

Systematic Review: D-Dimer to Predict Recurrent Disease after Stopping Anticoagulant Therapy for Unprovoked Venous Thromboembolism

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Background: The optimal duration of anticoagulation for a first episode of unprovoked venous thromboembolism (VTE) is uncertain. Methods for predicting risk for recurrence may identify low-risk patients who are less likely to benefit from prolonged anticoagulation.

Purpose: To synthesize evidence evaluating the value of D-dimer as a predictor of recurrent disease in patients who have stopped anticoagulant therapy after a first unprovoked VTE.

Data Sources: The MEDLINE, EMBASE, CINAHL, and Cochrane databases were searched until March 2008 without language restrictions. The strategy was supplemented with manual review of reference lists and contact with content experts.

Study Selection: Randomized, controlled trials or prospective cohort studies that measured D-dimer after anticoagulant therapy in patients who received at least 3 months of anticoagulant treatment of unprovoked VTE.

Data Extraction: Two authors independently reviewed articles and extracted data.

Data Synthesis: Seven studies, totaling 1888 patients with a first unprovoked VTE, were eligible for analysis. During 4500 person-years of follow up, annual rates of recurrent VTE differed statistically significantly: 8.9% (95% CI, 5.8% to 11.9%) in patients with positive D-dimer results and 3.5% (CI, 2.7% to 4.3%) in patients with negative D-dimer results.

Limitation: The duration of anticoagulation, timing of D-dimer testing, and D-dimer assay varied across studies.

Conclusion: In patients who have completed at least 3 months of anticoagulation for a first episode of unprovoked VTE and after approximately 2 years of follow-up, a negative D-dimer result was associated with a 3.5% annual risk for recurrent disease, whereas a positive D-dimer result was associated with an 8.9% annual risk for recurrence. These rates should inform decisions about the balance of risks and benefits of prolonging anticoagulation.

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The optimal duration of anticoagulation for patients with a first episode of unprovoked venous thromboembolism (VTE), which occurs in the absence of a known risk factor, is uncertain (1, 2). At least 6 months of anticoagulation has been recommended because of presumed higher rates of recurrence with shorter durations of treatment (1, 3, 4). However, recent randomized trials indicate that the duration of anticoagulation seems to have little effect on the rate of disease recurrence in patients with unprovoked VTE; longer treatment only delays recurrence until after anticoagulation is stopped (5, 6). The key clinical decision, therefore, becomes whether to stop or to continue anticoagulation rather than the duration of treatment. This decision is important because stopping anticoagulant therapy may place some patients at risk for morbidity and mortality due to recurrent VTE, whereas continuing anticoagulation exposes patients to the increased bleeding risk, inconvenience, and costs of such treatment. Consequently, identifying patients at low risk for recurrent VTE and who may derive little benefit from prolonged anticoagulation will probably help clinicians decide whether to stop or to continue anticoagulant therapy.

A simple and easy-to-implement strategy is to measure D-dimer, a fibrin degradation product, after anticoagulation is interrupted. A negative (or low) D-dimer level may identify patients at low risk for recurrent VTE, in whom anticoagulation therapy may be stopped. Similarly, a posi-

tive (or increased) D-dimer level may identify patients with a persistent prothrombotic tendency who, because they are at relatively high risk for recurrent VTE, warrant long-term anticoagulation. Prospective studies initially showed that D-dimer predicted recurrent VTE (7-9), and a subsequent trial found that patients with an elevated D-dimer level 1 month after stopping anticoagulant therapy had a VTE recurrence rate of 15%, compared with 2.9% in those who resumed anticoagulation (10). Although the findings are promising, debate continues about using D-dimer to help decide whether to stop or to continue anticoagulation (11, 12).

Contributing to the controversy is the low power of individual studies to provide precise estimates of the effect of D-dimer levels on the risk for recurrent VTE after inter-

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Context

A test to identify patients at low risk for recurrent venous thromboembolism could help with the decision whether to continue or stop anticoagulant treatment.

Contribution

The authors' systematic review identified 7 studies that measured D-dimer 3 to 6 weeks after treatment for a first unprovoked venous thromboembolism was stopped. Recurrence rates within approximately 2 years were 8.9% and 3.5% in patients with a positive and negative D-dimer test result, respectively.

Caution

The studies used different D-dimer assays.

Implication

D-Dimer tests are a promising method for discriminating between patients with higher and lower risks for recurrent VTE. Proper evaluation of these tests requires additional studies of recurrence rates in D-dimer-negative patients.

—The Editors

rupting anticoagulation. Furthermore, some studies have reported findings in a heterogeneous patient population, which limits the findings' applicability to patients with unprovoked VTE.

Given the uncertainty about the role of D-dimer testing in predicting disease recurrence and the limitations of individual studies, we did a systematic review and meta-analysis of studies that measured D-dimer in patients who had stopped anticoagulant therapy for a first episode of unprovoked VTE to assess the value of D-dimer as a predictor of recurrent disease. Our objective was to provide precise and reliable estimates of the risk for recurrent VTE in patients with negative and positive D-dimer results.

METHODS

We did all parts of the systematic review independently and in duplicate. We included studies that measured D-dimer after stopping anticoagulant therapy in patients with a first unprovoked VTE who received at least 3 months of anticoagulation. We calculated the pooled annualized risk and predictive values for positive and negative D-dimer results.

Data Sources and Search Strategy

We searched for prospective cohort or randomized, controlled trials, regardless of language, that used D-dimer to predict recurrent VTE by searching MEDLINE (1950 to March 2008, week 1; in-process and other nonindexed citations, 14 March 2008), EMBASE (1980 to 2008, week 11), CINAHL (1982 to March 2008, week 1), and the Cochrane Central Register of Controlled Trials (2008, first

quarter). The **Appendix Table** (available at www.annals.org) shows the search strategies, which were supplemented by manual review of reference lists and contact with content experts.

Study Inclusion Criteria

Two investigators independently selected studies and resolved disagreements through consensus. We included a study if it was a randomized, controlled trial or prospective cohort study that measured D-dimer 3 weeks to 2 months after stopping anticoagulant therapy in patients with VTE who received at least 3 months of anticoagulation. Studies included patients with a first unprovoked VTE. Although we lack a formally established definition for unprovoked VTE, people agree that unprovoked VTE occurs in the absence of a transient (for example, surgery) or permanent (for example, cancer) risk factor, although uncertainty remains about how to classify some patients with VTE who have a weak antecedent risk factor, such as exposure to hormonal therapy. For our study, VTE in patients who were exposed to hormonal therapy may have been classified as provoked or unprovoked on the basis of the classification in the original studies. All included studies followed patients for recurrence of symptomatic VTE after stopping anticoagulation, and outcomes were objectively confirmed and independently adjudicated.

We considered abstracts and unpublished studies, and if the study was assessed to be potentially relevant, we contacted authors for additional study data as required. For studies by the same authors with overlapping enrollment dates, we contacted authors to explain. Studies published in languages other than English were translated and then assessed by both investigators, according to the inclusion and exclusion criteria.

Data Extraction

We extracted data and present them according to guidelines proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group (13). For each study, 2 investigators who were blinded to the study authors and journal in which the studies were published independently extracted data on study design, patient characteristics, D-dimer testing (assay type, threshold, timing of testing), anticoagulant therapy for VTE, duration of follow-up, and recurrent events.

If any of these core data were missing, we contacted the study authors to request the relevant data. Furthermore, if the D-dimer testing was done outside of the range of 3 weeks to 2 months or if patients had experienced several VTE events, we obtained individualized data for patients who met study inclusion criteria. For studies that randomly assigned patients to resume anticoagulation after a positive D-dimer result (10, 14), we excluded patients in the treatment group and considered only patients with negative or positive D-dimer results in the control group. For data presented in more than 1 publication, we extracted data from the most recent publication and used

earlier publications to clarify data. We resolved disagreements about study data extraction by consensus or by discussion with a third reviewer.

Quality Assessment

Two investigators who were blinded to the identities of the study authors and journal of publication independently assessed study quality. The Newcastle–Ottawa Score for observational studies (15) served as a template. We assessed for methodological features that are associated with study quality, including study design (prospective vs. retrospective), method of patient enrollment (consecutive vs. nonconsecutive), method of outcome assessment (blinded vs. nonblinded), duration of anticoagulation (≥ 12 months or < 12 months), number of patients lost to follow-up, and funding source.

Data Synthesis and Quantitative Pooling

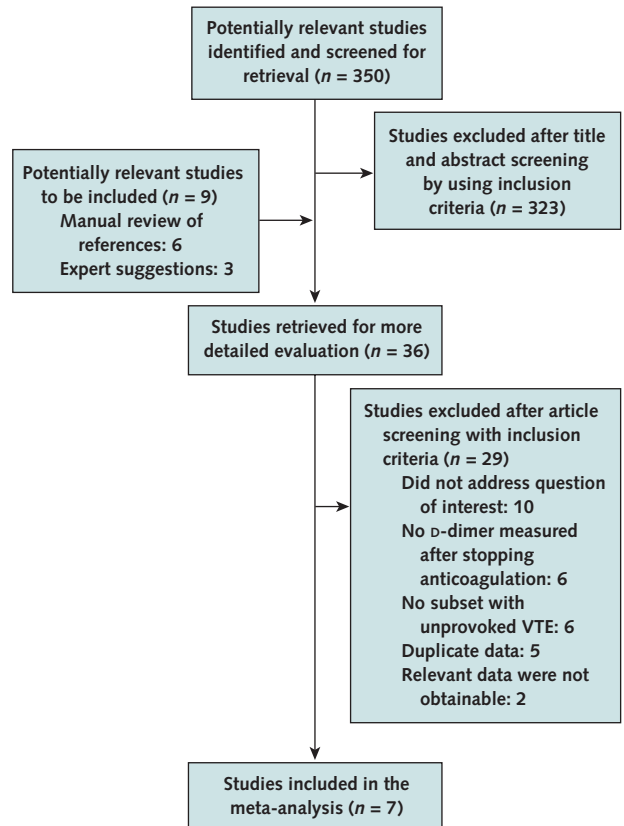
For each study, we determined the annualized risk (that is, risk per patient-year of follow-up) and 95% CIs of recurrent VTE in patients with unprovoked VTE, on the basis of the definition used in each study, with positive or negative D-dimer values after stopping anticoagulation. By taking the reciprocal of the variance of the rate as weights, we then calculated pooled annualized rates and 95% CIs. The pooled effect of D-dimer was further evaluated by using a mixed-effect Poisson model in which a positive or negative D-dimer result was treated as a fixed effect, study was treated as a random effect, and person-time served as the exposure variable (offset). We estimated the pooled incidence rate ratio from the model. The model was fitted by using the GLIMMIX procedure in SAS software, version 9.2 (SAS Institute, Cary, North Carolina). We did heterogeneity testing before pooling the rates. If the test indicated existence of statistically significant heterogeneity, we used a random-effects model to calculate the pooled rate; otherwise, we used a fixed-effects model (RevMan, version 4.2, Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen). Funnel plots were generated to assess for publication bias. To explore potential sources of heterogeneity, we considered variability in participants, D-dimer testing, and study design.

RESULTS

Study Identification and Selection

We identified 350 potentially relevant studies: 245 from MEDLINE, 100 from EMBASE, 4 from the Cochrane Library, and 1 from CINAHL (Figure). We excluded 323 studies after screening titles and abstracts by using the predefined inclusion and exclusion criteria and retrieved the remaining 27 studies for more detailed evaluation (7–10, 14, 16–37). We identified another 6 studies by manually reviewing the reference list of retrieved articles (38–43). Through contact with content experts, we identified 3 additional nonindexed studies (44–46). Of the 36 retrieved studies, 29 were excluded for the following reasons: did not address the question of interest ($n = 10$) (16–22, 38, 39, 41); had duplicate data ($n = 5$) (7, 23–26); D-

Figure. Study flow diagram.



VTE = venous thromboembolism.

dimer was not measured after stopping anticoagulation ($n = 6$) (32–35, 42, 43); no subset with unprovoked VTE was reported ($n = 6$) (27–31, 36); and relevant data were not obtainable ($n = 2$) (37, 40). Therefore, we included 7 studies in this review (8–10, 14, 44–46).

Five studies were prospective cohort studies (8, 9, 44–46) and 2 were randomized trials (10, 14) (Table 1), with a total of 3225 patients. Of these patients, 1888 had a first unprovoked VTE and met criteria for our analysis. Five of the cohorts (8, 14, 44–46) were reported as subgroups of mixed-population studies (unprovoked and provoked VTE; first and recurrent VTE). The remaining 2 studies consisted solely of patients with a first unprovoked VTE (9, 10). All patients received treatment with a vitamin K antagonist, usually warfarin, for at least 3 months.

Table 2 shows the characteristics of the D-dimer testing. D-Dimer was measured 3 weeks to 2 months after stopping anticoagulant therapy in 6 of the studies. For the study by Shrivastava and colleagues (14), only data for patients tested 20 to 30 days after stopping anticoagulation were included in our analysis.

Study Quality

Table 3 shows the assessment of study quality. All 7 studies used regularly scheduled clinic visits to monitor for

Table 1. Study Characteristics

Author, Year (Reference)	Study Design	Inclusion Criteria	Exclusion Criteria	Index VTE	Anticoagulant Therapy (Target INR)
Palareti et al., 2003 (8)	Prospective cohort, single center	Adults with first VTE episode	Lupus anticoagulant	Leg DVT and/or PE	Warfarin or acenocoumarol (2.0–3.0)
Eichinger et al., 2003 (9)	Prospective cohort, single center	Adults with first unprovoked VTE episode	Surgery, trauma, or pregnancy in the previous 3 mo; cancer; lupus anticoagulant; natural coagulation inhibitor deficiency; long-term anticoagulant treatment	DVT and/or PE	Phenprocoumon or acenocoumarol (2.0–3.0)
Palareti et al., 2006 (10)	Randomized, controlled trial; multicenter	Adults with first unprovoked VTE episode	Pregnancy or puerperium; recent fracture or plaster casting of leg; immobilization for ≥ 3 d (consecutively); surgery with general anesthesia >30 min; cancer; antiphospholipid antibody; antithrombin deficiency; serious liver or renal disease; other indication for or contraindication to anticoagulation; limited life expectancy; too far from study center	Proximal leg DVT and/or PE	Warfarin or acenocoumarol (2.0–3.0)
Shrivastava et al., 2006 (14)	Randomized, controlled trial; multicenter	Adults with unprovoked VTE	Surgery or trauma within 90 d of index event; antiphospholipid antibody; history of metastatic cancer; active cancer; life expectancy <3 y	Leg DVT and/or PE	Warfarin (2.0–3.0)
Tait et al., 2007 (46)	Prospective cohort, multicenter	Adults with acute VTE in the previous 5 wk	Life expectancy <3 mo; anticipated duration of anticoagulation >1 y; unavailable for follow-up (e.g., geographic or unreliable)	DVT and/or PE	Warfarin (2.0–3.0)
Baglin et al., 2008 (45)	Prospective cohort, single center	Adults with first VTE episode	Postoperative or pregnancy-associated thrombosis; APS; cancer; thrombosis within 6 wk of surgery; other indication for prolonged anticoagulation	Proximal leg DVT and/or PE	Warfarin (2.0–3.0)
Poli et al., 2008 (44)	Prospective cohort, single center	First unprovoked VTE or VTE episode due to transient risk factors	APS or active cancer	Proximal leg DVT and/or PE	Warfarin (2.0–3.0)

APS = antiphospholipid syndrome; DVT = deep venous thrombosis; ELISA = enzyme-linked immunosorbent assay; INR = international normalized ratio; LIA = latex immunoassay; OAT = oral anticoagulant therapy; PE = pulmonary embolism; VTE = venous thromboembolism.

* bioMérieux, Marcy l'Etoile, France.

† Diagnostica Stago, Parsippany, New Jersey.

‡ 505 patients were not randomly assigned to resume OAT.

§ Inverness Medical Professional Diagnostics, Louisville, Colorado.

|| 250 patients were not randomly assigned to resume OAT.

¶ Patients with a single previous episode of VTE and D-dimer testing 20 to 30 days after stopping anticoagulant therapy.

** Trinity Biotech, Wicklow, Ireland.

†† Instrumentation Laboratory, Milan, Italy.

VTE recurrence and confirmed recurrence with diagnostic imaging (for example, compression ultrasonography or venography for deep venous thrombosis; ventilation–perfusion lung scanning or spiral computed tomography for pulmonary embolism). Independent observers who were blinded to clinical data, including D-dimer status, assessed outcomes in all studies. All 5 prospective cohort studies enrolled consecutive patients. The duration of follow-up was greater than 12 months in all 7 studies. Only 2 studies reported the number of patients lost to follow-up (10, 45); the rates of loss to follow-up were 1.8% and 0.005%.

Incidence of Recurrent VTE after Stopping Anticoagulant Therapy, according to D-Dimer Result

Of 1888 patients, 907 (48.0%) had a positive D-dimer result after stopping anticoagulation; of these, 165 (18.2%) had recurrent VTE during 2462 person-years of follow-up.

Recurrent VTE occurred in 7.5% of patients with a negative D-dimer result after stopping anticoagulation during 2040 person-years of follow-up. Analysis of annualized risk showed a higher risk for VTE recurrence per patient-year of follow-up in the positive D-dimer posttreatment group: 8.9% (95% CI, 5.8% to 11.9%) per year in patients with a positive D-dimer result and 3.5% (CI, 2.7% to 4.3%) per year in patients with a negative D-dimer result (Table 4). From the mixed-effect Poisson model, the pooled incidence rate ratio was 2.20 (CI, 1.65 to 2.94; $P = 0.002$), suggesting that the risk for recurrent VTE in patients with a positive D-dimer result is 2.2 times that in patients with a negative D-dimer result.

Study Heterogeneity and Potential Publication Bias

We found no statistical heterogeneity across studies for the outcome of a negative posttreatment D-dimer result (chi-

Table 1—Continued

Minimum Duration of Therapy, mo	Assay (Type)	Normal D-Dimer Value, $\mu\text{g/L}$	Recurrence Monitoring	Study Patients, n	Patients Included in Unprovoked VTE Meta-analysis
3	VIDAS (ELISA)*	≤ 500	Clinical visits 3 mo after OAT discontinuation, then every 6 mo; instructed to contact if symptomatic	599	282
3	Asserachrom (ELISA)†	< 250	Clinical visits every 3 mo for 1 y, then every 6 mo	610	610
3	Liatest (immunoturbidometric)†	Qualitative (abnormal vs. normal)	Clinical visits every 3–6 mo; instructed to contact if symptomatic	608‡	505
3	Clearview Simplify (Qualitative)§	< 500	Clinical visits every 2 mo	501	45¶
3	VIDAS (ELISA)*	< 500	Nurse visit at 3 mo, 1 y, and 2 y after OAT discontinuation; instructed to contact if symptomatic	340	129
3	MDA (LIA)**	< 500	Yearly follow-up	272	142
6	IL-Test (LIA)††	< 250	Follow-up twice in the first year and once thereafter; instructed to contact if symptomatic	295	175

square = 2.81; $I^2 = 0\%$; $P = 0.832$) but statistically significant heterogeneity for the outcome of a positive posttreatment D-dimer result (chi-square = 23.8; $I^2 = 75\%$; $P < 0.001$). As shown in **Appendix Figures 1** and **2** (available at www.annals.org), publication bias was assessed with funnel plots for the outcomes of a negative or a positive posttreatment D-dimer result. The funnel plot for the negative D-dimer outcome showed symmetric clustering of findings, suggesting the absence of publication bias. The funnel plot for the positive D-dimer outcome showed a wider dispersion of findings, suggesting that unpublished studies with results at the extremes of this outcome may exist. The asymmetry in the positive D-dimer funnel plot may also reflect the noted statistical heterogeneity.

DISCUSSION

We aimed to provide reliable and precise estimates of the annual risk for recurrent VTE in patients with a first unprovoked VTE based on D-dimer levels obtained after stopping anticoagulant therapy. Our findings reflect a pooled analysis of approximately 1900 patients who had, on average, approximately 2 years of follow-up after anti-

coagulation was stopped. We found that patients with a negative D-dimer result have an annual risk for recurrent VTE of 3.5%, whereas patients with a positive D-dimer result have an annual risk for recurrent VTE of 8.9%. To our knowledge, this report is the first to provide a pooled analysis of D-dimer as a predictor for recurrent VTE.

We believe our findings are reliable and precise for several reasons. First, we identified high-quality studies in which patients received a standardized course of anticoagulation for at least 3 months, had regularly scheduled follow-up, and had recurrent VTE that was objectively confirmed and independently adjudicated without previous knowledge of posttreatment D-dimer test results. Second, we used studies that had well-defined and similar patient populations with a first symptomatic, unprovoked VTE. Third, all included patients had D-dimer testing after anticoagulation had been stopped. Although the timing of D-dimer testing varied from 3 weeks to 2 months, testing was sufficiently remote from the receipt of anticoagulant therapy to rule out an effect of therapy on D-dimer levels but was close enough to the time of stopping anticoagulation to minimize a recurrent VTE in the intervening period. Finally, when study findings were uncertain (for example,

Table 2. Patient Characteristics

Author, Year (Reference)	Age, y	Women, %	Duration of Anticoagulation (Median), mo	Timing of D-Dimer Testing after Oral Anticoagulant Therapy Discontinuation	Follow-up after Oral Anticoagulant Therapy Discontinuation, mo
Palareti et al., 2003 (8)	Median, 67	50	≤3 (NR)	21–37 d	Median, 17.6
Eichinger et al., 2003 (9)	NR	56	≤3 (NR)	3 wk	Mean, 38
Palareti et al., 2006 (10)	Mean, 63	48	≤3 (NR)	20–40 d	Range, 9–18
Shrivastava et al., 2006 (14)	NR	47	≤3 (6.5)	12 d–2 y*	Median, 25 (range, 0.4–51.6)
Tait et al., 2007 (46)	NR	49	≤3 (NR)†	24–28 d	Median, 19.5 (range, 0.8–46.6)
Baglin et al., 2008 (45)	Median, 65	48	≤3 (6.0)	1–2 mo	Median 38.6 (range, 2–71)
Poli et al., 2008 (44)	Median, 62	47	≤6 (12)‡	30–37 d	Median, 25 (range, 1–120)

NR = not reported.

* Only patients with D-dimer testing 20–30 d after anticoagulant therapy were included.

† 6 patients received <3 mo of anticoagulant therapy (range, 32–89 d).

‡ Unprovoked venous thromboembolism subgroup.

timing of posttreatment D-dimer testing) or not specific to the patient population of interest (for example, reported without distinguishing between patients with a first and recurrent VTE), we contacted study authors to obtain individual patient-level data for patients meeting inclusion criteria. This strategy enabled us to include the maximum numbers of studies and patients, including studies published only in abstract form, which avoided loss of precision in our findings.

The studies were statistically heterogeneous for the outcome of a positive posttreatment D-dimer result—although not for the outcome of a negative posttreatment D-dimer result—and warrant commentary. We identified 2

potential sources of heterogeneity. First, the studies differed in the events that they defined as VTE. Although 90% to 100% of patients in 5 studies (8, 10, 14, 44, 45) had proximal lower-limb deep venous thrombosis or pulmonary embolism as the index event, 1 study (9) also included 140 (23%) patients with calf venous thrombosis and 27 (4%) patients with upper-limb thrombosis. Another study (46) included 16 (12%) patients with calf venous thrombosis and 2 (2%) patients with upper-limb thrombosis. Calf venous and upper-limb thrombosis may be less prone to recur. The relatively high proportion of index events at these sites in the first study (9) may have contributed to the lower rates of recurrence and predictive

Table 3. Study Quality Assessment

Author, Year (Reference)	Method of Patient Enrollment	Outcome Assessment	Duration of Follow-up >12 Months	Patients Lost to Follow-up after D-Dimer Testing, n (%)	Funding Source
Palareti et al., 2003 (8)	Consecutive	Independent, blinded	Yes (17.4 mo)	NR	NR
Eichinger et al., 2003 (9)	Consecutive	Independent, blinded	Yes (mean, 38 mo)	NR	Grant from the Jubiläumsfonds, Oesterreichische Nationalbank, Vienna, Austria
Palareti et al., 2006 (10)	NA	Independent, blinded	Yes (9–18 mo)	3 (0.005)	The Italian Federation of Anticoagulation Clinics and the Department of Angiology and Blood Coagulation of the South Orsola-Malpighi University Hospital, Bologna, Italy
Shrivastava et al., 2006 (14)	NA	Independent, blinded	Yes (median, 25 mo)	NR	NR
Tait et al., 2007 (46)	NR	Independent, blinded	Yes (median, 19.5 mo)	NR	NR
Baglin et al., 2008 (45)	Consecutive	Independent, blinded	Yes (median, 38.6 mo)	5 (1.8)	NR
Poli et al., 2008 (44)	Consecutive	Independent, blinded	Yes (median, 25 mo)	NR	NR

NA = not applicable; NR = not reported.

Table 4. Annualized Risk for Recurrence in Patients with Unprovoked Venous Thromboembolism

Author, Year (Reference)	Patients, n	Person-Years	Recurrent Venous Thromboembolism, n	Annualized Risk (95% CI), %
Patients with positive D-dimer result after anticoagulation				
Palareti et al., 2003 (8)*	139	316	23	7.3 (4.3–10.3)
Eichinger et al., 2003 (9)*	401	1409	63	4.5 (3.4–5.6)
Palareti et al., 2006 (10)	120	166	18	10.9 (5.9–15.9)
Shrivastava et al., 2006 (14)	15	26.5	3	11.3 (0.0–24.1)
Tait et al., 2007 (46)	71	125	18	14.4 (7.7–21.1)
Baglin et al., 2008 (45)	91	261	23	8.8 (5.2–12.2)
Poli et al., 2008 (44)	70	158.1	17	10.8 (5.6–15.9)
Pooled	907	2461.6	165	8.9 (5.8–11.9)†
Patients with negative D-dimer result after anticoagulation				
Palareti et al., 2003 (8)*	143	363	10	2.8 (1.0–4.5)
Eichinger et al., 2003 (9)*	209	536	16	3.0 (1.5–4.4)
Palareti et al., 2006 (10)	30	550	24	4.4 (2.6–6.1)
Shrivastava et al., 2006 (14)	30	54.7	2	3.7 (0.0–8.7)
Tait et al., 2007 (46)	58	104	4	3.8 (0.1–7.6)
Baglin et al., 2008 (45)	51	167	8	4.8 (1.5–8.1)
Poli et al., 2008 (44)	105	265.5	10	3.8 (1.4–6.1)
Pooled	981	2040.2	74	3.5 (2.7–4.3)‡

* Person-years were estimated on the basis of survival curves.

† Heterogeneity test: chi-square = 23.8 ($I^2 = 75\%$; $P < 0.001$); therefore, a random-effects model was used to find the pooled rate.

‡ Heterogeneity test: chi-square = 2.81 ($I^2 = 0\%$; $P = 0.83$).

values seen in this study. The second study (46) found a higher risk for recurrent VTE in patients with a positive posttreatment D-dimer result; this study may have been an outlier because of the small number of patients that we included from it.

Second, studies used different D-dimer level cutoffs to define a positive or negative result. Six of 7 studies used the manufacturer-defined cutoffs to determine positive or negative posttreatment D-dimer status. However, 1 study (9) arbitrarily stratified patients into D-dimer quartiles post hoc, and it used a cutoff of 250 $\mu\text{g/L}$ to determine rates of VTE recurrence in patients with D-dimer results above and below this level. The manufacturer suggested using a level greater than 500 $\mu\text{g/L}$ as a positive result for this assay (Asserachrom D-dimer enzyme-linked immunosorbent assay, Diagnostica Stago, Parsippany, New Jersey). On the funnel plot for positive posttreatment D-dimer results, this study is the outlier (9).

Other studies have assessed predictors of recurrent disease in patients with unprovoked VTE. For patients with deep venous thrombosis, the presence of residual disease on venous ultrasonography may predict an increased risk for disease (47, 48), although some studies do not show this effect (24, 49). Male sex is a consistent predictor of recurrent VTE (50, 51). Although prothrombotic blood abnormalities, such as the factor V Leiden or prothrombin mutation, are associated with an increased risk for a first VTE, the presence of these abnormalities may not confer a clinically important increased risk for recurrent VTE (43, 52, 53). Other putative risk factors for recurrent disease include increasing age and obesity (42).

Our study has potential limitations. First, because none of the included studies was blinded to history of VTE, there is potential for biased ascertainment of outcomes because of studying a sample deemed susceptible to disease recurrence. However, biased ascertainment is unlikely, because all patients—regardless of D-dimer results—were assessed for recurrent VTE through standardized patient follow-up or patient self-report. Second, the duration of anticoagulation varied across studies, which is not unexpected because this is uncertain for unprovoked VTE. However, the duration of anticoagulation does not seem to influence the risk for recurrent VTE in patients with unprovoked VTE (5). Third, the timing of D-dimer testing after anticoagulation was stopped varied across studies. This might have influenced the rate of false-positive and false-negative results if D-dimer levels were spuriously low because they were measured too soon after anticoagulation was stopped. However, the across-study consistency in our findings, especially for a negative posttreatment D-dimer result, suggests that as long as D-dimer is measured 3 weeks to 2 months after anticoagulation is stopped, it consistently predicts the risk for recurrent VTE. The D-dimer cutoff that best predicts recurrent VTE is not known, especially in patient subgroups, such as elderly persons, in whom baseline D-dimer levels are increased (54). Fourth, although quality varied across studies, key methodological features, such as independent adjudication of outcomes, were present across all studies. Finally, the studies did not all use the same assays of D-dimer—a real-world predicament because several commercially available D-dimer assays are widely used. Without a worldwide standard for D-dimer

testing, comparison of data obtained with different assays is difficult. However, assay heterogeneity was a minor problem given the consistent findings across studies that used different D-dimer assays.

Our findings should influence decision making. The low risk for recurrence with a negative D-dimer result suggests that long-term anticoagulation may not be necessary in all patients with unprovoked VTE. The annual recurrence rate of 3.5% (as high as 4.3% based on an upper bound of 95% CI) is similar to the risk for recurrent VTE in patients with a first secondary VTE (occurring after exposure to a transient risk factor) (4), in whom 3 months of anticoagulation is recommended. This rate, however, may not be low enough for some clinicians or patients to stop anticoagulation. A negative D-dimer result also could be used in combination with other factors associated with a low risk for disease recurrence, such as female sex (55) and younger age (42). In the case of a positive D-dimer result, the annual risk for recurrent VTE of 8.9% (as high as 11.9% based on an upper bound of 95% CI) may justify resumption of and indefinite continuation of anticoagulation. Ultimately, the clinician must weigh the risk and clinical effect of recurrent VTE if anticoagulation is stopped against the risk (56) and clinical effect of bleeding with prolonged anticoagulation in the context of the patient's values and preferences. We do not endorse the use of D-dimer as a stand-alone test to determine whether to stop or to continue anticoagulation in patients with a first unprovoked VTE. Ideally, D-dimer should be part of a clinical prediction rule that incorporates both clinical and laboratory features to better predict recurrent VTE in an individual patient. Furthermore, additional research is needed to establish the optimal interval between stopping anticoagulation and performing D-dimer testing, to identify the optimal D-dimer cutoff that predicts recurrence and to develop a clinical prediction rule for recurrent VTE.

In summary, measuring D-dimer after stopping anticoagulant therapy helps to predict whether VTE will recur. A negative D-dimer result defines a low risk for recurrent VTE.

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References

1. Büller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Anti-thrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:401S-428S. [PMID: 15383479]
2. Snow V, Qaseem A, Barry P, Hornbake ER, Rodnick JE, Tobolic T, et al. The Joint American College of Physicians/American Academy of Family Physicians Panel on Deep Venous Thrombosis/Pulmonary Embolism. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med*. 2007;146:204-10. [PMID: 17261857]
3. Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Lärfaars G, Nicol P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group. *N Engl J Med*. 1995;332:1661-5. [PMID: 7760866]
4. Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med*. 1996;125:1-7. [PMID: 8644983]
5. Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, et al. Warfarin Optimal Duration Italian Trial Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. *N Engl J Med*. 2001;345:165-9. [PMID: 11463010]
6. Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, et al. Warfarin Optimal Duration Italian Trial Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med*. 2003;139:19-25. [PMID: 12834314]
7. Palareti G, Legnani C, Cosmi B, Guazzaloca G, Pancani C, Coccheri S. Risk of venous thromboembolism recurrence: high negative predictive value of D-dimer performed after oral anticoagulation is stopped. *Thromb Haemost*. 2002;87:7-12. [PMID: 11848459]
8. Palareti G, Legnani C, Cosmi B, Valdré L, Lunghi B, Bernardi F, et al. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. *Circulation*. 2003;108:313-8. [PMID: 12847064]
9. Eichinger S, Minar E, Bialonczyk C, Hirschl M, Quehenberger P, Schneider B, et al. D-dimer levels and risk of recurrent venous thromboembolism. *JAMA*. 2003;290:1071-4. [PMID: 12941680]
10. Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, et al. PRO-LONG Investigators. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med*. 2006;355:1780-9. [PMID: 17065639]
11. Kearon C. Indefinite anticoagulation after a first episode of unprovoked venous thromboembolism: yes. *J Thromb Haemost*. 2007;5:2330-5. [PMID: 18034763]
12. Baglin T. Unprovoked deep vein thrombosis should be treated with long-term anticoagulation—no. *J Thromb Haemost*. 2007;5:2336-9. [PMID: 17892533]
13. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008-12. [PMID: 10789670]
14. Shrivastava S, Ridker PM, Glynn RJ, Goldhaber SZ, Moll S, Bounameaux H, et al. D-dimer, factor VIII coagulant activity, low-intensity warfarin and the risk of recurrent venous thromboembolism. *J Thromb Haemost*. 2006;4:1208-14. [PMID: 16706961]
15. Wells G, Shea B, O'Connell D, Robertson J, Peterson D, Welch V, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Proceedings of the Third Symposium on Systematic Reviews. Beyond the Basics: Improving Quality and Impact, Oxford, United

- Kingdom, 3-5 July 2000.
16. Arcelus JI, Caprini JA, Monreal M, Suárez C, González-Fajardo J. The management and outcome of acute venous thromboembolism: a prospective registry including 4011 patients. *J Vasc Surg.* 2003;38:916-22. [PMID: 14603194]
 17. Calvo Romero JM. [Negative D-dimer in patients with venous thromboembolic disease] [Letter]. *Med Clin (Barc).* 2004;123:635-6. [PMID: 15546524]
 18. de Raucourt E, Meyer G, Landais P, Gouaref Z, Morinet P, Monge F, et al. Markers of hemostatic system activation in pulmonary embolism. Changes during and after cessation of anticoagulant treatment. *Blood Coagul Fibrinolysis.* 2000;11:249-53. [PMID: 10870805]
 19. Krieger E, van Der Loo B, Amann-Vesti BR, Rousson V, Koppensteiner R. C-reactive protein and red cell aggregation correlate with late venous function after acute deep venous thrombosis. *J Vasc Surg.* 2004;40:644-9. [PMID: 15472590]
 20. Ombandza-Moussa E, Samama MM, Horellou MH, Chatelier AL, Elalamy I, Conard J. [Influence of oral anticoagulant treatment on D-dimers levels]. *Ann Biol Clin (Paris).* 2001;59:579-83. [PMID: 11602388]
 21. Stain M, Schönauer V, Minar E, Bialonczyk C, Hirschl M, Weltermann A, et al. The post-thrombotic syndrome: risk factors and impact on the course of thrombotic disease. *J Thromb Haemost.* 2005;3:2671-6. [PMID: 16359506]
 22. Tardy B, Tardy-Poncet B, Laporte-Simitsidis S, Mismetti P, Decousus H, Guyotat D, et al. Evolution of blood coagulation and fibrinolysis parameters after abrupt versus gradual withdrawal of acenocoumarol in patients with venous thromboembolism: a double-blind randomized study. *Br J Haematol.* 1997;96:174-8. [PMID: 9012705]
 23. Palareti G, Guazzaloca G, Legnani C, Fortunato G, Grauso F, De Rosa V, et al. [High negative predictive value for recurrence of venous thromboembolism with d-dimer carried out three months after the suspension of treatment with oral anticoagulants in patients over 60]. *Minerva Cardioangiol.* 1998;46:374-5. [PMID: 10021815]
 24. Cosmi B, Legnani C, Cini M, Guazzaloca G, Palareti G. D-dimer levels in combination with residual venous obstruction and the risk of recurrence after anticoagulation withdrawal for a first idiopathic deep vein thrombosis. *Thromb Haemost.* 2005;94:969-74. [PMID: 16363238]
 25. Legnani C, Mattarozzi S, Cini M, Cosmi B, Favaretto E, Palareti G. Abnormally short activated partial thromboplastin time values are associated with increased risk of recurrence of venous thromboembolism after oral anticoagulation withdrawal. *Br J Haematol.* 2006;134:227-32. [PMID: 16846482]
 26. Palareti G, Legnani C, Cosmi B, Guazzaloca G, Cini M, Mattarozzi S. Poor anticoagulation quality in the first 3 months after unprovoked venous thromboembolism is a risk factor for long-term recurrence. *J Thromb Haemost.* 2005;3:955-61. [PMID: 15869591]
 27. Cosmi B, Legnani C, Cini M, Guazzaloca G, Palareti G. The role of D-dimer and residual venous obstruction in recurrence of venous thromboembolism after anticoagulation withdrawal in cancer patients [Letter]. *Haematologica.* 2005;90:713-5. [PMID: 15921399]
 28. Hoibraaten E, Qvigstad E, Andersen TO, Mowinckel MC, Sandset PM. The effects of hormone replacement therapy (HRT) on hemostatic variables in women with previous venous thromboembolism—results from a randomized, double-blind, clinical trial. *Thromb Haemost.* 2001;85:775-81. [PMID: 11372667]
 29. Hoke M, Kyrle PA, Philipp K, Pabinger I, Kaider A, Schönauer V, et al. Prospective evaluation of coagulation activation in pregnant women receiving low-molecular weight heparin. *Thromb Haemost.* 2004;91:935-40. [PMID: 15116254]
 30. Poli D, Zanazzi M, Antonucci E, Marcucci R, Rosati A, Bertoni E, et al. High rate of recurrence in renal transplant recipients after a first episode of venous thromboembolism. *Transplantation.* 2005;80:789-93. [PMID: 16210966]
 31. Sallah S, Husain A, Sigounas V, Wan J, Turturro F, Sigounas G, et al. Plasma coagulation markers in patients with solid tumors and venous thromboembolic disease receiving oral anticoagulation therapy. *Clin Cancer Res.* 2004;10:7238-43. [PMID: 15534097]
 32. Fattorini A, Crippa L, Viganò D'Angelo S, Pattarini E, D'Angelo A. Risk of deep vein thrombosis recurrence: high negative predictive value of D-dimer performed during oral anticoagulation [Letter]. *Thromb Haemost.* 2002;88:162-3. [PMID: 12152661]
 33. Kuruvilla J, Wells PS, Morrow B, MacKinnon K, Keeney M, Kovacs MJ. Prospective assessment of the natural history of positive D-dimer results in patients with acute venous thromboembolism (DVT or PE). *Thromb Haemost.* 2003;89:284-7. [PMID: 12574808]
 34. Meissner MH, Zierler BK, Bergelin RO, Chandler WC, Manzo RA, Strandness DE Jr. Markers of plasma coagulation and fibrinolysis after acute deep venous thrombosis. *J Vasc Surg.* 2000;32:870-80. [PMID: 11054218]
 35. Palareti G, Legnani C, Guazzaloca G, Frascaro M, Grauso F, De Rosa F, et al. Activation of blood coagulation after abrupt or stepwise withdrawal of oral anticoagulants—a prospective study. *Thromb Haemost.* 1994;72:222-6. [PMID: 7831656]
 36. de Groot MR, Njo TL, van Marwijk Kooy M, Büller HR. Abrupt versus gradual withdrawal of vitamin K antagonist treatment in patients with venous thromboembolic disease: assessment of hypercoagulability and clinical outcome. *Clin Lab.* 2000;46:575-81. [PMID: 11109505]
 37. Ombandza-Moussa E, Samama MM, Horellou MH, Elalamy I, Conard J. Potential use of D-dimer measurement in patients treated with oral anticoagulant for a venous thromboembolic episode. *Int Angiol.* 2003;22:364-9. [PMID: 15153820]
 38. Andreescu AC, Cushman M, Rosendaal FR. D-dimer as a risk factor for deep vein thrombosis: the Leiden Thrombophilia Study. *Thromb Haemost.* 2002;87:47-51. [PMID: 11858188]
 39. Sié P, Cadroy Y, Elias A, Boccalon H, Boneu B. D-dimer levels in patients with long-term antecedents of deep venous thrombosis [Letter]. *Thromb Haemost.* 1994;72:161-2. [PMID: 7974367]
 40. Cushman M, Folsom AR, Wang L, Aleksic N, Rosamond WD, Tracy RP, et al. Fibrin fragment D-dimer and the risk of future venous thrombosis. *Blood.* 2003;101:1243-8. [PMID: 12393393]
 41. Kévorkian JP, Halimi C, Segrestaa JM, Drouet L, Soria C. Monitoring of patients with deep-vein thrombosis during and after anticoagulation with D-dimer [Letter]. *Lancet.* 1998;351:571-2. [PMID: 9492784]
 42. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ 3rd. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med.* 2000;160:761-8. [PMID: 10737275]
 43. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet.* 2003;362:523-6. [PMID: 12932383]
 44. Poli D, Antonucci E, Ciuti G, Abbate R, Prisco D. Combination of D-dimer, F1 + 2 and residual vein obstruction as predictors of VTE recurrence in patients with first VTE episode after OAT withdrawal [Letter]. *J Thromb Haemost.* 2008;6:708-10. [PMID: 18194414]
 45. Baglin T, Palmer CR, Luddington R, Baglin C. Unprovoked recurrent venous thrombosis: prediction by D-dimer and clinical risk factors. *J Thromb Haemost.* 2008;6:577-82. [PMID: 18182040]
 46. Tait R, Lowe GDO, McColl MD, McMahon AD, Robertson L, King L, et al. Predicting risk of recurrent venous thrombosis using a 5-point scoring system including fibrin D-dimer. *J Thromb Haemost.* 2007;5(Suppl 2):60.
 47. Prandoni P, Lensing AW, Prins MH, Bernardi E, Marchiori A, Bagatella P, et al. Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. *Ann Intern Med.* 2002;137:955-60. [PMID: 12484710]
 48. Young L, Ockelford PA, Milne D, McKelvie S, Rolfe-Vyson V, West T, et al. Post treatment residual thrombus is associated with an increased risk of DVT recurrence, mortality and a trend towards increased vascular death. *J Thromb Haemost.* 2005;3(Suppl 1):365.
 49. Rodger MA, Kovacs MJ, Zeng W. Residual venous thrombosis after 5-7 months of oral anticoagulant (OAC) therapy as a predictor of subsequent recurrent venous thromboembolism. *J Thromb Haemost.* 2007;5(Suppl 2):508.
 50. Baglin T, Luddington R, Brown K, Baglin C. High risk of recurrent venous thromboembolism in men. *J Thromb Haemost.* 2004;2:2152-5. [PMID: 15613020]
 51. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. *N Engl J Med.* 2004;350:2558-63. [PMID: 15201412]
 52. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA.* 2005;293:2352-61. [PMID: 15900005]
 53. Ho WK, Hankey GJ, Quinlan DJ, Eikelboom JW. Risk of recurrent venous thromboembolism in patients with common thrombophilia: a systematic review. *Arch Intern Med.* 2006;166:729-36. [PMID: 16606808]
 54. Aguilar C, del Villar V. Diagnostic performance of D-dimer is lower in

elderly outpatients with suspected deep venous thrombosis [Letter]. *Br J Haematol*. 2005;130:803-4; author reply 805. [PMID: 16115146]

55. **McRae S, Tran H, Schulman S, Ginsberg J, Kearon C.** Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. *Lancet*. 2006;

368:371-8. [PMID: 16876665]

56. **Beyth RJ, Quinn LM, Landefeld CS.** Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med*. 1998;105:91-9. [PMID: 9727814]

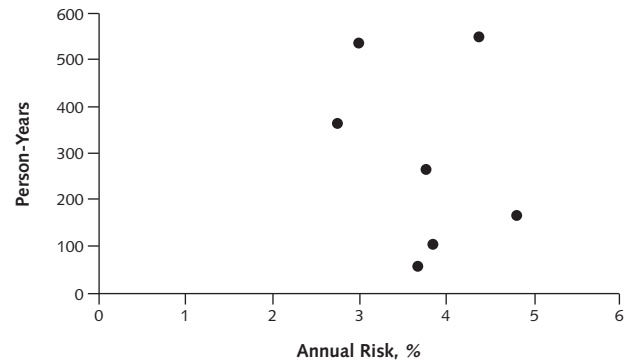
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Appendix Table. Literature Search Strategy*

Exp Anticoagulants (146 200)
 Anticoagulant\$mp. (53 721)
 Anticoagulant\$mp. (16 757)
 1 or 2 or 3 (162 965)
 Adult (3 059 203)
 Exp fibrin fibrinogen degradation products (5250)
 D-dimer mp. (3617)
 6 or 7 (6844)
 Exp Recurrence or recurrence mp. (244 525)
 Recurrent \$ mp. (133 809)
 9 or 10 (320 718)
 Exp predictive value of tests or predictive value mp. (103 031)
 11 or 12 (417 703)
 Thromboembolism mp. or exp thromboembolism (41 020)
 Venous thrombosis mp. or exp venous thrombosis (41 958)
 Pulmonary embolism mp. or exp pulmonary embolism (29 612)
 14 or 15 or 16 (94 141)
 4 and 5 and 8 and 13 and 17 (222)

* Database search done on Ovid MEDLINE 1950 to March 2008, week 1. Numbers in parentheses are the number of citations found by search strategy.

Appendix Figure 1. Funnel plot for negative posttreatment D-dimer result: annual risk.



Appendix Figure 2. Funnel plot for positive posttreatment D-dimer result: annual risk.

