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Elevated on-treatment D-dimer level is associated with major bleeding during extended anticoagulation for venous thromboembolism

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Abstract

Assessing optimal anticoagulant duration in venous thromboembolism (VTE) requires balancing the risks of recurrent VTE and anticoagulant-associated bleeding with fixed-duration or indefinite anticoagulation. In unprovoked VTE, elevated on-treatment D-dimer level is a predictor of recurrent thromboembolism after anticoagulant cessation, but its impact on anticoagulant-associated bleeding is unknown. We performed a *post-hoc* pooled analysis of two prospective cohorts (BLEEDRISK and REVERSE-2 studies) that enrolled unprovoked VTE patients who continued anticoagulation after ≥3 months of initial treatment. We calculated incidence rates of major bleeding, intracranial hemorrhage and fatal bleeding by D-dimer quartiles, then determined hazard ratios with the lowest D-dimer quartile as reference. Among 3,337 participants, incidence rates of anticoagulant-associated major bleeding from the lowest to highest D-dimer quartile were 0.45, 0.91, 1.43 and 2.20 events per 100 person-years respectively. Accounting for age, sex and anticoagulant type, individuals in the highest D-dimer quartile had a 2.7-fold higher risk of anticoagulant-associated major bleeding compared to the lowest quartile (adjusted hazard ratio [aHR] 2.70, 95% CI 1.35 – 5.41, p=0.005). This association remained robust after additional adjustment for hemoglobin, creatinine and concurrent anti-platelet use in the BLEEDRISK cohort. We did not observe differences in risks of intracranial hemorrhage or fatal bleeding by D-dimer quartiles. Elevated on-treatment D-dimer levels predicted higher risks of major bleeding during indefinite anticoagulation. Given the established relationship between elevated on-treatment D-dimer levels and recurrent VTE after time-limited anticoagulation, our findings underscore the need for additional risk stratification tools in this population to personalize anticoagulant treatment that maximizes its net clinical benefit.

Introduction

Venous thromboembolism (VTE), comprised of deep vein thrombosis and pulmonary embolism, accounts for more than 500,000 hospital admissions in North America each year and is the third leading cause of cardiovascular mortality after myocardial infarction and stroke.[1-3] Half of all VTE events are not attributable to a major transient or persistent risk factor, thus classifying them as unprovoked.[4] Anticoagulation for a minimum of 3 months is recommended after a first episode of VTE during which the risk of recurrence is the greatest.[5, 6] Subsequently, decision-making about anticoagulant duration requires consideration of net clinical benefit by assessing the trade-off between incidence and case fatality rates of both recurrent VTE and major bleeding with fixed-duration and indefinite anticoagulant treatment respectively.[7] While major society guidelines recommend indefinite anticoagulation for patients with a first unprovoked VTE,[5, 8] the annual risk of anticoagulant-associated major bleeding nonetheless ranges between 1.1% to 1.7% in a recent systematic review and meta-analysis.[9] Furthermore, 70% of females and 60% of males with a first episode of unprovoked VTE remain free of recurrent events at 10 years after anticoagulant cessation.[10] Combined with observations that the case fatality of major bleeding is 2- to 3-fold higher than that of recurrent VTE,[10, 11] the need for risk stratification to identify patient populations who are most likely to derive net clinical benefit from indefinite treatment is critical to inform safe and effective anticoagulant management.

D-dimer is a fibrin degradation product with a well-established association with recurrence risk in unprovoked VTE. An elevated D-dimer level while on anticoagulant treatment has been demonstrated to be an independent predictor of recurrent VTE after therapy cessation in several prospective cohorts.[12, 13] However, whether D-dimer levels predict major bleeding during long-term anticoagulant treatment has not been well investigated. D-dimer level is a highly plausible prognostic factor for anticoagulant-associated bleeding: on one hand, elevated D-dimer level is associated with several risk factors for anticoagulant-associated bleeding (e.g., increasing age and renal dysfunction).[14, 15] On the other hand, several inherited thrombophilic states shown to be protective against anticoagulant-associated bleeding may also manifest with elevated D-dimer levels.[16, 17] Taken together, understanding the prognostic value and directionality of on-treatment D-dimer levels on risk of subsequent major bleeding during indefinite anticoagulant treatment is critical to risk stratify individuals with unprovoked VTE to personalize anticoagulant treatment that maximizes net clinical benefit. We therefore aimed to determine the association between on-treatment D-dimer level and major bleeding among patients with unprovoked VTE undergoing long-term anticoagulation.

Methods

Study populations

We performed a post-hoc analysis that combined data from two prospective cohort studies (BLEEDRISK and REVERSE-II) that included patients with a first unprovoked VTE who continued anticoagulation after at least 3 months of initial treatment.[18, 19] Detailed study protocols are provided in the ***Online Supplementary Methods***. Enrolment in both cohorts occurred after ≥3 months of initial treatment with therapeutic anticoagulation, and we only included participants who continued anticoagulant treatment following study enrolment.

The BLEEDRISK study enrolled adults with a first unprovoked or weakly provoked VTE who planned to continue either vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) after ≥3 months of initial treatment.[18] Participants were recruited from between 2008 and 2016. Participants were followed every 6 months for bleeding outcomes. The REVERSE-II study was a multinational prospective management study validating the HERDOO2 clinical decision rule among patients with a first unprovoked VTE (including patients on exogenous estrogen at time of their event).[19] Participants were enrolled across 44 centers in 7 countries and underwent baseline clinical assessment with follow-up visits at 6 and 12 months.[19]

Exposure and outcomes

The primary exposure was on-treatment D-dimer level measured in ng/mL fibrinogen equivalent units (FEU). Any quantitative D-dimer assay was eligible; however, VIDAS® D-dimer Exclusion II assay (BioMerieux) was the most frequently used D-dimer assay in the two studies (88.4%). On-treatment D-dimer levels were measured at the enrolment visit (i.e., after ≥3 months of initial treatment with therapeutic anticoagulation). Plasma samples were processed according to local study protocols, including double centrifugation and frozen transport when required. D-dimer levels were measured while participants remained on therapeutic anticoagulation, and patients without available D-dimer measurements were excluded.

Primary outcome was major bleeding defined by the International Society on Thrombosis and Haemostasis, including fatal bleeding, and/or symptomatic bleeding in a critical area or organ, bleeding causing a fall in hemoglobin levels of ≥20 g/L, or leading to a transfusion of ≥2 packed red cell units.[20] Secondary outcomes included intracranial hemorrhage and fatal bleeding. All outcomes were independently adjudicated in both cohorts by blinded evaluators.

Statistical analysis

Participants from both cohorts were merged into a combined dataset and categorized into quartiles based on on-treatment D-dimer levels. Follow-up began at time of study enrolment (i.e., ≥3 months after treatment initiation). Baseline characteristics were summarized across D-dimer quartiles. Incidence rates of major bleeding, intracranial hemorrhage, and fatal bleeding were calculated per 100 person-years with 95% confidence intervals (CI). Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% CI for bleeding outcomes across D-dimer quartiles, using the lowest quartile as reference. Proportional hazards assumption was

assessed by including a time-varying interaction term between D-dimer quartiles (exposure) and log(time). We adjusted for adjusted for age, sex, and anticoagulant type (VKA versus DOAC) in both cohorts; in the BLEEDRISK cohort, we further adjusted for additional components of the CHAP bleeding risk model (creatinine, hemoglobin, and concurrent antiplatelet use).[18]

We performed subgroup analysis by sex given given differences in prognostic impact of D-dimer for recurrent VTE among females compared to males.[13] A two-stage random-effects meta-analysis was performed as sensitivity analysis to account for study-level clustering. Statistical analyses were performed using SAS (Cary, NC), with a two-sided p-value <0.05 considered statistically significant.

The study was approved by The Ottawa Health Science Network Research Ethics Board (Protocol ID: 20250565-01H).

Results

Baseline characteristics

From 2008 to 2016, the combined cohort of BLEEDRISK and REVERSE-II studies included 4,952 individuals with a first unprovoked or mildly provoked VTE who continued anticoagulation after ≥3 months of initial treatment. Among these individuals, on-treatment D-dimer levels were available for 3,337 participants (**Figure 1**).

Mean age of the combined cohort was 55 years and 42.9% were female (**Table 1**). Self-reported racial category of participants included White (85.6%), Asian (9.7%), Black (2.8%) and Other (1.9%). Median follow-up duration was 1 year (interquartile range, 1 – 1 year). Majority (78%) of participants received a VKA during follow-up, while 17% were treated with a DOAC (**Table 1**). Median D-dimer level was 256.4 (interquartile range [IQR] 150-502) ng/mL FEU in the overall cohort, which was similar among participants tested using the VIDAS® D-dimer assay (median 245, IQR 147 - 445.8 ng/mL FEU). Distribution of D-dimer levels was right-skewed, with majority of participants concentrated in the lower D-dimer range (**Online Supplementary Figure 1**). Study-specific baseline characteristics are included in **Online Supplementary Table 2**.

Increasing D-dimer quartiles were associated with higher mean age, as well as prevalence of post-thrombotic syndrome, anemia, concurrent anti-platelet use, and hypertension at cohort enrolment (**Supplementary Table 1**). Meanwhile, creatinine clearance and prevalence of inherited thrombophilia (factor V Leiden, prothrombin gene mutation) decreased with increasing D-dimer quartiles (**Table 1** and **Online Supplementary Table 1**). Taken together, the proportion

of participants at elevated risk of anticoagulant-associated major bleeding increased by D-dimer quartiles (**Table 1**).

Risk of major bleeding by D-dimer quartile

In the combined cohort, we observed 65 major bleeding events over 5,232 person-years of follow-up, for an overall incidence rate of 1.24 (95% CI 0.96 – 1.58) events per 100 person-years. Crude rates of major bleeding during follow-up by D-dimer quartiles were 0.45, 0.91, 1.43 and 2.20 events per 100 person-years respectively (**Table 2**). Of the 65 major bleeding events, 31 occurred among males and 34 occurred among females.

With participants in the lowest D-dimer quartile as reference, individuals in the highest D-dimer quartile experienced a 4.8-fold higher risk of major bleeding during long-term anticoagulation (hazard ratio [HR] 4.80, 95% CI 2.56-9.01, p<0.001). This remained statistically significant after adjusting for age, sex, and anticoagulation type (adjusted HR 2.70, 1.35-5.41, *p*=0.005, **Table 2**). The relationship between increasing D-dimer quartiles and risk of major bleeding was dose-dependent: each increase in D-dimer quartile was associated with a 1.4-fold increase in risk of anticoagulant-associated major bleeding during indefinite treatment (adjusted HR 1.40, 95% CI 1.16-1.69, *p*=0.0006, **Figures 2 and 3**). Finally, the association between D-dimer quartiles and major bleeding remained consistent after adjustment for three additional risk factors captured in the BLEEDRISK study (renal function, hemoglobin, concurrent anti-platelet use, **Figure 3**).

Risks of intracranial hemorrhage and fatal bleeding by D-dimer quartile

There were 11 intracranial hemorrhages and 4 fatal bleeding events in the combined cohort. Incidence rate of intracranial hemorrhage was 0.21 (95% CI 0.10 – 0.38) events per 100 person-years, and 0.08 (95% CI 0.02-0.20) events per 100 person-years for fatal bleeding. We observed a 5.8-fold higher risk of intracranial hemorrhage among participants in the highest D-dimer quartile compared to those in the lowest quartile (HR 5.75, 95% CI 1.07 - 30.82, *p*=0.041, **Table 2**); however, this difference was attenuated after adjustment by age, sex and anticoagulant type (aHR 1.95, 95% CI 0.32 – 11.84, **Table 2**). D-dimer quartile was not a predictor of fatal bleeding in the crude or adjusted analysis.

Subgroup and sensitivity analyses

In sex-stratified analysis, on-treatment D-dimer was associated with higher risk of anticoagulant-associated major bleeding among females (aHR 1.59 per quartile increase, 95% CI 1.32 – 1.93, p<0.001) after accounting for age, renal function, hemoglobin, concurrent anti-platelet use, and anticoagulant type. The prognostic impact of D-dimer levels on major bleeding was consistent

among males but did not reach statistical significance (aHR 1.32 per quartile increase, 95% CI 0.78 – 2.22, p=0.301). Two-stage meta-analysis at the study level showed consistent results with the main analysis (**Online Supplementary Table 3**).

Discussion

In a post-hoc analysis of two multinational cohort studies that included 3,337 patients with a first unprovoked VTE on indefinite anticoagulation, we observed a dose-dependent increase in the risk of anticoagulant-associated major bleeding with stepwise increases in on-treatment D-dimer levels. Participants in the highest D-dimer quartile experienced a 4.8-fold higher risk of major bleeding compared to those in the lowest D-dimer quartile, which remained statistically significant after adjusting for established risk factors for anticoagulant-associated bleeding in this setting. Elevated on-treatment D-dimer level had a similar impact on the risk of intracranial hemorrhage in the crude analysis, which was attenuated after multivariable adjustment. On-treatment D-dimer levels did not predict fatal bleeding.

In our study, on-treatment D-dimer level was an independent predictor of anticoagulant-associated major bleeding, which suggests the potential role of increased fibrinolytic activity on anticoagulant safety. The association between elevated D-dimer level and bleeding risk has previously been observed among patients with atrial fibrillation in a *post-hoc* analysis of the ARISTOTLE trial, which randomized patients with atrial fibrillation and ≥1 $CHADS_2$ risk factor for stroke or systemic embolism to warfarin (target international normalized ratio 2-3) or therapeutic apixaban.[21] Of 7,982 VKA-exposed participants at the time of randomization who also had blood samples collected, individuals with on-treatment D-dimer levels in the highest quartile (> 690 ng/mL) experienced a 2-fold higher risk of major bleeding compared to those with D-dimer levels in the lowest quartile (≤289 ng/mL; HR 1.97, 95% CI 1.44–2.69).[21] Specific to VTE the effect of elevated D-dimer level on the risk of *recurrent VTE* after anticoagulant cessation is well-established: in a systematic review and meta-analysis of 7 prospective studies with 1,888 participants with a first unprovoked VTE, Verhovsek *et al* observed a 2.2-fold higher risk of recurrent VTE among individuals with elevated D-dimers compared to those with a normal D-dimer level.[22] In a follow-up study, D-dimer levels collected during and after anticoagulant treatment were both prognostic for VTE recurrence.[23] While a higher risk of major bleeding during acute VTE treatment was identified among individuals with severely elevated D-dimer levels (≥4300 ng/mL) at VTE diagnosis prior to anticoagulant initiation,[24, 25] the association between on-treatment D-dimer levels and anticoagulant-associated bleeding in the context of secondary VTE prevention has not been evaluated to date. By determining the impact of elevated on-treatment D-dimer levels on anticoagulant-associated major bleeding, our findings highlight the high-risk nature of this patient population, who are not only at risk for recurrent VTE with time-limited treatment, but also for major bleeding with indefinite anticoagulation.

The clinical implications of our results require careful consideration. With increasing utilization of anticoagulants in the context of an aging population, emergency department visits for anticoagulant-associated bleeds have risen by 28% between 2016 and 2020 in the United States.[26] We found on-treatment D-dimer levels to be positively correlated with several risk factors for anticoagulant-associated major bleeding, such as age, renal dysfunction and concurrent anti-platelet therapy. In routine clinical practice, our findings suggest the need to optimize modifiable risk factors for bleeding when embarking on indefinite anticoagulant treatment among individuals with elevated on-treatment D-dimer levels, such as workup and management of anemia and renal dysfunction. Reassessing the need for concurrent anti-platelet therapy among patients with both unprovoked VTE and stable atherosclerotic cardiovascular disease is particularly salient, as emerging data demonstrate increased risk of major bleeding and all-cause mortality with the concomitant use of both anticoagulant and antiplatelet therapy in this population.[27]

Given on-treatment D-dimer levels being prognostic of both recurrent VTE and major bleeding, our results highlight the possibility that an elevated D-dimer level after 3 to 6 months of acute VTE treatment may identify a heterogenous profile of patients with unprovoked VTE that comprises of individuals with increased thrombin generation (hypercoagulable state) and those with increased fibrinolysis (coagulopathic state). Rather than a binary cutoff based on the predicted risk of recurrent VTE alone, refinement of on-treatment D-dimer thresholds to also account for the risk of anticoagulant-associated bleeding will further enhance the clinical utility of this biomarker. Finally, evaluation of agents with non-antithrombotic properties in VTE represents an urgent area of unmet need, as it offers an alternative option to secondary VTE prevention that does not directly alter the coagulation system. Anti-inflammatory agents, such as statins and low-dose colchicine that have demonstrated efficacy in arterial cardiovascular disease,[28, 29] may indeed provide a personalized approach to anticoagulant therapy among patients at high risks of both thromboembolism and treatment-related adverse events.

To our knowledge, this is the first evaluation of on-treatment D-dimer level's prognostic impact on anticoagulant-associated major bleeding during secondary prevention phase of VTE treatment. Our prospectively collected D-dimer levels and clinical predictors with centrally adjudicated outcome data provide additional validity to our findings. Nonetheless, our study has limitations. First, majority of participants in our study were treated with VKAs due to enrolment period of the two included cohorts. While DOAC users comprised approximately 1 in 4 individuals in the study and was accounted for in the multivariable analysis, the prognostic impact of D-dimer levels in the DOAC-treated population requires robust validation in future studies, as prior work has shown higher on-treatment D-dimer levels among patients with VTE treated with DOACs compared to their VKA-treated counterparts.[30] Second, we could not confidently attribute the impact of D-dimer levels on rarer bleeding events, such as intracerebral

hemorrhage or fatal bleeds. Similarly, sex-stratified analysis to determine the prognostic impact of on-treatment D-dimer level was limited by the number of primary outcomes and therefore was under-powered to confirm sex-specific heterogeneity. While a missed opportunity given differences in prognostic impact of D-dimer for recurrent thromboembolic events among females compared to males,[13] it highlights the need for future research, including the role of individual patient data meta-analysis across additional cohorts. Third, individuals whose index VTE was accompanied by the presence of a weak risk factor (e.g., exogenous estrogen) were included in the cohorts, who may have a different risk profile compared to non-estrogen associated (e.g., idiopathic) VTE events.[31, 32] Nonetheless, our combined cohort comprised of individuals in whom the treating physician deemed their recurrent VTE risk to be sufficiently elevated to warrant long-term anticoagulation. Fourth, D-dimer levels in this study were primarily measured using the VIDAS® assay. Given the impact of inter-assay variability and variable prognostic impact between D-dimer assays,[33, 34] further studies are required to generalize our findings to other D-dimer assays. Fifth, the median follow-up duration was 1 year among the included studies, with limited number of participants followed beyond 3 years. Nonetheless, incidence rate of major bleeding during secondary VTE prevention has been observed to be relatively constant,[9] and our findings are therefore likely generalizable to long-term risks of anticoagulant-associated bleeding. Finally, the post-hoc nature of this analysis suggests that our findings are intended to be hypothesis-generating that require replication and prospective validation.

In conclusion, we observed an association between elevated on-treatment D-dimer levels and anticoagulant-associated major bleeding during indefinite VTE treatment. Our findings highlight the need for novel clinical predictors and biomarkers that risk stratify patients with unprovoked VTE for risks of recurrent VTE and major bleeding with fixed-duration *vs.* indefinite therapy, thereby maximizing the net clinical benefit of anticoagulation in this high-risk population.

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Table 1. Baseline characteristics of combined cohort

	Overall (N=3337)	**D-dimer Q1 (N=855)**	**D-dimer Q2 (N=813)**	**D-dimer Q3 (N=835)**	**D-dimer Q4 (N=834)**
D-dimer values					
Any D-dimer assay (median, IQR)*	256.4 (150.0 – 502.0)	110.0 (83.3 – 133.0)	200.0 (177.0 – 224.0)	345.0 (294.0 – 414.0)	947.7 (662.2 – 2039.0)
VIDAS D-dimer (median, IQR)*	245.0 (147.0 – 445.8)	107.8 (83.1 – 128.1)	200.0 (175.0 – 225.1)	344.3 (293.0 – 412.5)	805.3 (619.2 – 1200.0)
Demographic factors					
Age (mean ± SD)	55.4 ± 16.6	44.8 ± 13.7	52.6 ± 15.1	60.2 ± 14.6	64.0 ± 15.8
Female sex (%)	1431 (42.9%)	320 (37.4%)	352 (43.3%)	399 (47.8%)	360 (43.2%)
Characteristics of index VTE					
Index VTE					
DVT	1428 (42.8%)	294 (34.4%)	324 (39.9%)	348 (41.7%)	462 (55.5%)
PE	1250 (37.5%)	390 (45.6%)	306 (37.6%)	306 (36.7%)	248 (29.8%)
PE+DVT	656 (19.7%)	171 (20.0%)	183 (22.5%)	180 (21.6%)	122 (14.7%)
Heterozygous Factor V Leiden or Prothrombin Gene Variant Positive (%)	371/2804 (13.2%)	129/776 (16.6%)	106/698 (15.2%)	76/722 (10.5%)	60/608 (9.9%)
Anticoagulant modality					
Vitamin K antagonist	2603 (78.0%)	706 (82.6%)	614 (75.5%)	603 (72.2%)	680 (81.5%)
Rivaroxaban	515 (15.4%)	96 (11.2%)	137 (16.9%)	160 (19.2%)	122 (14.6%)
Edoxaban	18 (0.5%)	3 (0.4%)	6 (0.7%)	7 (0.8%)	2 (0.2%)
Apixaban	7 (0.2%)	0	2 (0.3%)	3 (0.4%)	2 (0.2%)
Dabigatran	12 (0.4%)	2 (0.2%)	3 (0.4%)	6 (0.7%)	1 (0.1%)
Other	182 (5.4%)	48 (5.6%)	51 (6.3%)	56 (6.7%)	27 (3.2%)
BLEEDRISK cohort only					
CHAP high-risk (n/N)	216 / 914 (23.6%)	16 / 207 (7.7%)	39 / 208 (18.8%)	45 / 192 (23.4%)	116 / 307 (37.8%)

* Of 3,337 participants, 2949 had D-dimers measured using the VIDAS assay.

Table 2. Impact of elevated D-dimer on anticoagulant-associated bleeds in the combined cohort

	Overall	**D-dimer Q1**	**D-dimer Q2**	**D-dimer Q3**	**D-dimer Q4**
Major bleeding					
Incidence per 100 person-years (95% CI)	1.24 (0.96 - 1.58)	0.45 (0.17 - 0.98)	0.91 (0.47 - 1.58)	1.43 (0.85 - 2.26)	2.20 (1.47 - 3.15)
Crude Hazard Ratio (95% CI) P-value		Ref	**1.84 (1.01 - 3.34) *p*=0.044**	**3.22 (1.55 - 6.71) *p*=0.018**	**4.80 (2.56 - 9.01) *p*<0.001**
Adjusted Hazard Ratio* (95% CI) P-value		Ref	1.36 (0.72-2.56) *p*=0.338	2.00 (0.91-4.41) *p*=0.086	**2.70 (1.35 - 5.41) *p*=0.005**
Intracranial hemorrhage					
Incidence per 100 person-years (95% CI)	0.21 (0.1 - 0.38)	0.08 (0 - 0.42)	0.08 (0 - 0.42)	0.24 (0.05 - 0.69)	0.45 (0.17 - 0.99)
Crude Hazard Ratio (95% CI) P-value		Ref	1.01 (0.86 - 1.18) *p*=0.913	3.21 (0.29 - 36.01) *p*=0.345	**5.75 (1.07 - 30.82) *p*=0.041**
Adjusted Hazard Ratio* (95% CI) P-value		Ref	0.57 (0.35-0.95) *p*=0.0308	1.50 (0.15 - 15.23) *p*=0.733	1.95 (0.32 - 11.84) *p*=0.468
Fatal bleeding					
Incidence per 100 person-years (95% CI)	0.08 (0.02-0.20)	0.08 (0 - 0.42)	0	0.08 (0-0.44)	0.15 (0.02-0.55)
Crude Hazard Ratio (95% CI) P-value		Ref	0.32 (0.01, 16.47) *p*=0.574	1.05 (0.07 - 16.82) *p*=0.972	1.77 (0.15 - 21.15) *p*=0.652
Adjusted Hazard Ratio* (95% CI) P-value		Ref	0.09 (0 - 5.41) *p*=0.253	0.22 (0.01 - 3.8) *p*=0.296	0.25 (0.02 - 3.46) *p*=0.302

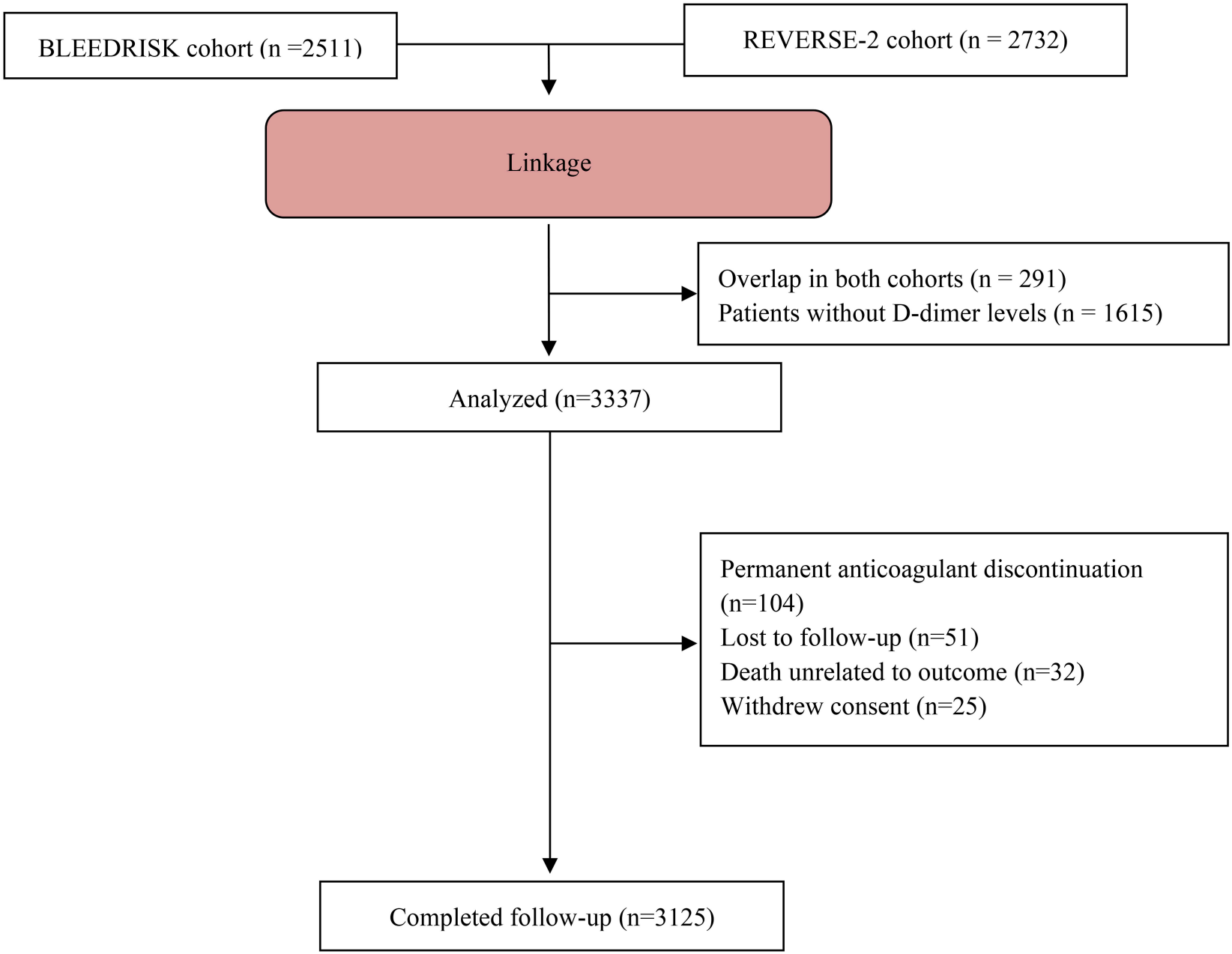
*Adjusted for age, sex, and anticoagulant type (VKA vs. DOAC)

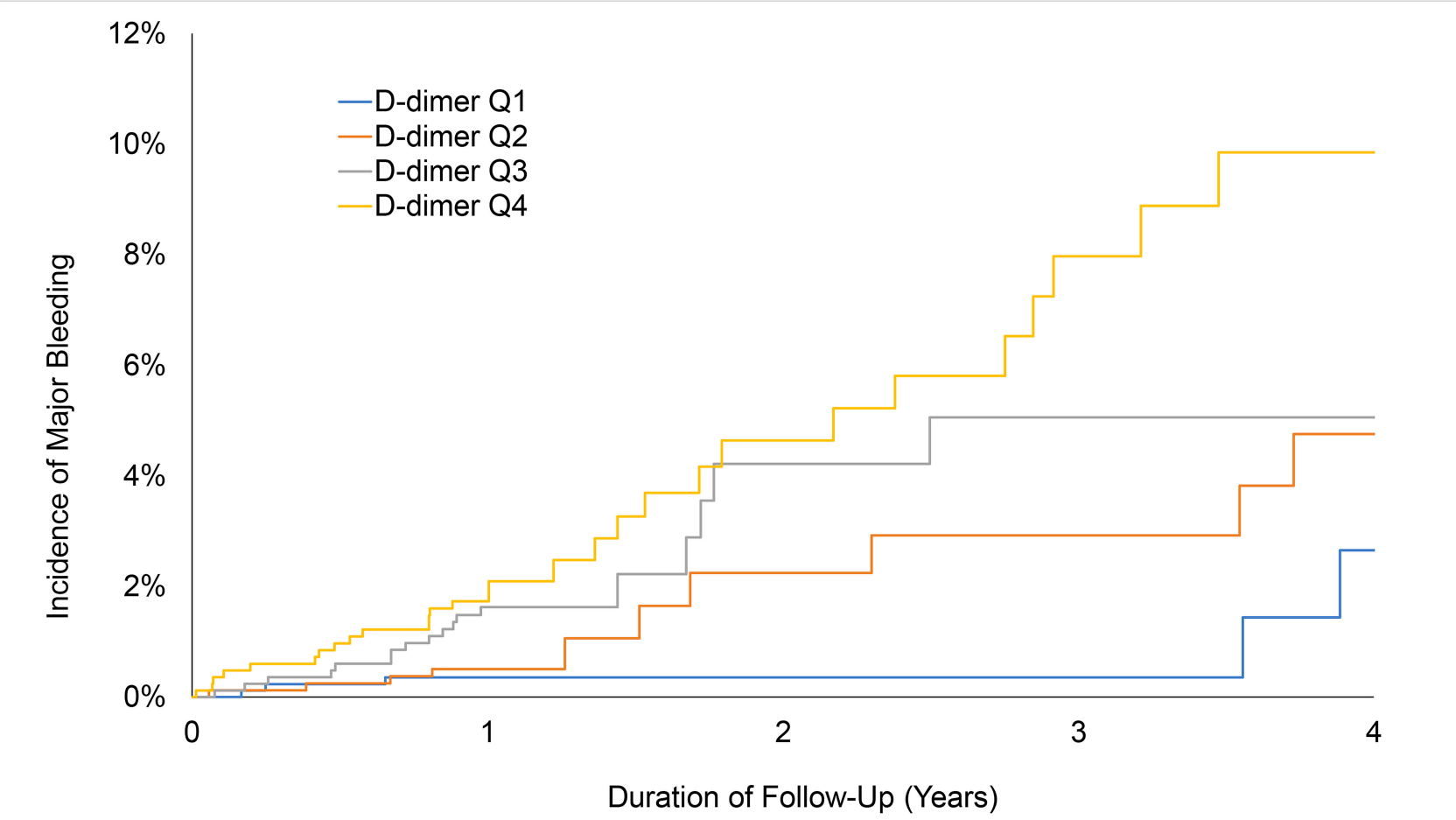
Figure Legends

Figure 1. STROBE flow diagram.

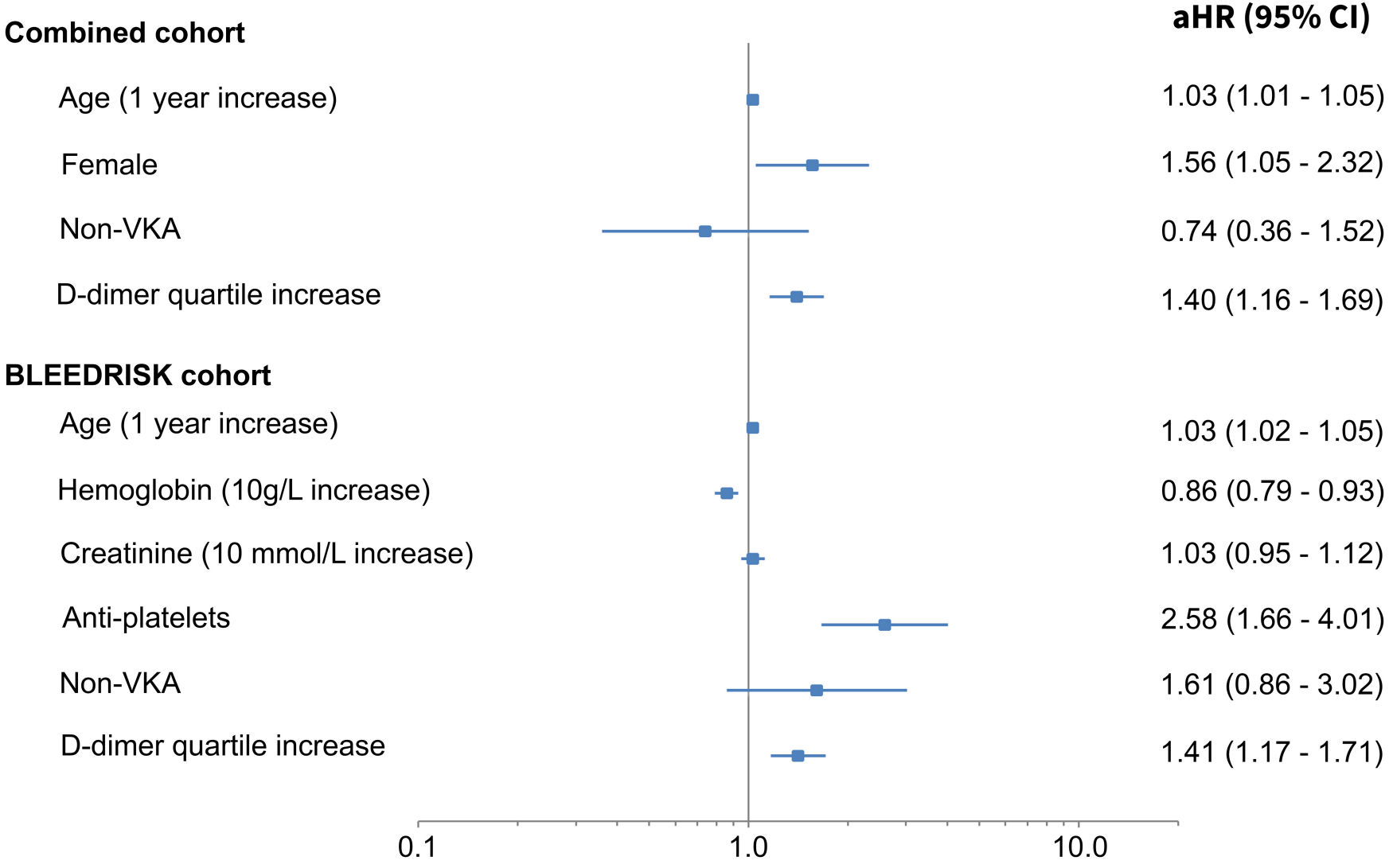
Figure 2. Cumulative incidence of major bleeding in patients across D-dimer quartiles

Figure 3. Predictors of anticoagulant-associated major bleeding during extended treatment for unprovoked venous thromboembolism. Variables with adjusted hazard ratios >1 indicate increased risk when present; adjusted hazard ratios <1 indicate decreased risk when present. VKA, vitamin K antagonist; aHR, adjusted hazard ratio.


BLEEDRISK cohort (n =2511)
REVERSE-2 cohort (n = 2732)
Linkage
Overlap in both cohorts (n = 291)
Patients without D-dimer levels (n = 1615)
Analyzed (n=3337)
Permanent anticoagulant discontinuation (n=104)
Lost to follow-up (n=51)
Death unrelated to outcome (n=32)
Withdrew consent (n=25)
Completed follow-up (n=3125)



Q1	855	592	163	122	72
Q2	813	512	156	128	92
Q3	835	522	137	99	73
Q4	834	487	191	122	61


Combined cohort
aHR (95% CI)
Age (1 year increase)
1.03 (1.01 - 1.05)
Female
1.56 (1.05 - 2.32)
Non-VKA
0.74 (0.36 - 1.52)
D-dimer quartile increase
1.40 (1.16 - 1.69)
BLEEDRISK cohort
Age (1 year increase)
1.03 (1.02 - 1.05)
Hemoglobin (10g/L increase)
0.86 (0.79 - 0.93)
Creatinine (10 mmol/L increase)
1.03 (0.95 - 1.12)
Anti-platelets
2.58 (1.66 - 4.01)
Non-VKA
1.61 (0.86 - 3.02)
D-dimer quartile increase
1.41 (1.17 - 1.71)
0.1
1.0
10.0

Supplementary Methods

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (2007).[1]

Study populations

We performed a post-hoc analysis that combined data from two prospective cohort studies (BLEEDRISK and REVERSE-II) that included patients with a first unprovoked VTE who continued anticoagulation after at least 3 months of initial treatment.[2, 3]

BLEEDRISK (NCT00788736) enrolled individuals ≥18 years with a first episode of unprovoked or weakly provoked VTE who continued anticoagulation beyond 3 months of initial treatment.[2] The purpose of the study was to develop a clinical prediction model identifying characteristics of patients at high risk of major bleeding during long-term anticoagulation for unprovoked or weakly provoked VTE. Participants were enrolled between September 2008 and September 2016. At enrolment, eligible participants must have received vitamin K antagonist (VKA) with a target international normalized ratio of 2.0 to 3.0 or a direct oral anticoagulant (DOAC) at therapeutic dosing for at least 3 months, with plans to receive indefinite anticoagulation for secondary prevention. Exclusion criteria included patients with VTE provoked by major transient or persistent risk factors including major surgery or active cancer, a major bleeding event while receiving oral anticoagulant therapy for the index VTE event, or active bleeding at study enrollment. Patients were enrolled in Canada, the United States, and the United Kingdom. On-treatment D-dimer was measured at the time of enrolment (i.e., ≥3 months after treatment initiation), along with collection of data on risk factors for anticoagulant-associated major bleeding. Participants were followed every 6 months following enrollment for assessment of major bleeding with a median follow-up of 2.6 years, and were censored if they stopped taking anticoagulant agents, experienced a major bleeding event, were lost to follow-up, withdrew consent, or died (whichever occurred first). Weakly provoked VTE was defined as VTE associated with minor persistent risk factors (e.g., lower extremity paralysis or paresis) or minor transient risk factors (e.g., admission for medical illness, long-distance travel, or estrogen). Unprovoked VTE was defined as VTE occurring in the absence of major risk factors (surgery or malignancy) or minor risk factors listed above.

REVERSE-II (NCT00967304) was a multinational prospective management study involving 44 centres in 7 countries to validate the "Men continue and HERDOO2" rule, a clinical decision rule to identify patients at low risk of recurrence following a first episode of unprovoked VTE who can safely discontinue anticoagulation after time-limited treatment.[3] Participants were enrolled between November 2008 to February 2015. After baseline clinical data collection, on-treatment D-dimer levels were measured for 98.6% of enrolled participants at the initial study visit (i.e., 5-12 months after treatment initiation), who were contacted at 6- and 12-months

following enrolment to assess study outcomes. Unprovoked VTE consisted of proximal DVT or PE not associated with lower extremity fracture or plaster cast, immobilization for ≥3 days, major surgery in the 3 months before the index event, and no diagnosis of a malignancy in the past 5 years (except for localized skin cancer). Specific to the current study, individuals who were risk stratified to low risk of recurrent VTE and subsequently stopped anticoagulation were excluded. Meanwhile, those on exogenous estrogen at the time of index VTE diagnosis who continued on indefinite anticoagulation were included. Exclusion criteria included discontinuation of oral anticoagulation prior to enrolment, need for ongoing anticoagulation for other indications (such as mechanical heart valves, atrial fibrillation, known high risk thrombophilia prior to enrolment, and pregnancy-associated VTE. Participants were followed for one year after enrolment and were censored at the time they withdrew consent and did not permit the collection of further follow-up data, were lost to follow-up, or died (whichever occurred first).

Exposure

The main study exposure was on-treatment D-dimer levels, reported in ng/mL fibrinogen equivalent units (FEU). While D-dimer level measured by any quantitative assay was eligible for inclusion, VIDAS® D-dimer Exclusion II assay (BioMerieux) was the most frequently used D-dimer assay in the two included studies (88.4%). In both cohorts, on-treatment D-dimer levels were measured at enrolment while patients were receiving therapeutic anticoagulation. Among DOAC-treated participants, plasma samples for D-dimer quantitation were collected at time of anticipated peak effect (dabigatran 4-8 hours, apixaban 2-6 hours, rivaroxaban 2-6 hours, and edoxaban 2-6 hours).[3] Plasma samples were double centrifuged prior to D-dimer testing. If testing was not available locally, samples were immediately frozen at −70°C after centrifugation and transported on dry ice.

Outcomes

The primary outcome was major bleeding as defined by the International Society on Thrombosis and Haemostasis, which comprises the following: fatal bleeding, and/or symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), bleeding causing a fall in hemoglobin levels of ≥20 g/L, or leading to a transfusion of ≥2 packed red cell units.[4] In BLEEDRISK and REVERSE-2 cohorts, this outcome was independently adjudicated by blinded evaluators. Secondary outcomes included intracranial hemorrhage and fatal bleeding.

Statistical analysis

Participants across the two studies were merged into a combined cohort. The combined cohort was then divided into four quartiles based on on-treatment D-dimer levels. We established the distribution of baseline demographics in each D-dimer quartile. Specific to the BLEEDRISK cohort, we determined the prevalence of bleeding risk factors including anemia, hypertension,

creatinine clearance, and concurrent antiplatelet use. Anemia was defined as hemoglobin <130 g/L in males or <120 g/L in females, and hypertension as active treatment for hypertension at study enrollment.[2] We calculated crude incidence rates of major bleeding, intracranial hemorrhage, and fatal bleeding across the four quartiles. Using the participants in the lowest D-dimer quartile as the reference quartile, we then calculated the hazard ratios for major bleeding, intracranial hemorrhage, and fatal bleeding across the D-dimer quartiles using the Cox proportional hazards model.

To determine the independent effect of on-treatment D-dimer level on anticoagulant-associated major bleeding, we adjusted for three established predictors of anticoagulant-associated major bleeding: age, sex, and anticoagulant type, in the combined cohort. Among BLEEDRISK cohort participants, we further accounted for additional components of the CHAP model (creatinine, hemoglobin, concurrent anti-platelet therapy).[2] Finally, we performed sub-group analysis by restricting the cohort by participant sex (male or female), given differences in prognostic impact of D-dimer for recurrent VTE among females compared to males.[5] In a sensitivity analysis to account for clustering at the study level, we performed a two-stage meta-analysis at the study level using a random-effects model to assess for consistent of findings to analysis using the pooled cohort.

Sample Size

While a general rule of thumb suggests a minimum of 10 events per candidate predictor parameter in risk assessment model research, we used recommendations by Riley *et al* to avoid risk of overfitting.[6] Based on i) known predictors of major bleeding during indefinite anticoagulation for VTE (age, renal function, hemoglobin, concurrent anti-platelet therapy)[2] and incorporation of D-dimer as a predictor; ii) Nagelkerke $R^2 = 0.15$; and iii) target shrinkage ≥ 0.90,[6] we estimated 53 events to be required. Based on the number of major bleeds identified in the combined cohort (65 events), the number of outcomes provided adequate sample size to enable the planned *post-hoc* analysis.

Data analysis was conducted in SAS (Cary, NC), with a *p*-value threshold of < 0.05 considered statistically significant.

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Supplementary Table 1. Additional baseline characteristics of included participants by D-dimer quartiles

	Overall (N=3337)	D-dimer Q1 (N=855)	D-dimer Q2 (N=813)	D-dimer Q3 (N=835)	D-dimer Q4 (N=834)
Demographic factors					
Weight in kg (mean ± SD)	87.3 ± 23.6	88.1 ± 21.8	88.6 ± 23.1	89.6 ± 23.6	82.8 ± 25.1
Body mass index in kg/m2 (mean ± SD)	29.8 ± 9.5	29.0 ± 6.3	30.2 ± 13.3	31.1 ± 9.9	28.9 ± 6.8
Median follow-up in years (IQR)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1.6)
Characteristics of index VTE					
Post-thrombotic syndrome (%)	445 (21.1%)	76 (14.5%)	101 (19.5%)	129 (24.5%)	139 (25.7%)
Prior provoked VTE	185 (5.6%)	30 (3.5%)	42 (5.2%)	46 (5.5%)	67 (8.0%)
Exogenous estrogen use (%)	424 (12.7%)	209 (24.4%)	126 (15.5%)	66 (7.9%)	23 (2.8%)
BLEEDRISK cohort only					
Median creatinine clearance (IQR)	109.5 (80.6 – 139.3)	123.9 (97.2 – 151.9)	114.3 (90.7 – 144.4)	109.1 (77.2 – 140.4)	93.9 (66.5 – 125.0)
Hypertension (n/N, %)	331 / 994 (35.1%)	47 / 215 (21.9%)	72 / 216 (33.3%)	82 / 197 (41.6%)	130 / 316 (41.1%)
Anemia (n/N, %)	102 / 935 (10.9%)	6 / 212 (2.8%)	17 / 196 (7.9%)	21 / 196 (10.7%)	58 / 312 (18.6%)
Concurrent anti-platelet use (n/N)	49 / 944 (5.2%)	8 / 215 (3.7%)	8 / 216 (3.7%)	7 / 197 (3.6%)	26 / 316 (8.2%)
CHAP high-risk (n/N)	216 / 914 (23.6%)	16 / 207 (7.7%)	39 / 208 (18.8%)	45 / 192 (23.4%)	116 / 307 (37.8%)

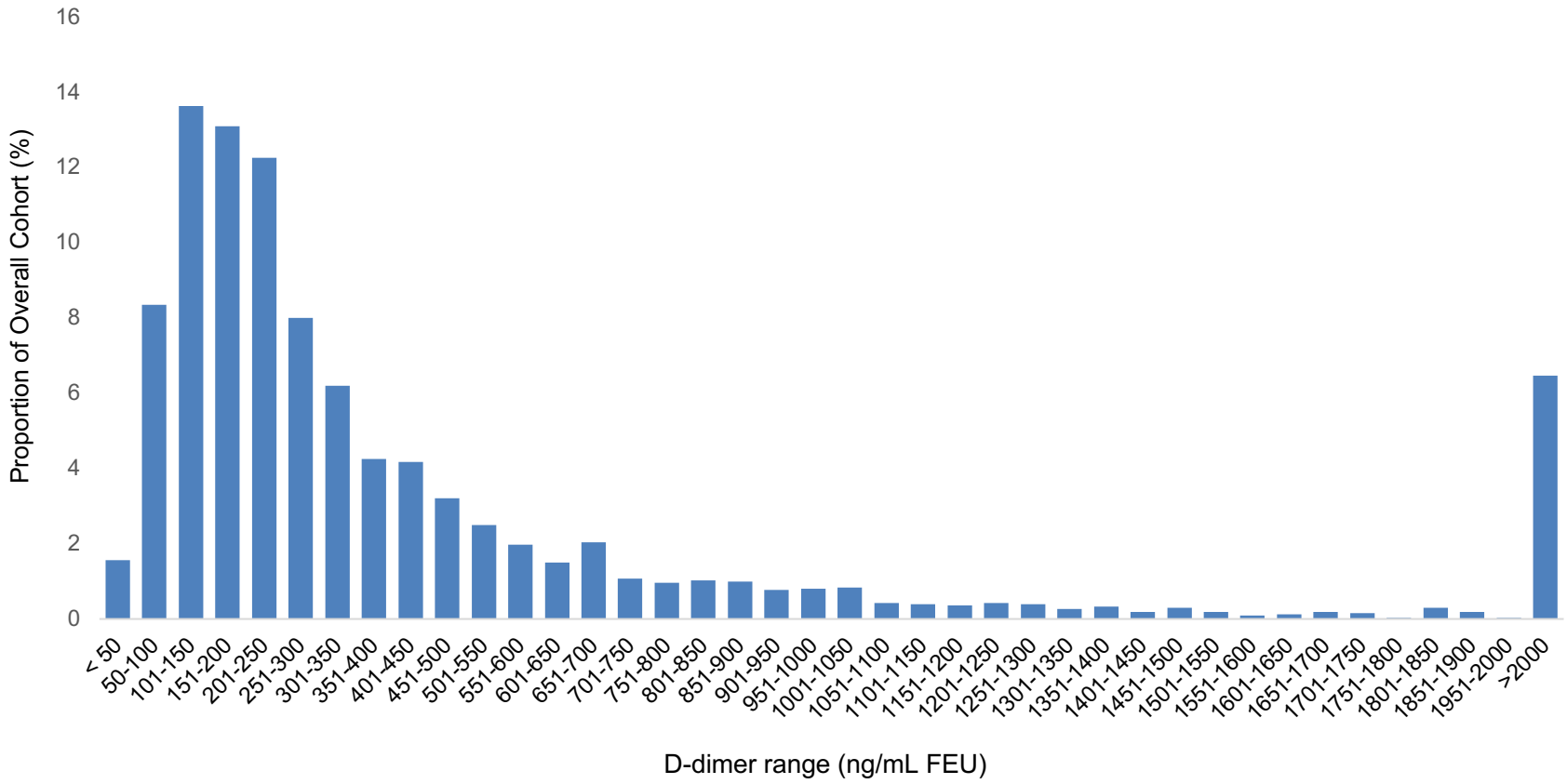
Supplementary Table 2. Baseline characteristics of participants in the combined cohort and component studies.

	Overall (N=3337)	REVERSE-2* (N=2393)	Bleedrisk* (N=944)
D-dimer values			
Any D-dimer assay (median, IQR)*	256.4 (150.0 – 502.0)	247 (145.6 – 450)	296.5 (161.2 – 836)
VIDAS D-dimer (median, IQR)*	245.0 (147.0 – 445.8)	247 (145.6 – 450)	236.6 (150 – 426)
Demographic factors			
Age (mean ± SD)	55.4 ± 16.6	53.8 ± 16.9	59.4 ± 14.9
Female sex (%)	1431 (42.9%)	1123 (46.9%)	308 (32.6%)
Characteristics of index VTE			
Index VTE			
DVT	1428 (42.8%)	938 (39.2%)	490 (52.1%)
PE	1250 (37.5%)	957 (40.0%)	293 (31.1%)
PE+DVT	656 (19.7%)	498 (20.8%)	158 (16.8%)
Anticoagulant modality			
Vitamin K antagonist	2603 (78.0%)	1770 (74.0%)	833 (88.2%)
Rivaroxaban	515 (15.4%)	421 (17.6%)	94 (10.0%)
Edoxaban	18 (0.5%)	3 (0.1%)	15 (1.6%)
Apixaban	7 (0.2%)	7 (0.3%)	0 (0.0%)
Dabigatran	12 (0.4%)	10 (0.4%)	2 (0.2%)
Other	182 (5.4%)	182 (7.6%)	0 (0.0%)

*291 participants enrolled in both REVERSE-2 and Bleedrisk cohorts were evaluated in the REVERSE-2 cohort.

Supplementary Table 3. Two-stage, random effects meta-analysis on the impact of D-dimer levels on anticoagulant-associated major bleeding.

	D-dimer Q1	**D-dimer Q2**	**D-dimer Q3**	**D-dimer Q4**
Major bleeding – Bleedrisk				
Adjusted Hazard Ratio (aHR, 95% CI)	Ref	2.12 (0.56 - 7.96)	2.14 (0.56 - 8.12)	3.78 (1.09 - 13.19)
Major bleeding – REVERSE-2				
aHR (95% CI)	Ref	0.59 (0.10 - 3.64)	2.08 (0.49 - 8.78)	1.79 (0.38 - 8.36)
Major bleeding – 2 stage meta-analysis				
aHR (95% CI)	Ref	1.31 (0.39–4.40)	2.11 (0.79–5.62)	2.81 (1.07–7.42)
Heterogeneity by I^2	N/A	19.2%	0%	0%



Supplementary Figure 1. Distribution of D-dimer level among participants in the combined cohort.