Annals of Internal Medicine | Review

Patient-Level Meta-analysis: Effect of Measurement Timing, Threshold, and Patient Age on Ability of D-Dimer Testing to Assess Recurrence Risk After Unprovoked Venous Thromboembolism

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Background: In patients with a first unprovoked venous thromboembolism (VTE), an elevated D-dimer level after anticoagulation is stopped is a risk factor for recurrent VTE. However, questions remain about the utility of measuring D-dimer in clinical practice.

Purpose: To determine whether the timing of testing, patient age, and the cut point used to define a positive or negative result affect the ability of D-dimer testing to distinguish risk for recurrent disease.

Data Sources: Comprehensive search of electronic databases (MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials) until July 2010, supplemented by reviewing conference abstracts and contacting content experts.

Study Selection: 7 prospective studies that investigated an association between D-dimer, measured after stopping anticoagulation, and disease recurrence in patients with a first unprovoked VTE (proximal deep venous thrombosis, pulmonary embolism, or both).

Data Extraction: Patient-level databases were obtained, transferred to a central database, checked, completed with further information provided by study investigators, and pooled into a single database.

Data Synthesis: 1818 patients with a first unprovoked VTE were followed for a mean of 26.9 months (SD, 19.1). A study-stratified multivariate Cox regression model, which included patient age, sex, hormone therapy use at the time of the index event, body mass index, timing of postanticoagulation D-dimer testing, and inherited thrombophilia as possible confounders, indicated that the hazard ratio for D-dimer status (positive vs. negative) was 2.59 (95% CI, 1.90 to 3.52). Only male sex had a significant effect on risk for recurrent VTE independent of D-dimer status. The Cox regression model and the log-rank test confirmed that the risk for recurrent VTE was higher in patients with a positive D-dimer result than in those with a negative result, regardless of the timing of postanticoagulation D-dimer testing or patient age. No study- or assay-specific D-dimer effect was found, and reassessing the analysis after recoding data according to specific quantitative D-dimer cut points (500 μg/L and 250 μg/L) did not change the results.

Limitations: Unmeasured variables could have affected the risk for recurrent VTE. The study population was predominantly white.

Conclusion: In patients with a first unprovoked VTE who have their D-dimer level measured after stopping anticoagulation, the timing of D-dimer testing, patient age, and the assay cut point used do not affect the ability of D-dimer to distinguish patients with a higher or lower risk for recurrent VTE.

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In patients with a first unprovoked venous thromboembolism (VTE), in whom VTE occurs without exposure to an antecedent clinical risk factor, the optimal duration of anticoagulation is uncertain (1–3). Clinical practice guidelines recommend at least 3 months of anticoagulation after a first unprovoked VTE; in patients at low risk for bleeding who have reliable anticoagulation monitoring, indefinite (or lifelong) treatment is recommended (4). Identifying patients at low risk for recurrent VTE who do not need indefinite anticoagulation is desirable, especially because up to 50% of all patients with VTE have unprovoked VTE (5, 6).

One strategy for stratifying patients according to risk for recurrent VTE is to measure D-dimer, a fibrin degradation product and a marker of coagulation activation, after anticoagulation is stopped (7). A negative D-dimer result is already used to exclude VTE in patients with suspected acute VTE (8); however, it can also identify patients at low risk for recurrent VTE in whom anticoagulation may be stopped. A positive D-dimer result identifies patients with a high risk for recurrence (because of a persistent prothrombotic tendency) in whom indefinite anticoagulation may be justified (9). Several D-dimer assays are available, which use a cut point of either 500 or 250 μg/L (depending on the assay) to define a negative or positive result.

A study-level meta-analysis (10) found that measuring D-dimer level after anticoagulation is stopped can stratify patients with unprovoked VTE by their risk for recurrent VTE. The annual risk for recurrence was 3.5% in patients with a negative D-dimer result and 8.9% in patients with a positive result. However, questions remain about the clinical application of postanticoagulation D-dimer testing for distinguishing risk for recurrent VTE. First, does the pre-

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Context

Guidelines recommend more than 3 months of anticoagulation for unprovoked venous thromboembolism (VTE) and indefinite treatment if patients are at low bleeding risk and have access to monitoring. Identifying patients with low risk for recurrence could help such patients avoid prolonged anticoagulation.

Contribution

This patient-level meta-analysis of 7 studies involving 1818 patients confirmed that positive D-dimer results after cessation of anticoagulation is associated with recurrent VTE and found that timing of testing, patient age, and D-dimer cut point do not affect this association.

Implication

Clinicians need not consider timing of testing, patient age, or D-dimer cut point when using D-dimer testing to decide about duration of anticoagulation for unprovoked VTE.

—The Editors

dictive utility of D-dimer testing vary depending on whether it is measured less than 3 weeks (early) or more than 5 weeks (late) after anticoagulation is stopped? Second, because D-dimer levels increase with age (11, 12), are findings in elderly patients applicable? Finally, does the predictive utility of D-dimer depend on the assay or the cut point used to define a negative or positive result? These questions are best addressed by a patient-level meta-analysis, which—unlike study-level meta-analyses—can address questions pertinent to patient subgroups, adjust for potential confounders, and allow time-to-event analyses (13–15).

We did a patient-level meta-analysis of patients with a first unprovoked VTE who had D-dimer testing after anticoagulation was stopped and were followed for recurrent VTE. We sought to determine whether the timing of post-anticoagulation D-dimer testing, patient age, or the D-dimer cut point used affected the ability of D-dimer testing to distinguish risk for disease recurrence.

METHODS

The process for obtaining patient-level data and the research protocol for this meta-analysis were developed by a core group of reviewers and approved by all study reviewers before data collection.

Study Selection

We adopted the search strategy used by 1 reviewer for a study-level meta-analysis (10) and updated it to include more recent studies. Major electronic databases (MEDLINE, EMBASE, CINAHL, and the Cochrane Register of Controlled Trials) were searched from their inception to July 2010 (**Appendix Table 1**, available at www.annals.org).

Source Study Characteristics

The individual studies pooled for our meta-analysis (16–22) were randomized trials or prospective cohort studies of patients with a first symptomatic VTE, with some patients having unprovoked VTE that consisted of proximal venous thrombosis, pulmonary embolism, or both (patients with only distal venous thrombosis were excluded). All study patients received standard anticoagulation, which consisted of heparin for 5 to 10 days and a vitamin K antagonist for 3 or more months. In all studies, D-dimer level was measured *after* anticoagulation was stopped and patients had subsequent follow-up for recurrent symptomatic VTE; outcomes were objectively confirmed and independently adjudicated.

Source Study Quality Assessment

Because standardized quality criteria for meta-analyses of prognosis studies are lacking (23, 24), we used a modified Newcastle–Ottawa Scale (NOS) (25) to assess the quality of included studies on the basis of patient selection (4 criteria), comparability of study groups (1 criterion), and assessment of outcome (3 criteria). We evaluated studies only on the basis of selection and outcome criteria, because the availability of patient-level data makes compa-

Table 1. **Patient Characteristics**

Study, Year (Reference)	Patients, *n*			Age, *y*		Body Mass Index, *kg/m²*	
	Analyzed	Men	Women	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
Palareti et al, 2003 (18)	292	147	145	66.9 (15.6)	71.0 (21.0–90.0)	–	–
Eichinger et al, 2003 (19)	422	194	228	49.8 (17.2)	50.6 (14.7–85.6)	27.2 (4.9)	26.6 (17.4–47.5)
Palareti et al, 2006 (17)	497	259	238	61.3 (15.8)	64.6 (18.7–84.3)	–	–
Shrivastava et al, 2006 (16)	110	60	50	54.1 (12.2)	52.5 (31.0–80.0)	32.3 (7.7)	30.7 (20.4–61.0)
Tait et al, 2007 (22)	131	63	68	57.2 (15.0)	60.5 (21.5–89.0)	28.5 (6.4)	28.0 (7.3–52.6)
Baglin et al, 2008 (21)	197	113	84	62.6 (17.7)	65.4 (0–95.0)	26.8 (7.2)	25.8 (0–57.0)
Poli et al, 2008 (20)	169	99	70	61.3 (15.6)	63.0 (14.0–92.0)	–	–
Pooled data	1818	935	883	58.9 (17.1)	61.6 (0–95.0)	28.1 (6.3)	27.2 (0–61.0)*

DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.
* Data for 808 patients.

rability criteria irrelevant. In accordance with the quality assessment standards of other meta-analyses (26), a study with an NOS score of 4 or greater was considered high quality. We planned to include the NOS score as a regression analysis variable to evaluate its impact on effect size.

Development of Individual Patient Database

We contacted the principal investigator of each eligible study to explain our meta-analysis objectives and analysis plan. After all investigators agreed to share their databases, the databases were transferred to a central location under the auspices of 2 reviewers. Data were checked, explanations for coding and uncertain or missing data were clarified, and a single pooled database was developed. For the 2 trials in which some patients with a positive D-dimer result were randomly allocated to resume anticoagulation (16, 17), such patients were excluded from the analyses.

Patient Population

We defined unprovoked VTE a priori as VTE that occurred in the absence of a major clinical VTE risk factor, such as surgery, trauma, active cancer, immobility, or pregnancy and puerperium. This definition was applied to all source studies. A VTE event that occurred in association with hormone therapy (oral contraceptive or estrogen replacement) or a thrombophilic abnormality and no other risk factors for VTE was also classified as unprovoked. Patients with antiphospholipid antibodies or antithrombin deficiency were excluded from our analysis, because such patients were also excluded from the source studies.

Patient Follow-up and Outcomes

Follow-up began when anticoagulation was stopped and ended at the end of the study or if the patient had symptomatic recurrent VTE, died of another cause, or restarted anticoagulation for another reason. No patients resumed anticoagulation during follow-up unless recurrent VTE occurred or they developed another indication for such treatment.

Statistical Analysis

We used Cox regression analysis to assess the ability of postanticoagulation D-dimer status (positive or negative) to distinguish patients according to risk for recurrent VTE; this was done with both univariate and multivariate analysis to account for potential confounding variables. The risk for recurrent VTE according to D-dimer status was expressed as a hazard ratio (HR) and associated 95% CI. Patient-level data were pooled with a fixed-effects approach, using a study-stratified analysis, and a random-effects approach, using a shared frailty model. The effect of D-dimer was also modeled under fixed- and random-effects assumptions.

We defined age, body mass index, sex (with or without previous hormone-associated VTE in women), thrombophilia status, postanticoagulation timing of D-dimer testing, duration of anticoagulation, NOS score, and D-dimer assay used as potential confounding variables a priori and included them in our regression analysis. In patients who had thrombophilia testing, only heterozygous carriers of the factor V Leiden or factor II mutations were included as variables; other blood abnormalities were excluded because of the anticipated small number of such abnormalities. The proportional hazards assumption was assessed by the analysis of Schoenfeld residuals. The baseline cumulative hazard function and the cumulative hazard function for patients with a positive or negative D-dimer result were estimated from the multivariate Cox regression.

Annualized risk for recurrent VTE, expressed as events per 100 patient-years of follow-up, was determined by considering studies as clusters for the jackknife CI calculation. Missing data were managed by the multiple-imputation approach (27). The cumulative hazard of recurrent VTE was estimated from Cox regression in patient subgroups on the basis of timing of D-dimer testing (<3, 3 to 5, or >5 weeks after stopping anticoagulation) or patient age (≤ 65 or >65 years). We estimated the annualized risk for recurrence in patients with a positive or negative D-dimer result and used a study-stratified log-rank test to compare this risk, by D-dimer status, across the subgroups.

We handled the different D-dimer assays used in the source studies and their respective cut points for a positive or negative result in a prespecified manner. First, we did

Table 1—Continued

Site of Index VTE, *n*	Hormone Therapy Use, *n*	Factor V Leiden Mutation (Heterozygous), *n*	Factor II Mutation (Heterozygous), *n*
Proximal DVT, 233; PE with or without DVT, 59	28	35	21
Proximal DVT, 196; PE with or without DVT, 226	119	90	19
Proximal DVT, 309; PE with or without DVT, 188	59	46	33
Proximal DVT with or without PE, 77; unspecified, 33	32	35	6
Proximal DVT, 75; PE with or without DVT, 56	31	14	7
Proximal DVT, 113; PE with or without DVT, 84	19	26	7
Proximal DVT, 102; PE with or without DVT, 67	19	17	15
Proximal DVT, 1028; PE with or without DVT, 680; proximal DVT with or without PE, 77; unspecified, 33	307	263	108

Table 2. **Results of Study-Stratified Multivariable Cox Regression Analysis**

Variable	Hazard Ratio for Recurrent VTE (95% CI)	*P* Value
D-Dimer result (positive vs. negative)	2.59 (1.90–3.52)	<0.001
Age (for 1-y increase)*	0.99 (0.98–1.00)	0.094
Body mass index (for 1-kg/m^2 increase)†	1.01 (0.97–1.05)	0.600
Men (vs. women with no previous hormone-associated VTE)*	1.79 (1.33–2.43)	<0.001
Women with hormone-associated VTE (vs. women with no hormone-associated VTE)*	0.45 (0.25–0.81)	0.007
D-Dimer test at <3 wk after anticoagulation (vs. at 3–5 wk)‡	0.83 (0.56–1.25)	0.40
D-Dimer test at >5 wk after anticoagulation (vs. at 3–5 wk)‡	0.73 (0.43–1.24)	0.30
Thrombophilic blood abnormality (present vs. absent)§	1.00 (0.70–1.41)	1.00
Duration of anticoagulation (for 1-mo increase)‖	1.00 (0.99–1.00)	0.90

VTE = venous thromboembolism.
* Data available for all patients.
† Data available for 44.1% of patients. Missing data were managed by a multiple-imputation approach.
‡ Data available for 88.7% of patients. Missing data were managed by a multiple-imputation approach.
§ Data available for 87.7% of patients. Missing data were managed by a multiple-imputation approach.
‖ Data available for all but 1 patient. Missing data were managed by a multiple-imputation approach.

Cox regression analyses that were based on the D-dimer cut points used in the source studies. Second, to explore the predictive utility of different D-dimer cut points, we did a sensitivity analysis that used cut points of 500 and 250 μg/L to define a negative or positive result; this analysis was applied to studies that provided quantitative D-dimer data. The 500-μg/L cut point is most often used by commercially available D-dimer assays; the 250-μg/L cut point, with its lower threshold for positivity, was also used because it may minimize false-negative results (patients with a negative D-dimer result who develop recurrent VTE). We did not construct receiver-operating characteristic curves to identify an optimal D-dimer cut point because D-dimer testing is used in everyday practice based on assay-specific cut points; a proposed different cut point would require validation in future trials and might be impracticable (requiring changes in laboratory-driven result reporting).

All calculations were done using STATA, version 9.2 (Statacorp, College Station, Texas). For additional post hoc analyses, see the **Appendix**, available at www.annals.org.

Role of the Funding Source

This study received no funding.

RESULTS

Appendix Figure 1, available at www.annals.org, provides the results of the study search and selection process. **Appendix Table 2**, available at www.annals.org, shows the characteristics and quality assessment scores of the source studies (16–22). All included studies were of high quality, which precluded using study quality (NOS score) as a variable in the regression analyses.

Appendix Figure 2, available at www.annals.org, shows the derivation of patients from the source studies. Of the 1863 patients with a first unprovoked VTE, 45 (2.4%) were excluded: 9 (0.5%) developed recurrent VTE after anticoagulation was stopped but before D-dimer testing; 9 (0.5%) did not have D-dimer testing; and 27 (1.4%) had D-dimer testing at the end of follow-up. **Table 1** describes the remaining 1818 patients. Among the 1806 patients who had thrombophilia testing, 269 had factor V Leiden mutations (263 heterozygous and 6 homozygous), 109 had factor II mutations (108 heterozygous and 1 homozygous), 74 had hyperhomocysteinemia, and 15 had protein C or S deficiency. Five types of D-dimer assay were used, with each study using a single assay. Six studies used a quantitative assay with a cut point of 500 μg/L (16, 18, 21, 22) or 250 μg/L (19, 20); quantitative D-dimer data were available from these 6 studies. One study (17) mainly used a qualitative D-dimer assay but also provided quantitative D-dimer data for most patients.

Patients were followed for a mean of 26.9 months (SD, 19.1) after anticoagulation was stopped, and the median follow-up was 22.4 months (range, 0.9 to 115.0 months). Postanticoagulation D-dimer results were negative in 992 patients (54.6%) and positive in 826 patients (45.4%) on the basis of source study–defined positive or negative results. Data on the timing of D-dimer testing were available for 1613 patients (88.7%); testing was conducted a mean of 38.5 days (SD, 59.7) and a median of 30.0 days (range, 2.0 to 544.0 days) after anticoagulation was stopped.

Risk for Recurrent VTE

The annualized risk for recurrent VTE (calculated accounting for the source study as a variable) was 3.7 per 100 patient-years (95% CI, 3.2 to 4.3 per 100 patient-years) in patients with a negative D-dimer result and 8.8 per 100 patient-years (CI, 6.2 to 11.3 per 100 patient-years) in those with a positive result.

Using univariate regression, the HR for recurrent VTE in all patients with a positive versus a negative D-dimer result was 2.59 (CI, 1.90 to 3.32). The addition of any of the potential confounders in bivariate analyses did not affect the predictive utility of D-dimer testing. **Table 2** shows the results of the multivariate Cox regression analysis that included all potential confounding variables. The D-dimer assay variable was dropped because it overlapped with the variable coding for the source study.

All Cox regression models were performed with either a fixed- or a random-effects model. We obtained a nonsignificant variance for the model, including a shared frailty

for the source study variable, which indicated the absence of significant within-study correlation and acceptance of a fixed-effects assumption for the study variable. Regression analysis showed no significant effect of study or study–D-dimer interaction, which indicated the absence of a study-specific D-dimer effect and allowed D-dimer to be modeled under a fixed-effects assumption. Among potential confounders, only patient sex and previous hormone-associated VTE (a 3-level variable comprising men and women with or without hormone-associated VTE) had a significant effect on recurrence risk. We calculated Cox-derived cumulative hazards for recurrent VTE over time, according to D-dimer status and sex and previous hormone-associated VTE (**Appendix Figure 3**, available at www.annals.org). Interaction terms between D-dimer and age and between D-dimer and test timing were assessed and found not to be statistically significant (data not shown). The Schoenfeld residuals were not statistically significant for either the whole model or variable by variable; thus, the proportional hazard assumption was not violated.

Effect of Other Factors on Association of D-Dimer and Risk for Recurrent VTE

Figure 1 shows the Cox-derived cumulative hazards for recurrent VTE for subgroups defined by the timing of D-dimer testing. D-Dimer testing was done less than 3 weeks after anticoagulation (mean, 2.2 weeks) in 220 patients (13.6%), 3 to 5 weeks after anticoagulation (mean, 4.0 weeks) in 1028 patients (63.7%), and more than 5 weeks after anticoagulation (mean, 11.7 weeks) in 365 patients (22.7%). **Table 3** shows the annualized risks for each subgroup. On the basis of the log-rank test, the risk for recurrence was significantly higher in patients with a positive D-dimer result than in those with a negative result, regardless of test timing.

Figure 2 shows the Cox-derived cumulative hazards for recurrent VTE for subgroups defined by patient age (≤65 or >65 years), and **Table 3** shows the annualized risks within each subgroup. On the basis of the log-rank test, the risk for recurrence was significantly higher in patients with a positive D-dimer result than in those with a negative result, regardless of age.

We reassessed the results after recoding patients according to a D-dimer cut point of 500 μg/L and then of 250 μg/L, when these cut points differed from that used by the source studies. For patients in 1 study (17), D-dimer values were used for recoding. Our findings from using either the 500- or 250-μg/L cut point were essentially unchanged from the primary analysis. Cox-derived cumulative hazards for recurrent VTE were calculated according to these cut points (**Appendix Figure 4**, available at www.annals.org). The absence of a significant interaction effect between the source study and D-dimer variables provides indirect evidence that the D-dimer assays used do not differ in their ability to distinguish recurrent VTE risk.

Discussion

We studied more than 1800 patients with a first unprovoked VTE who had D-dimer testing after stopping

Figure 1. **Cox-derived cumulative hazard for recurrent venous thromboembolism, by D-dimer status in patient subgroups defined by timing of D-dimer testing after anticoagulation.**

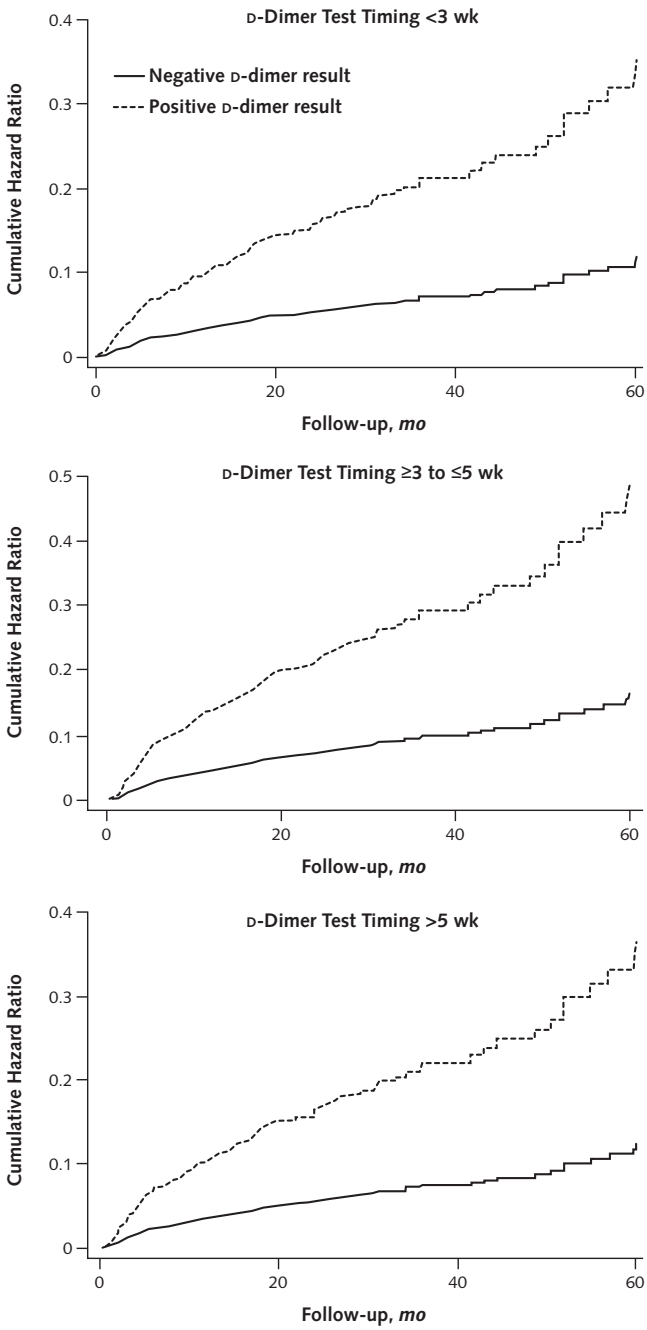


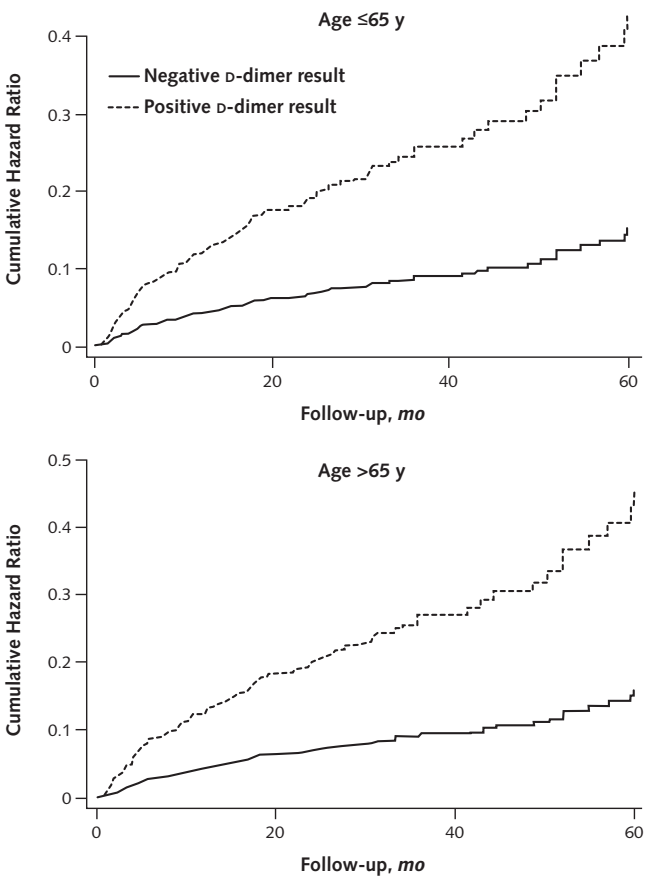
Table 3. **Annualized Risk for Recurrent VTE, by Timing of D-Dimer Testing After Anticoagulation and Patient Age**

Variable	Negative D-Dimer Result		Positive D-Dimer Result		Log-Rank Test*	*P* Value
	Patients, *n* (%)	Annualized Risk for Recurrent VTE per 100 Patient-Years (95% CI)	Patients, *n* (%)	Annualized Risk for Recurrent VTE per 100 Patient-Years (95% CI)		
Timing of D-dimer testing after anticoagulation					40.7†	<0.001
<3 wk	97 (44)	2.0 (1.1–2.0)	123 (56)	8.2 (2.1–13.9)		
3–5 wk	591 (57)	4.2 (3.8–4.5)	437 (43)	10.2 (7.3–13.5)		
>5 wk	223 (61)	3.0 (2.3–4.1)	142 (39)	7.4 (3.9–12.0)		
Patient age					35.6‡	<0.001
≤65 y	620 (65)	3.3 (2.4–4.4)	341 (35)	8.2 (4.4–12.0)		
>65 y	291 (45)	4.9 (3.9–6.8)	361 (55)	9.4 (7.6–11.3)		

VTE = venous thromboembolism.
* Comparison of survivor function of D-dimer–positive and –negative results at the end of follow-up.
† Stratified by test timing and study.
‡ Stratified by age and study.

anticoagulation. The HR for recurrent VTE in all patients with a positive versus a negative D-dimer result was 2.59 (CI, 1.90 to 3.52). The predictive utility of D-dimer testing for distinguishing patients at lower or higher risk for recurrent VTE was not affected by the timing of postanticoagulation D-dimer testing, whether early (<3 weeks), intermediate (3 to 5 weeks), or late (>5 weeks); advanced patient age (>65 years); or the D-dimer assay used.

Figure 2. **Cox-derived cumulative hazard for recurrent venous thromboembolism, by D-dimer status in patient subgroups defined by age.**



Determining whether the timing of D-dimer testing influences its utility to distinguish risk for recurrent VTE is important, because if D-dimer level is measured too early, it may not reflect ongoing coagulation activation due to the neutralizing effect of previous anticoagulation on D-dimer level (28, 29). In contrast, delaying D-dimer testing for too long may expose patients who would have a positive result to a period of heightened risk for recurrent VTE after anticoagulation is stopped. We found that recurrent VTE occurred in 0.5% of patients before D-dimer testing, which is similar to a reported 1% recurrence risk in the initial month after stopping anticoagulation (30). In our study, 63% of patients had D-dimer testing done 3 to 5 weeks after stopping anticoagulation; timing had no effect on the ability of D-dimer testing to distinguish recurrence risk across or within timing groups. This finding may reassure clinicians that D-dimer testing retains its ability to distinguish patients' risk for recurrence whether it is done less than 3 weeks or more than 5 weeks after anticoagulation is stopped. However, it is sensible to measure D-dimer approximately 4 weeks after anticoagulation to minimize the risk for recurrence before testing and expedite decisions about stopping or resuming anticoagulation.

Determining whether advanced patient age influences the predictive utility of D-dimer for recurrent VTE is also important, because up to 50% of patients with VTE may be older than 65 years and D-dimer levels increase with age (31, 32). In our study, in which 41% of patients were 65 years or older and 18% were 75 years or older, patient age did not affect the ability of D-dimer to distinguish risk for recurrence. The prevalence of a positive D-dimer result af-

ter anticoagulation increased considerably with age, from 35% in patients 65 years or younger to 55% in patients older than 65 years, which reduces the potential for stopping anticoagulation in elderly patients because fewer such patients would have a negative D-dimer result. However, the risk for recurrent VTE in patients older than 65 years who had a positive D-dimer result did not diminish, which suggests that a positive result in this group is unlikely to be falsely positive and reinforces the predictive value of D-dimer testing in elderly patients. Thus, clinicians may also be reassured that D-dimer testing retains its predictive utility for assessing recurrent VTE risk in elderly patients. Future studies may identify D-dimer cut points specific for elderly patients that minimize the proportion of patients with a positive test result but retain the ability to distinguish risk for recurrence.

The availability of several D-dimer assays, the lack of a single cut point for a positive or negative result, and the lack of an international standard for D-dimer assays may hinder the use of D-dimer testing for stratifying patients according to risk for recurrent VTE. Clinicians may use the assay manufacturer's cut point, which is typically based on studies that assessed D-dimer to exclude a diagnosis of suspected VTE. Developing a single D-dimer cut point that optimizes test sensitivity and specificity can lead to overestimations of accuracy when done in a post hoc manner (33). Having multiple cut points depending on age or other patient characteristics may be confusing and requires further study (34, 35). We aimed to simplify this issue by using the assay manufacturers' cut points that were used in each source study when performing our primary analyses. We found no heterogeneity of results across 5 different D-dimer assays and 2 different cut points (500 and 250 μg/L) for a negative or positive result, which suggests that D-dimer assays could be used interchangeably to distinguish a patient's risk for recurrent VTE. We also reanalyzed our findings using a single cut point for all the studies (either 500 or 250 μg/L) and found that the predictive utility of D-dimer was unchanged. Because it is unlikely that only 1 D-dimer assay will be available for clinical use, our findings may reassure clinicians of the predictive utility of D-dimer for recurrent VTE regardless of the assay and manufacturer-recommended cut point.

The principal strength of our study is that it represents, to our knowledge, the largest prospectively derived data source that assesses D-dimer testing as a predictor of disease recurrence after unprovoked VTE. However, our study has limitations. First, our analyses are limited to the data available from the source studies. Unmeasured variables, such as undetected genetic predispositions, could have affected our findings. Second, our definition of unprovoked VTE may be imprecise (either over- or underinclusive), although no standard definition exists (4). Unprovoked VTE was defined as being clearly distinguishable from provoked VTE, which occurs in association with a reversible major risk factor. Hormone-associated VTE was considered to be unprovoked, because hormone therapy is a weak risk factor for VTE and is unlikely to have a major pathogenic role compared with other risk factors, such as surgery (36). This premise is supported by a recent study (37) in which women with hormone-associated VTE had a similar risk for recurrent VTE as those with otherwise unprovoked VTE. Patients with thrombophilia were also considered to have unprovoked VTE, because it does not seem that such blood abnormalities confer an increased risk for recurrent VTE as they do for initial VTE (38). Furthermore, when we redid the regression analyses after excluding patients with a previous hormone-associated VTE and thrombophilia (heterozygous factor V Leiden or factor II mutation carriers), our findings remained unchanged compared with analyses when these patients were included (HR for recurrent VTE, 2.4 [CI, 1.1 to 5.1]). Third, the duration of anticoagulation was not fixed, which might affect rates of recurrent VTE. However, treatment duration does not seem to influence recurrent VTE risk in patients with unprovoked VTE; longer anticoagulation seems to simply delay recurrence (39, 40). Finally, our findings are based on a mainly white patient sample and may not be applicable to other ethnicities, which have different distributions of D-dimer level (41).

Our findings have practice implications for clinicians who may be considering D-dimer testing to help decide whether a patient with a first unprovoked VTE needs indefinite anticoagulation, because the timing of D-dimer testing after anticoagulation, patient age, and the D-dimer assay used seem not to affect that decision. Although a D-dimer assay may not be a standalone test for predicting risk for recurrent VTE, other disease prediction strategies that involve residual venous thrombosis or thrombophilia testing have limitations (42, 43). One clinical prediction rule that incorporated D-dimer testing during (but not after) anticoagulation seemed useful in women but not men (44). A clinical prediction guide that incorporates objective clinical, imaging, and laboratory-based parameters to predict recurrence is needed (45, 46), and studies to address this are planned. Meanwhile, our findings are relevant to the large number of patients worldwide who have an unprovoked VTE each year, including the estimated 100 000 in North America alone (47–49).

To summarize, in patients with a first unprovoked VTE who have D-dimer measured after stopping anticoagulation, the timing of D-dimer testing, patient age, and the assay cut point used do not affect the ability of D-dimer to distinguish patients at higher or lower risk for recurrent VTE.

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Administrative, technical, or logistic support: J. Douketis, M. Cushman, S. Eichinger.
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Appendix: Supplementary Analyses

We conducted additional post hoc analyses to address 2 potentially controversial issues: whether individual D-dimer levels are predictive of recurrent VTE, as opposed to the dichotomous approach used in ours and previous studies, and the appropriateness of classifying (as we did) patients with hormone- or thrombophilia-associated VTE as having unprovoked VTE.

To investigate the relationship between risk for VTE recurrence and D-dimer level, we did a multivariate Cox regression analysis by using D-dimer as a continuous variable and depicted the Cox-derived cumulative hazard for recurrent VTE as a function of increasing D-dimer level after 3 years of patient follow-up. This yielded a regression coefficient of 5.3×10^{-4} (CI, 3.5×10^{-4} to 7.1×10^{-4}), which corresponds to an HR for recurrent VTE of 1.00053 (or a 0.053% increase) for each 5.476-nmol/L increase in D-dimer level. We derived the baseline cumulative hazard function from this Cox model and traced the curve of the trend of the cumulative hazard at 3-year follow-up, according to D-dimer quantitative values (**Appendix Figure 5**).

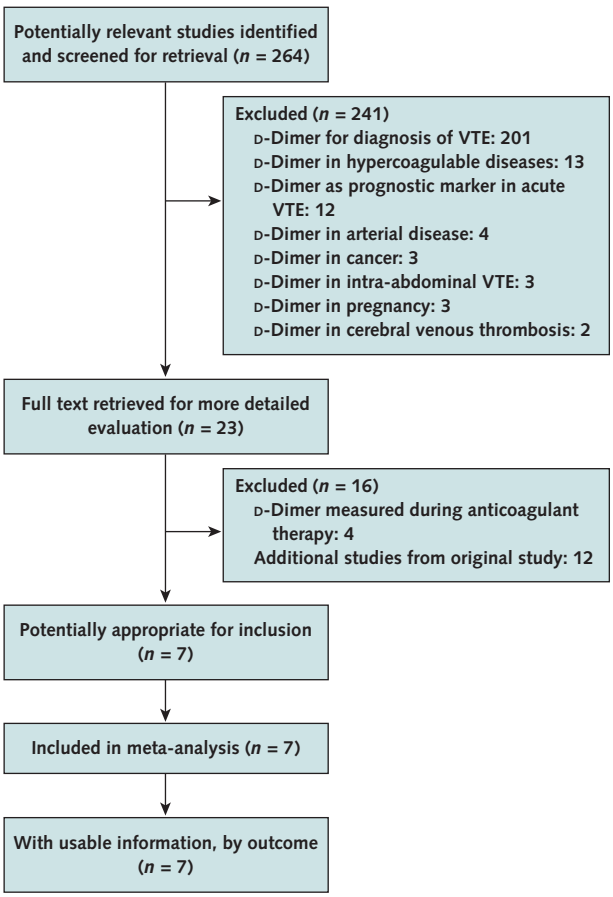
To test the sensitivity for recurrent VTE in patients with unprovoked VTE, we repeated the multivariate Cox regression analysis after excluding women with previous hormone-associated VTE or thrombophilia (heterozygous factor V Leiden or factor II mutation)–associated VTE. Our findings remained unchanged from the analyses that included these patient subgroups (HR for recurrent VTE, 2.4 [CI, 1.1 to 5.1]). Male sex maintained its significant effect on VTE recurrence risk, whereas patient age and timing of D-dimer testing did not affect recurrence risk.

Appendix Table 1. **Literature Search Strategy***

Database: Ovid MEDLINE, 1950 to week 2, July 2010
1. exp anticoagulants/ (158855)
2. anticoagulant$.mp. (61033)
3. anticoagulant$.mp. (61033)
4. 1 or 2 or 3 (170616)
5. Adult/ (3354712)
6. exp fibrin degradation products/ (5840)
7. D-dimer.mp. (4370)
8. 6 or 7 (7724)
9. exp recurrence/ or recurrence.mp. (277845)
10. recurrent$.mp. (152573)
11. 9 or 10 (365286)
12. exp predictive value of tests/ or predictive value.mp. (128598)
13. 11 or 12 (486309)
14. Thromboembolism.mp. or exp thromboembolism/ (45309)
15. Venous thrombosis.mp. or exp venous thrombosis/ (45293)
16. Pulmonary embolism.mp. or exp pulmonary embolism/ (32211)
17. 14 or 15 or 16 (102347)
18. 4 and 5 and 8 and 13 and 17 (264)

* Supplemented by reviewing recent (≤3 y) conference abstracts (from the International Society on Thrombosis and Haemostasis, American Society of Hematology, and International Conference on Thrombosis) and contacting content experts. No additional articles were identified through these search methods.

Appendix Figure 1. **Summary of evidence search and selection.**



VTE = venous thromboembolism.

Appendix Table 2. **Source Study Characteristics**

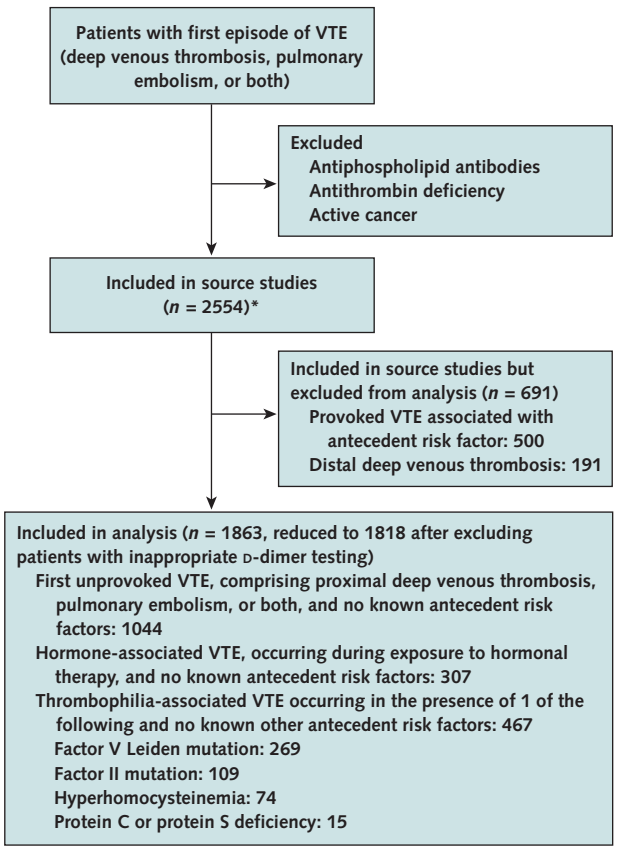
Study, Year (Reference)	Design	Inclusion (Exclusion) Criteria	Index VTE	Assay, Manufacturer (Type)	Normal D-Dimer Value, μg/L	Quantitative D-Dimer	Monitoring for Recurrent VTE	Study Quality Assessment, Selection/ Outcome Critieria, n/n*†
Palareti et al, 2003 (18)	Prospective cohort, single center	First VTE (lupus anticoagulant)	Leg DVT or PE	VIDAS, bioMérieux, Marcy l'Etoile, France (ELISA)	≤500	Available	Clinical visits 3 mo after stopping VKA therapy, then every 6 mo Instructions to contact physician if symptomatic	4/3
Eichinger et al, 2003 (19)	Prospective cohort, single center	First unprovoked VTE (surgery, trauma, or pregnancy within the past 3 mo; cancer; APS; natural coagulation inhibitor deficiency; or long-term anticoagulation)	Leg DVT or PE	Asserachrom, Diagnostica Stago, Asnières, France (ELISA)	<250	Available	Clinical visits every 3 mo for 1 y, then every 6 mo	3/3
Palareti et al, 2006 (17)	Randomized, controlled trial; multicenter	First unprovoked VTE (recent pregnancy or puerperium, fracture or plaster casting of leg, immobilization for ≥3 consecutive d, surgery with general anesthesia, active cancer, APS, antithrombin deficiency, serious liver or renal disease, other indication or contraindication for anticoagulation, limited life expectancy, or geographic inaccessibility)	Proximal leg DVT or PE	Clearview Simplify, Alere International, Cranfield, United Kingdom (qualitative)	Qualitative (abnormal vs. normal)	Available (VIDAS, ELISA)†	Clinical visits every 3–6 mo Instructions to contact physician if symptomatic	4/3
Shrivastava et al, 2006 (16)	Randomized, controlled trial; multicenter	Unprovoked VTE (surgery or trauma within 90 d of index event, APS, previous or active cancer, or life expectancy <3 y)	Leg DVT or PE	STA Liatest, Diagnostica Stago, Asnières, France (ELISA)	<500	Available	Clinical visits every 2 mo	3/3
Tait et al, 2007 (22)	Prospective cohort, multicenter	Acute VTE within the past 5 wk (life expectancy <3 mo; anticipated duration of anticoagulation >1 y; unavailable for follow-up)	DVT or PE	VIDAS, bioMérieux, Marcy l'Etoile, France (ELISA)	<500	Available	Nurse visit at 3 mo, 1 y, and 2 y after stopping VKA therapy Instructions to contact physician if symptomatic	Not applicable
Baglin et al, 2008 (21)	Prospective cohort, single center	First VTE (postoperative or pregnancy-associated VTE, APS, cancer, thrombosis within 6 wk of surgery, or other indication for prolonged anticoagulation)	Proximal leg DVT or PE	MDA, Trinity Biotech, Bray, Ireland (LIA)	<500	Available	Yearly follow-up	3/3
Poli et al, 2008 (20)	Prospective cohort, single center	First unprovoked VTE or VTE due to reversible risk factors (APS or active cancer)	Proximal leg DVT or PE	IL-Test, Instrumentation Laboratory, Lexington, Massachusetts (LIA)	<250	Not available	Follow-up twice in the first year and once thereafter Instructions to contact physician if symptomatic	4/3

APS = antiphospholipid antibody syndrome; DVT = deep venous thrombosis; ELISA = enzyme-linked immunosorbent assay; LIA = latex immunoassay; PE = pulmonary embolism; VKA = vitamin K antagonist; VTE = venous thromboembolism.

* According to modified Newcastle–Ottawa Scale criteria; studies were assessed on the basis of patient selection (4 criteria) and outcome (3 criteria).

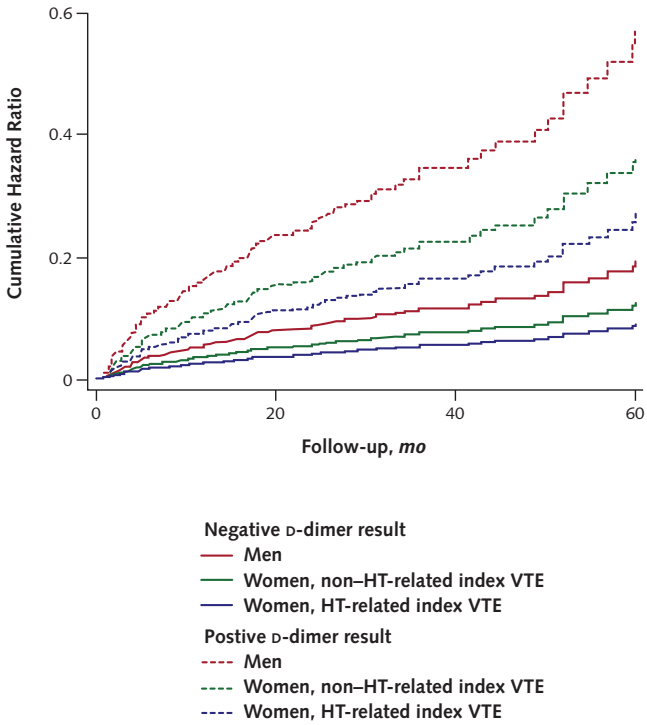
† If published results refer to a qualitative D-dimer assay, quantitative results were available and used in the sensitivity analysis.

Appendix Figure 2. **Derivation of patient population from source studies.**



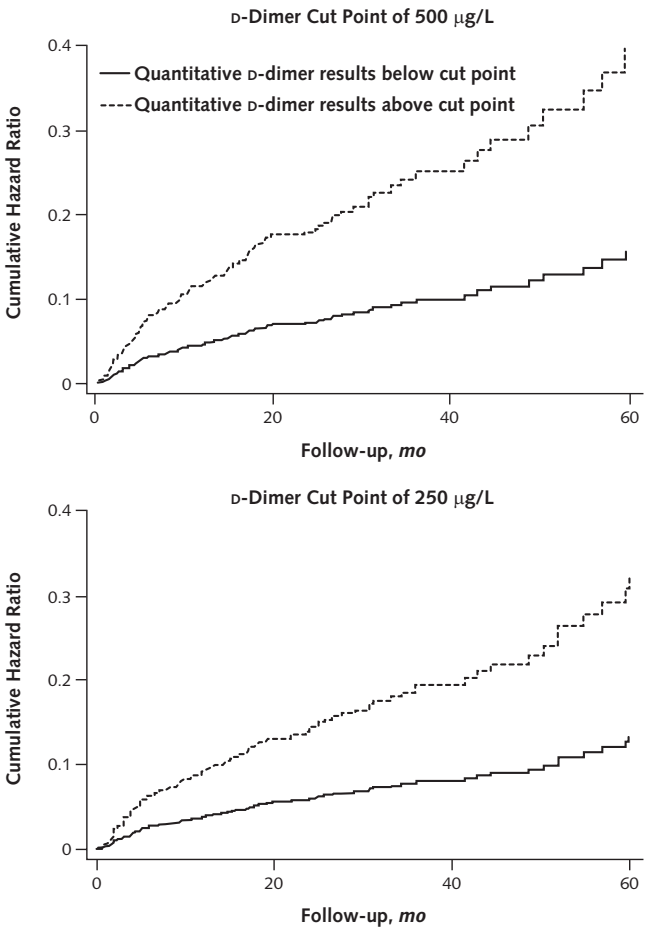
VTE = venous thromboembolism.
* References 16 to 22.

Appendix Figure 3. **Cox-derived cumulative hazard for recurrent VTE, by D-dimer status and patient sex (regardless of previous hormone-associated VTE).**

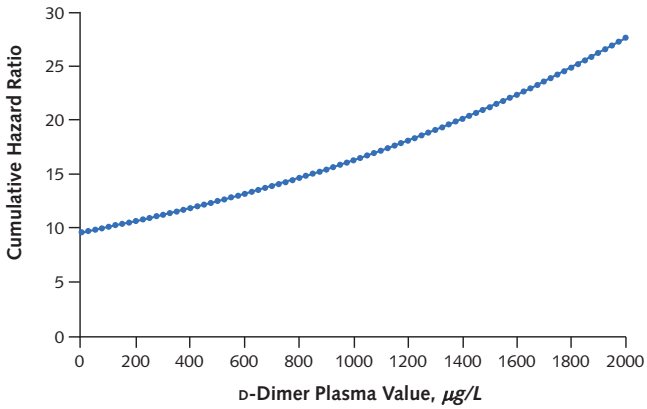


HT = hormone therapy; VTE = venous thromboembolism.

Appendix Figure 4. **Cox-derived cumulative hazard for recurrent venous thromboembolism, by D-dimer status as defined by 500- and 250-μg/L cut points.**



Appendix Figure 5. **Cox-derived cumulative hazard for recurrent venous thromboembolism, at 3-year follow-up, by quantitative D-dimer values.**



Curve truncated at 2000 μg/L.

Correction: D-Dimer Testing

In the recent article by Douketis and colleagues (1), the >5-week data under Negative D-Dimer Result in Table 3 should be 3.0 (2.3–4.1), not 4.6 (2.3–4.1). This has been corrected in the online version.

Reference

1. **Douketis J, Tosetto A, Marcucci M, Baglin T, Cushman M, Eichinger S, et al.** Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence after unprovoked venous thromboembolism. Ann Intern Med. 2010;153:523-31.