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ORIGINAL ARTICLE

Low D-dimer levels at diagnosis of venous thromboembolism are associated with reduced risk of recurrence: data from the TROLL registry

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Abstract

Background: Venous thromboembolism (VTE) is a frequent disease with a high risk of recurrence. It has been suggested that the D-dimer level at the time of VTE diagnosis can be used to identify patients at a low risk of recurrence.

Objectives: We aimed to investigate the impact of D-dimer levels measured at the time of VTE diagnosis on the risk of recurrence in a large cohort of patients with a first-time VTE.

Methods: The study included 2585 patients with first symptomatic non-cancer–associated VTE from the Venous Thrombosis Registry in Østfold Hospital (TROLL) (2005-2020). All recurrent events during the follow-up were recorded, and cumulative incidences of recurrence were estimated according to D-dimer levels of ≤1900 ng/mL (≤25th percentile) and >1900 ng/mL.

Results: During a median follow-up of 3.3 years, 395 patients experienced a recurrent VTE. The 1- and 5-year cumulative incidences of recurrence were 2.9% (95% CI: 1.8-4.6) and 11.4% (95% CI: 8.7-14.8), respectively, in those with a D-dimer concentration of ≤1900 ng/mL and 5.0% (95% CI, 4.0-6.1) and 18.3% (95% CI: 16.2-20.6), respectively, in those with a D-dimer concentration of >1900 ng/mL, respectively. In patients with unprovoked VTE, the 5-year cumulative incidence was 14.3% (95% CI: 10.3-19.7) in the ≤1900-ng/mL category, and 20.2% (95% CI: 17.3-23.5) in the >1900-ng/mL category.

Conclusions: D-dimer levels within the lowest quartile, measured at the time of VTE diagnosis, were associated with lower recurrence risk. Our findings imply that D-dimer levels measured at the time of diagnosis may be used to identify patients with VTE at a low risk of recurrent VTE.

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KEYWORDS
D-dimer, epidemiology, prediction, recurrenc, venous thromboembolism

1 | INTRODUCTION

Venous thromboembolism (VTE) is a frequent disease, causing considerable morbidity and mortality [1]. The risk of recurrence after a first VTE is high, and up to 30% to 40% of patients with VTE experience a recurrent event within 10 years [2]. Anticoagulant treatment efficiently prevents recurrences, albeit at the expense of an increased risk of bleeding [3,4]. In patients at a high risk of recurrence, prolonged treatment is necessary, and the subsequent increased bleeding risk can be justified. However, in patients with a low risk of recurrence, prolonged anticoagulant treatment introduces an unnecessary risk of bleeding. Therefore, identifying patients at low risk for recurrent VTE, in whom short-term anticoagulation will be sufficient, is desirable [3,5–7].

D-dimer is a global biomarker of coagulation activation and fibrinolysis [8]. Several studies have demonstrated the utility of D-dimer to stratify patients according to the risk of recurrent VTE and thereby provide guidance for the duration of anticoagulant therapy [9–12]. However, current strategies are based on D-dimer levels measured during or after discontinuation of the anticoagulant treatment [13–15], an approach requiring additional blood samples and revisits to the clinics. In addition, discontinuation of anticoagulant treatment leads to a rebound increase in thrombosis risk [16,17]. Therefore, this approach may expose the patient to a higher risk of recurrence after discontinuing anticoagulation. As D-dimer is commonly used in the diagnostic work-up of patients with suspected VTE [18], D-dimer assessment is widely available at the time of diagnosis. Thus, using the D-dimer level measured at the time of diagnosis to assess recurrence risk is potentially less resource-demanding and may guide the decision on treatment duration already at the initiation of anticoagulant therapy.

In a study of 454 patients with first-time VTE, Bjøri et al. showed that D-dimer levels measured at the time of diagnosis could aid in the identification of patients at a low risk of recurrence [19]. Patients with a D-dimer level of >1500 ng/mL had an estimated 5-year cumulative incidence of 23%, while the corresponding cumulative incidence was only 9% among patients with D-dimer levels of ≤1500 ng/mL. These findings are promising but need further investigation and confirmation in other, larger study populations. Therefore, the present study aimed to investigate the impact of D-dimer measured at the time of VTE diagnosis on the risk of recurrence in a large cohort of patients with a first-time VTE.

Essentials

- Can D-dimer levels at incident venous thromboembolism (VTE) predict recurrence risk?
- We explored the association in a cohort of 2585 patients with first symptomatic VTE.
- Low D-dimer levels measured at incident VTE diagnosis were associated with a low risk of recurrence.
- This implies that low D-dimer levels may be used to stratify patients with VTE already at diagnosis.

2 | METHODS

2.1 | Study population

The study population comprised patients enrolled in the Venous Thrombosis Registry in Østfold Hospital (TROLL) registry between January 1, 2005, and April 30, 2020. Østfold Hospital, located in Østfold county, Norway, serves a local population of approximately 317 000 inhabitants. Inclusion required objectively confirmed lower limb deep vein thrombosis (DVT) or pulmonary embolism (PE). Patients diagnosed with both DVT and PE were categorized as PE. The details of the TROLL registry have been described previously [20]. The study was approved by the Regional Committees for Health and Research Ethics South-East, Norway. All patients provided written informed consent to participate. Furthermore, the ethical committee has exempted deceased patients from the requirement of written consent.

Patients with a permanent address outside the hospital's catchment area (n = 46) were not included to increase the likelihood of a complete follow-up. A total of 3586 patients with first-time symptomatic VTE were eligible for the study. All patients with cancer (n = 787) were excluded since D-dimer may often be elevated in patients with cancer independently of VTE [8]. Furthermore, patients with no D-dimer measurement (n = 214) were excluded. Consequently, 2585 patients were included in the analyses and followed from the date of the first VTE to the end of the follow-up, ie, April 30, 2020.

2.2 | D-dimer

The D-dimer levels were assessed at the time of VTE diagnosis by the immunoturbidometric method of STA-Liatest D-Di Plus (Stago Diagnostics). For the diagnostic purpose (used in routine clinical practice), a positive D-dimer was defined as levels of ≥500 ng/mL and levels were reported as a continuous variable of up to >20 000 ng/mL (higher levels were truncated at this cut-off). In this study, we divided the population into quartiles based on the D-dimer levels (quartile 1: ≤1900 ng/mL; quartile 2: 2000-3500 ng/mL; quartile 3: 3600-8200 ng/mL; and quartile 4: >8200 ng/mL). Since the previous study by Bjøri et al. showed a threshold effect at the lowest quartile, we

merged the upper 3 quartiles yielding 2 final categories: ≤1900 ng/mL and >1900 ng/mL.

2.3 | Assessment of VTE

In- and outpatients diagnosed with VTE (ie, distal DVT, proximal DVT, or PE) were referred to and followed up at the hospital's thrombosis clinic. In addition, the hospital discharge diagnosis registry was searched to identify patients with VTE who had not been referred to the thrombosis clinic (ie, patients who died during hospitalization or who were not able to come to the thrombosis clinic). All recurrent events during the follow-up were verified and recorded by the thrombosis clinic. In addition, an extensive review of the medical records in search of recurrent events was conducted in all patients after the end of the follow-up. Recurrent events included distal DVT, proximal DVT, and/or PE (fatal and nonfatal). For fatal PE, the diagnosis was determined by imaging performed shortly before death or autopsy. Individuals without recurrence who died of unknown or uncertain causes during the follow-up were not considered as recurrent events.

The VTE event was categorized as provoked or unprovoked, determined by the presence of known provoking factors at the time of diagnosis. An event was defined as provoked by the presence of one or more of the following factors: recent surgery or trauma, immobilization due to medical conditions, paralysis of the lower extremities or long-distance travel (>4 hours) within the previous 12 weeks, or any other factor explicitly described as being provoking in the medical records.

2.4 | Statistics

For all included patients, person-time was counted from the date of the first VTE event to the first occurring date of recurrent VTE, the date of death, or the end of the study period, whichever came first. Patients who died during the follow-up were censored at the time of death.

All statistical analyses were performed using Stata version 17.0 (Stata Corporation LP). Crude incidence rates (IR) of VTE were calculated and expressed as the number of events per 100 person-years at risk. Hazard ratios (HRs) were estimated across categories D-dimer by Cox proportional hazards regression models. The highest category was set as the reference, and the HR was expressed with a 95% CI. Two different Cox models were used to estimate the HR. The first model was adjusted for age and sex, whereas the second model was additionally adjusted for the duration of anticoagulant treatment. The proportional hazard assumption was tested for all models using Shoenfeld residuals. Furthermore, 1-Kaplan-Meier plots were estimated to visualize cumulative incidences of VTE over time.

Patients with distal DVTs may have a lower risk of recurrent VTE and a lower D-dimer level at the time of diagnosis [21]. Therefore, sensitivity analyses were performed to assess the potential confounding by such low-risk groups. Accordingly, we conducted the analyses restricted to patients with unprovoked proximal DVT or PE. Anticoagulant therapy has a strong impact on the risk of recurrent VTE. In addition to adjusting for the duration of anticoagulant treatment in the second Cox model, we performed sensitivity analyses with follow-up restricted to the time after the discontinuation of anticoagulant therapy (ie, follow-up started on the date of discontinuation of anticoagulant therapy). We also performed analyses restricted to patients treated with anticoagulant therapy for 3 and 6 mo, starting from the date of discontinuation of therapy. D-dimer is associated with an increased risk of mortality [22]. To evaluate the potential impact of competing risks by death, sensitivity analyses were conducted using cumulative incidence functions [23]. The analyses were performed and visualized for overall VTE using Stata's stcrreg and the cif curve commands.

TABLE 1 Demographics and patient characteristics across categories of D-dimer measured at diagnosis.

	All patients	D-dimer ≤1900	D-dimer >1900
	n = 2585	n = 654	n = 1931
Age and median (IQR)	66 (53-78)	61 (48-72)	68 (55-79)
Male, No. (%)	1344 (52.0)	332 (50.8)	1012 (52.4)
PE, No. (%)	1445 (55.9)	319 (48.8)	1126 (58.3)
Unprovoked, No. (%)	1375 (53.2)	335 (51.2)	1040 (53.9)
Pregnancy/postpartum, No. (%)	37 (1.4)	11 (1.7)	26 (1.3)
Surgery, No. (%)	416 (16.1)	99 (15.1)	317 (16.4)
Trauma, No. (%)	276 (10.7)	91 (13.9)	185 (9.6)
Immobilization/hospitalization, No. (%)	1018 (39.4)	279 (42.7)	739 (38.3)
Clinical risk factors			
Estrogen, No. (%)	106 (4.1)	30 (4.6)	76 (3.9)
FHVTE, No. (%)	370 (14.3)	111 (17.0)	259 (13.4)
Treatment duration with AC			
0–3 months, No. (%)	451 (17.4)	123 (18.8)	328 (17.0)
3-6 months, No. (%)	705 (27.3)	240 (36.7)	465 (24.1)
6-12 months, No. (%)	709 (27.4)	157 (24.0)	552 (28.6)
>12 months, No. (%)	720 (27.9)	134 (20.5)	586 (30.3)
Duration of symptoms			
0–2 days, No. (%)	769 (33.3)	198 (33.6)	571 (33.2)
3-7 days, No. (%)	895 (38.8)	223 (37.8)	672 (39.1)
>7 days, No. (%)	645 (27.9)	169 (28.6)	476 (27.7)

IQR, interquartile range; PE, pulmonary embolism; AC, anticoagulant; FHVTE, family history of venous thromboembolism.

3 | RESULTS

The characteristics of the patients with VTE according to categories of D-dimer (≤1900 ng/mL and >1900 ng/mL) are presented in Table 1.

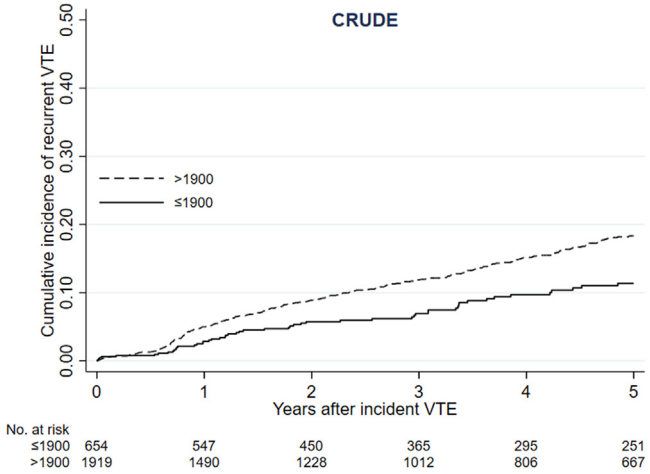

FIGURE 1 Cumulative incidence of venous thromboembolism (VTE) recurrence according to categories of D-dimer (≤1900 ng/mL and >1900 ng/mL) in regular 1-KM analysis.

As expected, the median age was the highest in the highest category of D-dimer. In addition, the proportion of unprovoked events was slightly higher in the upper category. Patients with unprovoked index events had a larger proportion of patients with a long duration of anticoagulation treatment (>12 months) than patients with a provoked VTE (Supplementary Table S1). The characteristics of patients excluded due to missing D-dimer values are presented in Supplementary Table S2. Compared with patients with recorded D-dimers, patients with missing D-dimers had a higher proportion of events provoked by surgery and immobilization/hospitalization. No other major differences were observed when comparing patients with and without missing D-dimer levels.

During a median follow-up of 3.3 years, 395 of 2585 patients experienced a recurrent VTE, yielding an overall IR of 3.57 (95% CI: 3.23-3.94) per 100 person-years. The 1- and 5-year cumulative incidences of recurrence were 2.9% (95% CI: 1.8-4.6) and 11.4% (95% CI: 8.7-14.8) in those with a D-dimer concentration of ≤1900 ng/mL, respectively, and 5.0% (95% CI, 4.0-6.1) and 18.3% (95% CI, 16.2-20.6) in those with a D-dimer concentration of >1900 ng/mL (Figure 1). The overall trend in the estimated cumulative incidence remained essentially similar when considering the competing risk by death, although a slight reduction in the estimates was observed in both categories of D-dimer (Supplementary Figure S1).

The cumulative incidence of recurrent VTE differed across the provoking status at the incident event, as shown in Figure 2. In patients with unprovoked VTE, the 5-year cumulative incidence of recurrence was 14.3% (95% CI: 10.3-19.7) in the ≤1900-ng/mL category and 20.2% (95% CI: 17.3-23.5) in the >1900-ng/mL category. Among patients with a provoked VTE, the 5-year cumulative incidence of recurrence in the ≤1900-ng/mL category was 8.5% (95% CI, 5.4-13.3), and that in the >1900-ng/mL category was 16.0% (95% CI: 13.2-19.3; Figure 2B). Analyses stratified by DVT and PE yielded similar cumulative incidences as observed in the analysis of overall VTE (Supplementary Figure S2).

In the sensitivity analysis restricted to patients with either an unprovoked proximal DVT or an unprovoked PE, the cumulative incidence in the ≤1900-ng/mL category was 3.6% (95% CI: 1.8-7.1) at 1 year and 14.6% (95% CI: 9.9-21.3) at 5 years (Supplementary Figure S3) while it was 4.3% (95% CI: 3.1-6.0) at 1 year and 19.8% (95% CI: 16.8-23.3) at 5 years in the >1900-ng/mL category.

In analyses with follow-up restricted to the time after the discontinuation of anticoagulant treatment, the association between low D-dimer and low risk of recurrent VTE persisted, with a cumulative incidence in the ≤1900-ng/mL category of 4.8% (95% CI: 3.1-7.2) at 1 year and 15.0% (95% CI: 11.5-19.5) at 5 years (Supplementary Figure S4A, Supplementary Table S3). In analyses restricted to patients initially treated for 3 months, the 5-year cumulative incidence after the discontinuation of anticoagulants was 11.1% (95% CI: 6.7-18.3) in the ≤1900-ng/mL category and 16.0% (95% CI: 11.2-22.6) in the >1900-ng/mL category (Figure 3A). Correspondingly, in patients initially treated for 6 months, the 5-year cumulative incidence was 10.0% (95% CI: 5.3-18.6.2) in the ≤1900-ng/mL category and 24.7% (95% CI: 20.5-29.6) in the >1900-ng/mL category (Figure 3B). In patients with unprovoked VTE who had been initially treated for 6 months, the 5-year cumulative incidences of recurrence after the discontinuation of anticoagulants were 15.9% (95% CI: 8.1-29.0) and 29.2 (95% CI: 23.3-36.2) in the ≤1900-ng/mL category and >1900-ng/mL category, respectively (Figure 3C).

HRs of recurrent VTE according to the categories of D-dimer are presented in Table 2. After adjustment for age and sex, patients with a D-dimer concentration of ≤1900 ng/mL had a 39% lower risk of recurrence (HR: 0.61; 95% CI: 0.47-0.79) than patients with a D-dimer concentration of >1900 ng/mL. The relative risk reduction was particularly prominent in patients with a provoked index event (HR: 0.49; 95% CI: 0.33-0.74) and somewhat more pronounced in patients with DVT (HR: 0.58; 95% CI: 0.41-0.82) than in patients with PE (HR: 0.63; 95% CI: 0.43-0.93), although the CIs overlapped. Including the duration of anticoagulant treatment in the adjustment model strengthened the relationship between D-dimer concentration of ≤1900 ng/mL and a lower risk of recurrent VTE (Table 2).

4 | DISCUSSION

In the present cohort of patients with a first VTE, those with a low D-dimer (≤1900 ng/mL) at the time of diagnosis had a 38% lower risk of VTE recurrence. The estimated 5-year cumulative incidence of recurrent VTE was 11% in those with a D-dimer concentration of ≤1900 ng/mL and 18% in those with a D-dimer concentration of >1900 ng/mL. The association between low D-dimer levels at the time of diagnosis and the reduced risk of recurrent VTE was consistent in the subgroups of the index event, including DVT, PE, and unprovoked and provoked VTE.

Our findings confirm those by Bjøri et al., who previously evaluated the association between D-dimer concentration measured at the time of diagnosis and the risk of recurrence in a study of 454 patients with VTE [19]. In their study, the D-dimer cut-off for the lowest

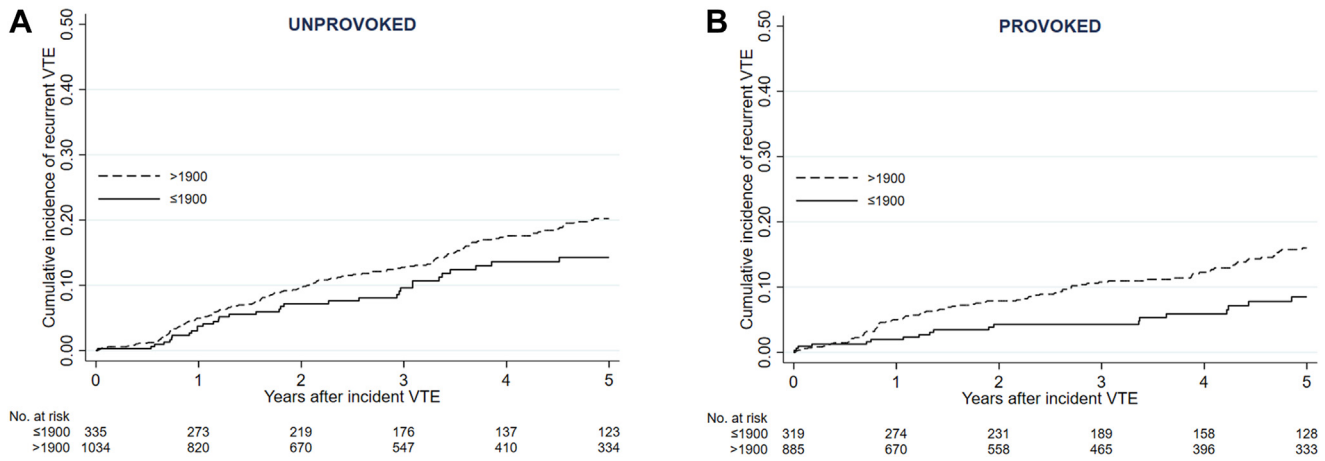

FIGURE 2 Cumulative incidence of thromboembolism (VTE) recurrence according to categories of D-dimer (≤1900 ng/mL and >1900 ng/mL) in patients with unprovoked VTE (panel A) and provoked VTE (panel B).

quartile was ≤1500 ng/mL, and the estimated 5-year cumulative incidences of recurrence were 9% and 23% among patients below and above this cut-off, respectively [19]. Overall, patients in the lowest quartile of D-dimer levels had a 53% lower relative risk of recurrent VTE. In the present study, we included 6-fold as many patients and confirmed the association between low D-dimer levels measured at

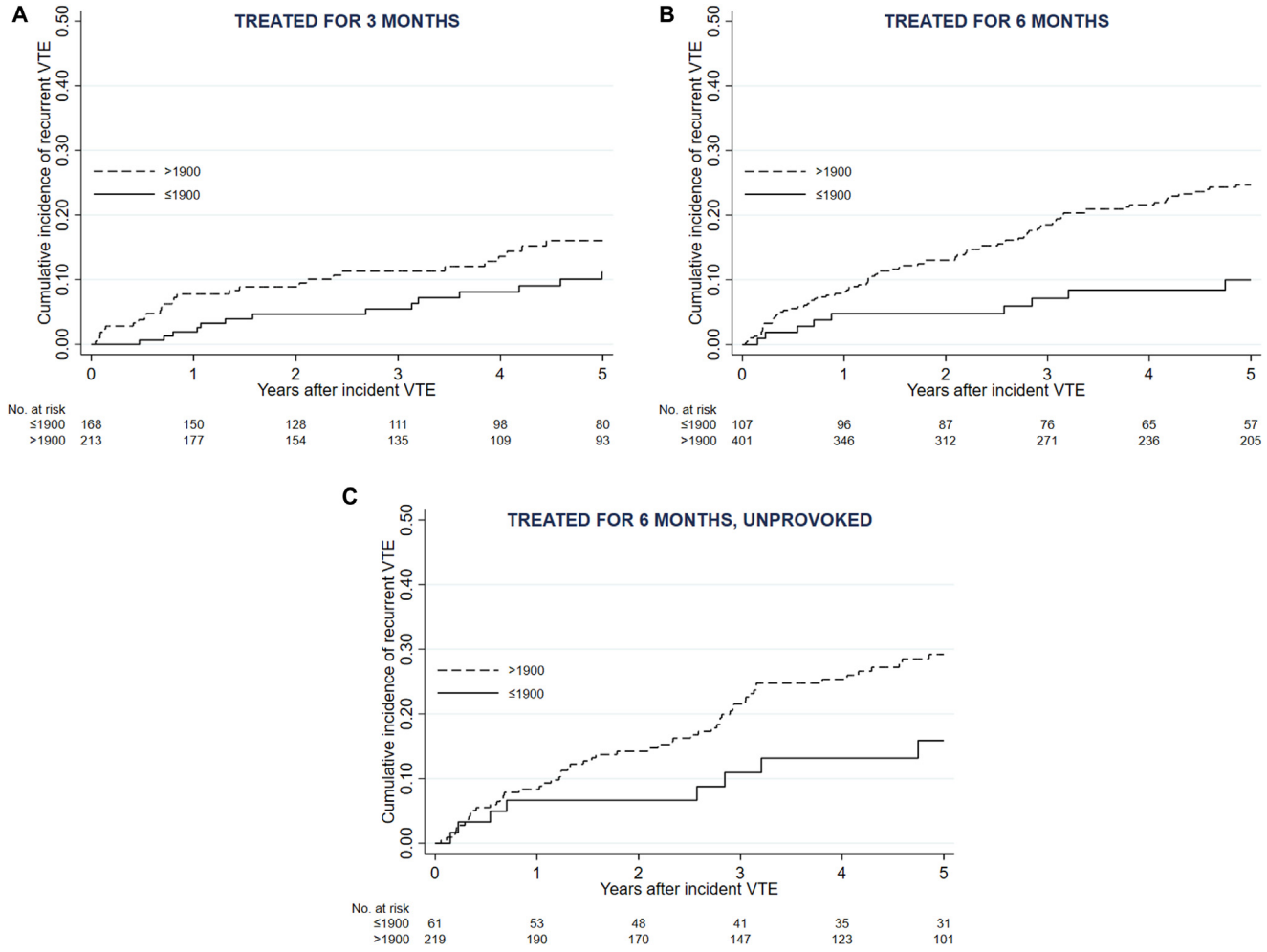

FIGURE 3 Cumulative incidence of venous thromboembolism (VTE) recurrence after discontinuation of anticoagulant therapy according to categories of D-dimer in patients initially treated for 3 months (panel A), 6 months (panel B), and patients with unprovoked VTE treated for 6 months (panel C).

TABLE 2 Incidence rates and risk of recurrent venous thromboembolism (VTE) by categories of D-dimer.

	No.	Rec.	IR (95% CI)[a]	HR.1 (95% CI)[b]	HR.2 (95% CI)[c]
Overall					
>1900	1931	323	4.02 (3.60-4.48)	Ref.	Ref.
≤1900	654	72	2.37 (1.88-2.98)	0.61 (0.47-0.79)	0.55 (0.42-0.71)
Unprovoked					
>1900	1040	182	4.41 (3.81-5.10)	Ref.	Ref.
≤1900	335	44	3.05 (2.27-4.10)	0.72 (0.51-1.00)	0.61 (0.44-0.85)
Provoked					
>1900	891	141	3.61 (3.06-4.25)	Ref.	Ref.
≤1900	319	28	1.75 (1.21-2.54)	0.49 (0.33-0.74)	0.46 (0.31-0.70)
PE					
>1900	1126	166	3.85 (3.31-4.48)	Ref.	Ref.
≤1900	319	31	2.35 (1.65-3.34)	0.63 (0.43-0.93)	0.55 (0.37-0.81)
DVT					
>1900	805	157	4.22 (3.60-4.93)	Ref.	Ref.
≤1900	335	41	2.38 (1.76-3.24)	0.58 (0.41-0.82)	0.55 (0.39-0.78)

CI, confidence interval; HR, hazard ratio; IR, incidence rate.
[a] Per 100 person-years.
[b] Adjusted for age and sex.
[c] Adjusted for age, sex, and duration of anticoagulant treatment.

VTE diagnosis and recurrence risk. The cut-off level for the lowest D-dimer quartile was somewhat higher in our study (≤1900 ng/mL) than that reported in the study by Bjøri et al. (≤1500 ng/mL) [19], potentially due to a higher proportion of patients with PE in our study (56% vs 44%). Accordingly, the cumulative incidences of recurrence at 1 and 5 years were slightly higher in our study (2.9% vs 1.7% at 1 year and 11.4% vs 8.5% at 5 years).

In the evaluation of the recurrence risk in cohort studies, the Subcommittee on Control of Anticoagulation of the International Society of Thrombosis and Haemostasis recommends a recurrence rate of <5% at 1 year and 15% at 5 years to justify the termination of anticoagulant treatment [24]. The 1 and 5-year cumulative incidences of recurrence for the ≤1900-ng/mL D-dimer category were below these accepted thresholds. Even though the optimal D-dimer cut-off remains to be determined, our findings support the utility of D-dimer to identify patients at a low risk of recurrence already at the time of diagnosis.

There is a general consensus to treat patients with VTE without contraindications with anticoagulation for at least 3 months [25–27] and to consider extended duration or indefinite treatment when the VTE is unprovoked [25,28]. D-dimer assessment after the initial treatment period has been proposed as a tool to guide decisions on whether or not to extend the length of treatment, particularly after a first unprovoked VTE [13–15]. Yet, the use of this approach is limited and not implemented in clinical guidelines [25–27]. Our results indicate that low D-dimer levels at the time of diagnosis may facilitate identification of patients with unprovoked VTE in whom anticoagulant treatment can be safely terminated after 6 months without requiring further D-dimer assessment after the initial treatment phase. However, whether D-dimer alone is sufficient to guide the treatment duration after unprovoked VTE is uncertain, as the CI surrounding the 5-year recurrence estimate in the subgroup of patients with unprovoked VTE who had discontinued treatment after 6 months was wide (likely due to a limited number of patients in this subgroup). Moreover, since the patients with VTE in our cohort were managed according to regular clinical practice (ie, D-dimer levels were not used to determine the treatment duration), the utility of our findings need to be further explored in an outcome study. In addition, whether the diagnostic D-dimer could be useful in combination with other predictive factors for VTE recurrence, particularly for the assessment of low risk among patients with unprovoked VTE, should be further explored.

Several risk assessment models for VTE recurrence, such as the Vienna [13], DASH [14], and HERDOO2 [15] prediction models, utilize D-dimer levels measured after the discontinuation of the anticoagulant treatment in combination with clinical risk factors. Although the information on the clinical risk factors included in the Vienna and DASH models is available at the time of diagnosis, the risk assessment model cannot be applied until the initial phase of anticoagulation is completed several months later. Whether the D-dimer level at the time of diagnosis could be utilized in these models remains unsettled and should be further tested in a prediction framework. A model that can be used already at the time of diagnosis may be beneficial for the patients and the healthcare system, as it can inform prognosis, guide decisions on treatment duration, and lower the need for follow-up consultations in patients with low recurrence risk.

The main strength of our study is the recruitment of patients with VTE from a general population for 15 subsequent years, yielding a large study population. Furthermore, the same diagnostic work-up, including the same highly sensitive D-dimer assay, was used during the entire study period. In addition, we only included patients residing within the hospital's catchment area and applied a comprehensive case validation through the outpatient clinic and extensive review of the patients' medical records, which enhanced the likelihood of a complete follow-up. Our study has some limitations that need to be addressed. This study was based on a longitudinal cohort with different treatment strategies applied during the study period, independent of D-dimer levels at the time of diagnosis. This likely affects the natural history of the disease and the observed recurrence risk in our study population. Nevertheless, adjustment for the duration of anticoagulation strengthened our risk estimates, and the association between low D-dimer levels and lower risk of recurrence persisted in analyses where follow-up was restricted to the time after the discontinuation of anticoagulant treatment. Second, 5.9% of the eligible patients were excluded due to missing D-dimer values. While D-dimer is often part of the diagnostic work-up for VTE, D-dimers are not measured in all settings, such as hospitalized patients [29,30]. When comparing patients with and without information on D-dimer in the present study, no major differences were observed in variables indicating the VTE-severity (ie, type of VTE, proportion treated with unfractionated heparin or thrombolysis, or proportion of death during follow-up). However, the proportion of events provoked by immobilization or hospitalization was higher in patients with missing D-dimer, indicating that the lack of D-dimer was particularly prevalent among already hospitalized patients. Thus, our findings may be less generalizable to this particular patient group. Finally, in some patients with expected prolonged diagnostic work-up (eg, outside regular working hours and pending radiological testing), empiric treatment with low-molecular-weight heparin may have been initiated by primary care physicians before referral to the hospital. This could potentially have introduced the misclassification of D-dimer levels in these patients. However, the extent of this approach is limited, which probably has negligible impact on our findings.

In conclusion, D-dimer levels within the lowest quartile (≤1900 ng/mL) measured at the time of incident VTE diagnosis was associated with a low risk of recurrent VTE. These findings imply that a low D-dimer may be used to stratify patients with VTE at a low risk of recurrent VTE already at the time of diagnosis. Future studies should explore whether the inclusion of diagnostic D-dimer in risk assessment models can improve the identification of patients at low recurrence risk in whom short-term anticoagulation would be sufficient.

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AUTHOR CONTRIBUTIONS

F.B.R. contributed to the data collection, data analysis, and writing of the manuscript. C.T.J. contributed to the data analysis, data interpretation, and revision of the content. H.H.P. and W.G. contributed to the data collection and revision of content. J.-B.H. contributed to the conception and design of the study, data interpretation, and revision of content. S.K.B. contributed to the conception and design of the study, interpretation, and writing of the manuscript. All authors read and approved the final paper.

DECLARATION OF COMPETING INTERESTS

C.T.J. reports lecture honoraria from Bayer. H.H.P. reports receiving fees from Sanofi and Novartis. W.G. reports receiving fees for participation in an advisory board from Amgen, Novartis, Pfizer, Principia Biopharma Inc—a Sanofi Company, Sanofi, SOBI, Grifols, UCB, Argenx, Cellphire; lecture honoraria from Amgen, Novartis, Pfizer, Bristol Myers Squibb, SOBI, Grifols, Sanofi, and Bayer; and research grants from Bayer, BMS/Pfizer, and UCB. The remaining authors F.B.R, S.K.B, and J.-B.H have no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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