin therapy. Six hundred sixty-one patients were included with a first unprovoked VTE; 14 (2%) experienced a recurrent VTE. The cut-off for elevated FVIII was 2.59 U/mL (90th percentile of the study population). The association between VTE recurrence and elevated FVIII was not significant in univariable analysis (HR, 0.7; 95% CI, 0.0-4.0). Multivariable analysis was not performed.

Mello et al. [40] studied risk factors (including FVIII, FIX, and FXI) of recurrent VTE in a prospective cohort study. A total of 343 patients with a first provoked or unprovoked VTE were included; 20% (69/343) had a recurrent VTE. The 90th percentile of the cohort was used as a cut-off for FVIII. The mean FVIII level was 180 mg/dL in the nonrecurrence group and 188 mg/dL in the recurrence group; however, this difference was not statistically significant. Univariable analysis data was not reported, and the coagulation factors were not further studied as risk factors for VTE recurrence.

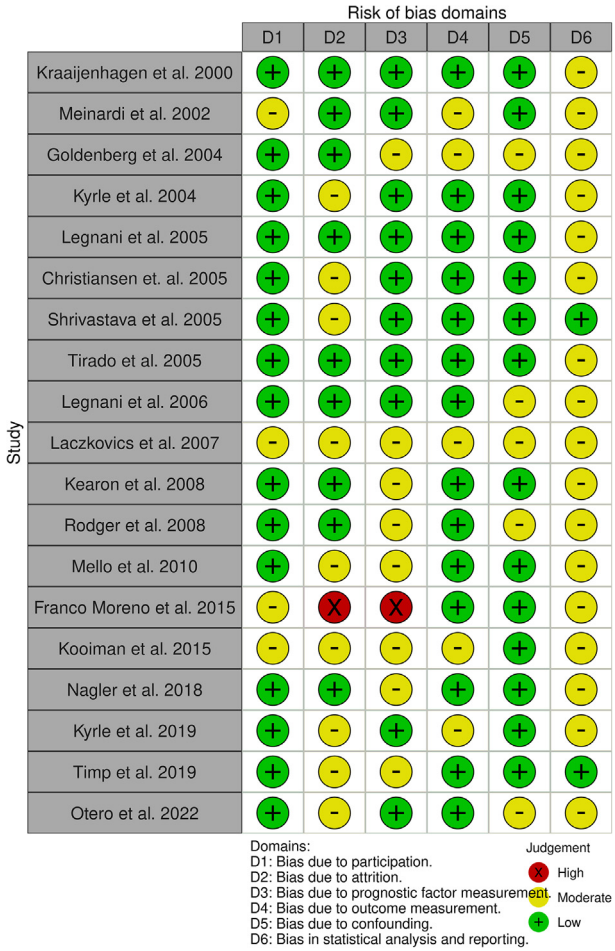

FIGURE 3 Traffic plot displaying risk of bias assessment using the quality in prognosis studies (QUIPS) tool. *Source*: [27]

3.2 | Studies in adult patients investigating FIX

The following 4 prospective cohort studies did not identify FIX as an independent risk factor for VTE recurrence [33,35,37,40].

Kyrle et al. [33] also investigated the predictive role of FIX for VTE recurrence; FIX was dichotomized at 138 U/dL (corresponding to the 75th percentile of the patient population). In univariable analysis, a high FIX had a RR of 1.8 (95% CI, 1.2-2.7) for recurrent VTE, and in multivariable analysis, the RR was 1.3 (95% CI, 0.8-2.0, Figure 2). The covariates of the model are shown in Table 2.

Christiansen et al. [35] further investigated FIX levels and the risk of VTE recurrence and found no increased risk of recurrence with elevated FIX (>129 U/dL). The unadjusted HR was 0.9 (95% CI, 0.5-1.7), and the adjusted HR was 1.2 (95% CI, 0.6-2.1, Figure 2). The covariates of the model are shown in Table 2.

Legnani et al. [37] investigated laboratory factors and VTE recurrence in a prospective cohort study, which included 628 patients with unprovoked VTE. Eleven percent (71/628) of patients experienced recurrent VTE. FIX was dichotomized at 1.51 U/dL (75th percentile of the cohort). In univariable analysis, the RR for FIX >1.51 U/dL and VTE recurrence was 3.06 (95% CI, 1.3-7.3). Results for the multivariable analysis were not reported.

Mello et al. [40] also studied the association between FIX dichotomized at the 90th percentile and VTE recurrence. The mean FIX level was 127 mg/dL in the nonrecurrence group and 133 mg/dL in the recurrence group; however, this difference was not statistically significant. Univariable analysis data was not reported, and the coagulation factors were not further studied as risk factors for VTE recurrence.

3.3 | Studies in adult patients investigating FXI

Only one prospective cohort study identified FXI as an independent risk factor for VTE recurrence [43], while 3 other prospective cohort studies [35,37,40] and one interventional study [47] did not.

Kyrle et al. [43] concluded that patients with a lower FXI have a decreased risk for recurrent VTE in a prospective cohort study. This study included 815 patients with a first unprovoked VTE; 265 (31%) patients had a recurrence. The adjusted HR for VTE recurrence was 0.9 (95% CI, 0.9-0.99, P = .02, Figure 2) for every 10 U/dL decrease in FXI. FXI levels over 100 IU/dL increased the risk for recurrent VTE linearly. When divided into tertiles, the adjusted HR for recurrence was 0.7 (95% CI, 0.5-0.99, P = .05) for FXI <96 U/dL and 1.1 (95% CI, 0.8-1.4) for FXI 96–115 U/dL compared to FXI >115 U/dL. The covariates of the model are shown in Table 2.

In contrast, Christiansen et al. [35] found no increased risk of recurrence with elevated FXI, dichotomized at a cut-off of 121 U/dL. Both the unadjusted and adjusted HR was 0.6 (95% CI, 0.3-1.1, Figure 2). The covariates of the model are shown in Table 2.

Legnani et al. [37] dichotomized FXI at 1.4 U/dL (75th percentile of cohort). In univariable analysis, the RR for FXI >1.4 U/dL and VTE recurrence was 2.14 (95% CI, 1.01-4.58); no results for the multivariable analysis were reported. Kearon et al. [47] also studied FXI as a predictor for VTE recurrence. The selected cut-off was 1.93 U/mL (90th percentile of the study population). In univariable analysis, FXI was not a predictor for VTE recurrence (HR 0.6; 95% CI, 0.0-3.5); multivariable analysis was not performed.

Lastly, Mello et al. [40] studied the predictive role of FXI dichotomized at the 90th percentile. The mean FXI level was 126 mg/dL in the nonrecurrence group and 124 mg/dL in the recurrence group; however, this difference was not statistically significant. Univariable analysis data were not reported, and the coagulation factors were not further studied as risk factors for VTE recurrence.

3.4 | Studies in pediatric patients

Only one prospective cohort study reported on FVIII and VTE recurrence in pediatric patients [32]; no studies were identified that reported on FIX or FXI and VTE recurrence in children.

Goldenberg et al. [32] studied the association between D-dimer and/or FVIII in patients with a first provoked or unprovoked VTE and a composite outcome that included post-thrombotic syndrome, persistent thrombus, and recurrent VTE in a prospective cohort study. In total, VTE recurred in 6/82 (7%) patients, including children. It was

found that elevated FVIII and/or elevated D-dimer at baseline and/or follow-up predicted the composite outcome.

4 | DISCUSSION

4.1 | General interpretation of results

This systematic review identified 19 studies that reported on FVIII, IX, or XI and VTE recurrence in both adults (18 studies) and children (1 study). The results of these studies are conflicting in determining the predictive role of FVIII and FXI for VTE recurrence. FVIII was identified as an independent risk factor for VTE recurrence in 7 studies [30,33,34,36,41,42,48], while the remaining 9 studies did not identify FVIII as an independent risk factor [31,35,38–40,44–47]. Similarly, FXI was reported as an independent predictor in 1 study [43], and 4 studies [35,37,40,47] did not find evidence of FXI as an independent risk factor. FIX was not identified as an independent risk factor in any of the 4 included studies [33,35,37,40]. In sum, there is not enough evidence in the existing literature indicating that FVIII, FIX, or FXI are useful risk factors for VTE recurrence, and hence, they may have only limited value for predicting this outcome in adults [51].

In pediatric patients, data is even scarcer. FVIII has only been studied as a composite exposure to predict a composite outcome [32]. FIX and FXI have not been studied in pediatric patients.

Noticeably, the study populations in this review were very heterogeneous in multiple aspects. Firstly, some studies included only unprovoked VTE, whereas provoked and unprovoked VTE were included in other studies. This is relevant, given the difference in risk of recurrent VTE in these 2 distinct populations, as described in the Background section. The studies were categorized into 4 subgroups according to the analytical approach: 1) stratified analysis, unprovoked VTE group, 2) stratified analysis, provoked VTE group, 3) adjusted analysis for provoked in unprovoked/provoked VTE, and 4) provoked/unprovoked with no stratification/adjustment (Figure 2). The measures of association remained conflicting throughout the subgroups, and due to the few studies in each subgroup, further interpretation is hampered. There is no evidence that FVIII, IX, or XI are more prominent risk factors in either provoked or unprovoked primary VTE for VTE recurrence (Figure 2). Importantly, definitions of provoked VTE differed among studies (Table 1). In 2016, the International Society on Thrombosis and Haemostasis published guidelines to classify provoked versus unprovoked primary VTE in an attempt to standardize the description of populations for future studies [1]. If studies adhere to these guidelines, interstudy comparison results will be more accessible and translatable to specific populations, thus enhancing external validity.

Secondly, FVIII, IX, and XI were not all measured with the same assays, and different cut-offs were used to dichotomize the variable for analysis. The International Council for Standardization in Haematology released the laboratory analysis and reporting guidelines in 2020 [52]. According to the guidelines, the aPTT-based one-stage clotting assay is the most common method for measuring FVIII, FIX, and FIX, and results should be reported in U/ml or U/dL. If no standardized calibrator is available for aPTT assays, normal pooled plasma is used, and results are reported in percentage (%). However, it is not valid to assume that pooled normal plasma contains 100 U/dL of FVIII; thus, laboratory results reported in U/ml or U/dL are not necessarily comparable to those reported in % levels. Chromogenic methods are suitable for FVIII and FIX measurements [53]. ELISA tests can evaluate factor antigens, but it has been shown that ELISA FVIII levels correlate the least to other FVIII measuring methods [54].

Furthermore, factor levels were dichotomized using different cut-offs in every study, and results can thus not be compared. Moreover, some studies analyzed the data using factor levels as continuous variables. Additionally, the time point of laboratory measurements varied between studies (Table 2). The timing of laboratory marker measurement plays a role, as the coagulation factor levels are influenced in multiple scenarios. During an acute event, FVIII as an acute phase protein can be elevated substantially from the baseline factor level due to inflammation; thus, FVIII laboratory testing should be performed at a later time point, eg, 3 months after the acute event [21]. It has been shown that elevated baseline FVIII levels are constant over the years; thus, repeat testing is not necessarily required [55]. Factor levels can also be altered during anticoagulant administration. For example, heparins may interfere with FVIII measurements [54] or FIX, as a vitamin K-dependent factor will be lower during warfarin therapy [56]. Additionally, different measures of association (OR, RR, HR) were reported, which cannot be directly compared across all studies [50]. Lastly, the variables used in each study for adjusted measures of association were vastly different between studies (Table 2), meaning that adjusted estimates cannot be directly compared between studies.

The risk of bias for most studies was low to moderate. Most studies scored a moderate risk of bias in statistical analysis and reporting (Figure 3) because they did not detail their model-building strategy. As a positive example, Timp et al. [44] described the model building distinctly and referred to the redundancy of confounders in prediction modeling.

The literature search was comprehensive and systematically approached, and relevant studies were identified. Ideally, the studies would have been combined to conduct a meta-analysis and determine the role of FVIII, FIX, and FXI in recurrent VTE across all studies. Due to the significant heterogeneity in the data regarding patient population, exposure, outcome, and study results, the data were synthesized narratively, which gives an overview of study findings related to this topic [50]. To display the variability of findings, all measures of association (OR, RR, and HR with their 95% CI) are displayed in Figure 2 for the studies that reported these. It is important to note that the purpose of the forest plot in this review is only to show heterogeneity; it cannot be used to compare OR, RR, and HR to each other; therefore, no overall pooled estimate was calculated [50]. When visualizing the measures of association (OR, HR, and RR) for elevated FVIII and VTE recurrence, there seems to be a tendency toward an increased risk of VTE recurrence. However, the data is conflicting and very heterogeneous, as outlined above; thus, the figure should be interpreted with caution.

Patients who have experienced a first VTE are at risk for recurrent thrombosis, regardless of etiology (provoked vs unprovoked) [1,57]. Data remain limited on identifying patients at risk of recurrent VTE and who would benefit from extended-phase anticoagulation even with the risk of bleeding. Based on the systematic review outlined in this study, the existing literature suggests that FVIII, FIX, and FXI are not strong single predictors of VTE recurrence. An individual patient data meta-analysis could be conducted to concretely analyze the published data on FVIII, FIX, FXI, and VTE recurrence. Though resource intensive, such a study would allow the modeling of more complex relationships between outcomes and predictors, while additional predictors could be standardized across all studies [58]. However, it has to be mentioned that variability in measurements is likely to remain in the population (different inclusion and exclusion criteria, provoked vs unprovoked primary VTE), outcome (definition of VTE recurrence), and prognostic factor (FVIII, FIX, and FXI) data, and missing data might be a challenge [59]. If the coagulation factors are not strong single predictors, they could be incorporated into more complex prediction models following current guidelines [60,61]. Examples of such prediction models, including factor VIII, have been previously published [44,62]. Ultimately, prospectively planned meta-analysis studies may overcome many of these challenges by harmonizing study populations, outcome assessments, and measurements of prognostic factors for individual site studies prior to study conduction [63,64]. These efforts could give more precise answers to prognostic factors in VTE recurrence.

Regarding pediatric studies, the challenge in this population is the relative rarity of both VTE and VTE recurrence, making these studies difficult to conduct. It is important to note that adult and pediatric VTE and VTE recurrence are different entities, and adult data does not necessarily apply to pediatrics. Observational studies will be important to establish the role of FVIII, IX, and XI in predicting pediatric VTE recurrence, alongside other possible factors such as D-dimers.

CONCLUSION

The currently available data on FVIII, IX or XI, and VTE recurrence are limited; it is contradictory for both FVIII and FXI, whereas no evidence exists that FIX levels predict the event. There is no strong evidence that coagulation factor data can be used to identify individuals at risk of recurrent VTE or to inform treatment decisions.

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AUTHOR CONTRIBUTIONS

A.B. was responsible for study design and conduction, analysis, interpretation of the data, and manuscript writing. L.A. contributed to the study concept, design and conduction, analysis, interpretation of data, critical review, and final approval of the manuscript. E.U. was responsible for the study conduction, critical review, and final approval of the manuscript.

RELATIONSHIP DISCLOSURE

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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SUPPLEMENTARY MATERIAL

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