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D-Dimer Testing to Select Patients With a First Unprovoked Venous Thromboembolism Who Can Stop Anticoagulant Therapy

A Cohort Study

Clive Kearon, MB, PhD; Frederick A. Spencer, MD; Denis O'Keeffe, MB; Sameer Parpia, PhD; Sam Schulman, MD, PhD; Trevor Baglin, MB; Scott M. Stevens, MD; Scott Kaatz, DO; Kenneth A. Bauer, MD; James D. Douketis, MD; Steven R. Lentz, MD, PhD; Craig M. Kessler, MD; Stephan Moll, MD; Jean M. Connors, MD; Jeffrey S. Ginsberg, MD; Luciana Spadafora; and Jim A. Julian, MMath, for the D-Dimer Optimal Duration Study Investigators*

Background: Normal D-dimer levels after withdrawal of anticoagulant therapy are associated with a reduced risk for recurrence in patients with unprovoked venous thromboembolism (VTE) and may justify stopping treatment.

Objective: To determine whether patients with a first unprovoked VTE and negative D-dimer test result who stop anticoagulant therapy have a low risk for recurrence.

Design: Prospective management study with blinded outcome assessment. (ClinicalTrials.gov: NCT00720915)

Setting: 13 university-affiliated clinical centers.

Patients: 410 adults aged 75 years or younger with a first unprovoked proximal deep venous thrombosis or pulmonary embolism who had completed 3 to 7 months of anticoagulant therapy.

Intervention: Anticoagulant therapy was stopped if D-dimer test results were negative and was not restarted if results were still negative after 1 month.

Measurements: Recurrent VTE during an average follow-up of 2.2 years.

Results: In 319 patients (78%) who had 2 negative D-dimer results and did not restart anticoagulant therapy, rates of recurrent VTE were 6.7% (95% CI, 4.8% to 9.0%) per patient-year overall (42 of 319), 9.7% (CI, 6.7% to 13.7%) per patient-year in men (33 of 180), 5.4% (CI, 2.5% to 10.2%) per patient-year in women with VTE not associated with estrogen therapy (9 of 81), and 0.0% (CI, 0.0% to 3.0%) per patient-year in women with VTE associated with estrogen therapy (0 of 58) (P = 0.001 for the 3-group comparison).

Limitations: Imprecision in female subgroups. Results may not be generalizable to different D-dimer assays from the one used in the study.

Conclusion: The risk for recurrence in patients with a first unprovoked VTE who have negative D-dimer results is not low enough to justify stopping anticoagulant therapy in men but may be low enough to justify stopping therapy in women.

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For author affiliations, see end of text.

* For a list of the members of the D-Dimer Optimal Duration Study Investigators, see **Appendix 1** (available at www.annals.org).

Venous thromboembolism (VTE) that is provoked by a reversible risk factor, such as recent surgery, has a low risk for recurrence after treatment is stopped (1, 2). The risk for recurrence of VTE provoked by cancer is high (3, 4), and anticoagulant therapy is usually continued indefinitely (2). There is an intermediate risk for recurrence if the initial thrombosis occurred without an apparent provoking factor ("unprovoked" or "idiopathic" VTE), and whether patients should be treated indefinitely has been debated (1, 2, 5). If we could stratify the risk for recurrence in patients with a first unprovoked VTE, those with lower risk could stop and those with higher risk could continue anticoagulant therapy. The risk for recurrence is higher in patients with unprovoked VTE who have an elevated D-dimer level after stopping therapy (6–8). However, whether posttreatment D-dimer levels should be used to decide which patients with unprovoked VTE should stop or continue anticoagulant therapy is uncertain.

We did a prospective cohort study to test whether the risk for recurrence in patients with a first unprovoked proximal deep venous thrombosis or pulmonary embolism who have normal posttreatment D-dimer levels is low enough to justify stopping anticoagulant therapy (that is, able to exclude a recurrence rate of 7% per patient-year). Patients with normal D-dimer levels during anticoagulant therapy and 1 month after stopping therapy did not restart treatment. Patients with abnormal D-dimer levels during anticoagulant therapy or 1 month after stopping therapy continued therapy indefinitely.

METHODS

Design Overview

This multicenter prospective management study enrolled patients at 13 tertiary care centers from September 2008 to March 2012 and followed them until 31 May 2013.

Study Patients

Patients aged 18 years or older with a first episode of symptomatic unprovoked proximal deep venous thrombosis of the legs or pulmonary embolism who had completed 3 to 7 months of uninterrupted warfarin

EDITORS' NOTES

Context

Current practice is to continue anticoagulation indefinitely to treat venous thromboembolism (VTE) caused by a persistent condition and to stop anticoagulation after a standard period when VTE is caused by a transient condition. It is uncertain which approach to take when the cause cannot be identified.

Contribution

The investigators studied patients without an identifiable condition who had 2 negative D-dimer test results after a standard period of anticoagulation. The recurrence rate was high in men and lower in women.

Caution

Different types of D-dimer assays could have different results.

Implication

In men, anticoagulation should be continued indefinitely. In women, the situation is more complicated.

therapy (target international normalized ratio, 2.0 to 3.0) were potentially eligible (**Figure 1**). **Appendix 2** (available at www.annals.org) provides a definition of unprovoked VTE.

Patients who met the inclusion criteria were ineligible if they had another indication for anticoagulant therapy, were older than 75 years, had a high risk for bleeding for other reasons, or had D-dimer testing within the past 2 months (**Figure 1**; detailed eligibility criteria are provided in **Appendix 2**). Patients provided written, informed consent. The study was approved by the institutional review boards of all participating clinical centers and was registered at ClinicalTrials.gov (NCT00720915).

Enrollment, D-Dimer Testing, and Related Anticoagulant Management

Clinical centers accessed an automated, centralized registration system to enroll patients. Registration had to occur before D-dimer testing, and all registered patients remained in the study.

D-Dimer testing was first done in all patients while they were receiving anticoagulant therapy. We used the Clearview Simplify assay (Alere), a point-of-care, slide-based test that yields a positive or negative D-dimer result (9, 10). Patients with a positive result continued anticoagulant therapy indefinitely and did not have a second D-dimer test. Patients with a negative result stopped therapy and had a second D-dimer test a month later. If the second test result was positive, anticoagulant therapy was restarted (warfarin, without initial heparin therapy); if it was negative, patients stopped therapy indefinitely.

Follow-up and Outcome Measures

Patients had a clinic visit after 1 month (when D-dimer testing was repeated in patients with an initial negative result), were then contacted every 3 months, and were told to immediately report symptoms suggestive of VTE or bleeding.

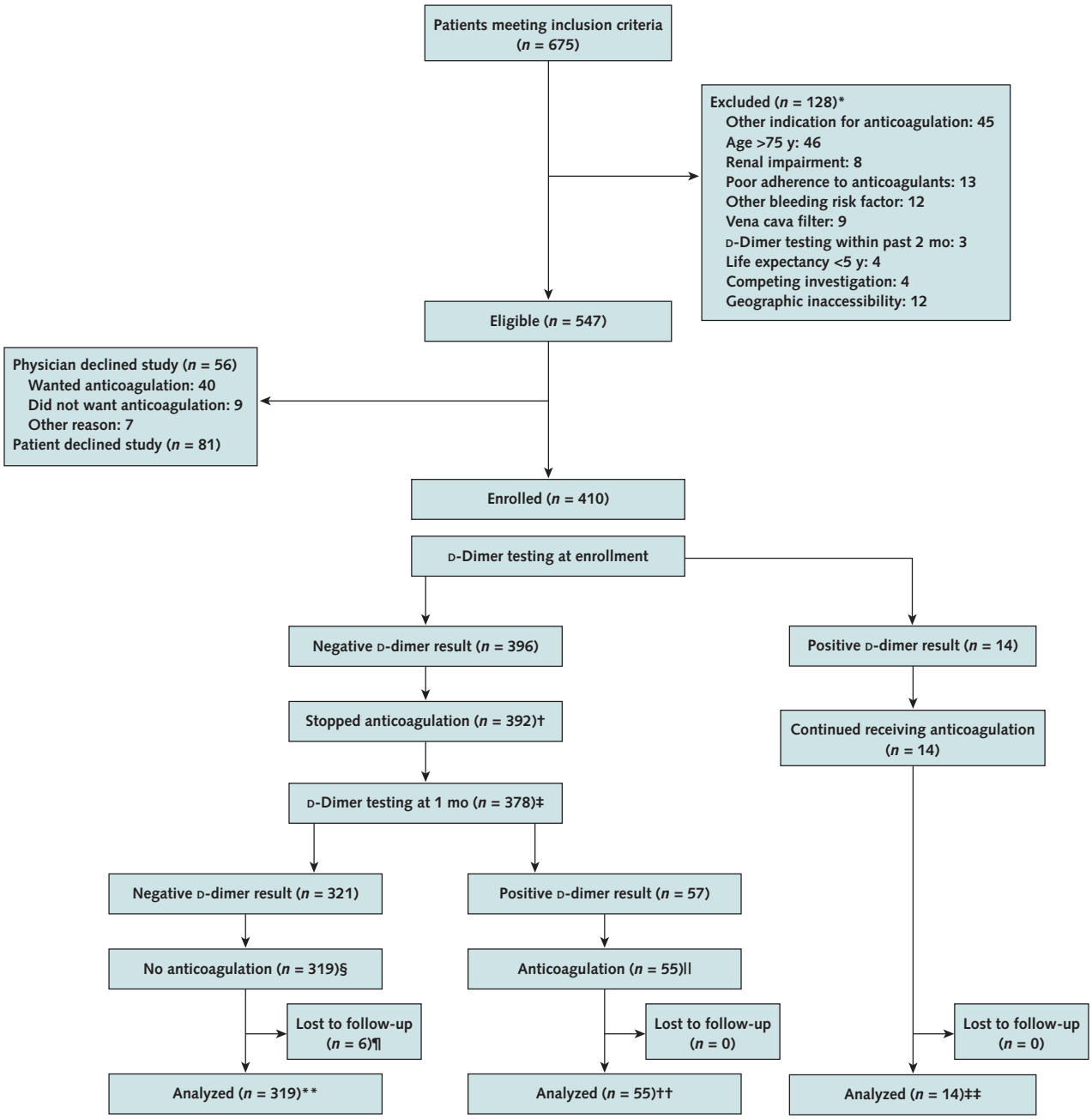
Suspected recurrent VTE was evaluated with diagnostic testing that did not include D-dimer testing. Recurrent thrombosis had to involve the proximal veins (calf vein trifurcation abnormalities did not qualify) or a segmental pulmonary artery (subsegmental abnormalities did not qualify) to be considered a study outcome (**Appendix 2**). Testing for VTE was done only if prompted by new symptoms. Sudden unexplained deaths were counted as pulmonary embolism. Bleeding was categorized as major or minor (**Appendix 2**). Cancer was diagnosed if there was unequivocal histologic or clinical evidence. All suspected outcome events and deaths were classified by a central adjudication committee whose members were unaware of the patient's D-dimer results at enrollment or whether patients were receiving anticoagulant therapy.

Statistical Analysis

The primary outcome was the rate of symptomatic recurrent VTE (proximal deep venous thrombosis or pulmonary embolism) in patients who stopped anticoagulant therapy after 2 negative D-dimer test results. We used the Kaplan–Meier method to present the time of the first recurrent VTE and calculated the overall rate of recurrent VTE as the total number of events in the observation period divided by the total number of years of observation. We obtained 95% CIs for these estimates from the Poisson distribution using exact methods. The period of observation for each patient was from enrollment until 31 May 2013, occurrence of the first event (such as recurrent VTE) for that analysis, death, or the last known contact. We did similar analyses for symptomatic VTE in patients who continued anticoagulant therapy, as well as for major and minor bleeding in those who continued and those who stopped anticoagulant therapy. After the study began, reports emerged that, among patients with unprovoked VTE who have negative D-dimer results 1 month after stopping therapy, men have a higher risk for recurrence than women and that women with VTE during estrogen therapy who then stop their therapy (estrogen women) have a lower risk for recurrence than women with unprovoked VTE (nonestrogen women) (6, 7). Consequently, after we started our study but before we began the analyses, we prespecified that we would compare recurrence rates among these 3 sex-based subgroups by using a log-rank test.

We hypothesized that the overall rate of recurrent VTE in patients who stopped anticoagulant therapy in response to 2 negative D-dimer test results would be low enough to exclude a recurrence rate of 7% per patient-year (corresponding to a cumulative probability of recurrence of about 17.5% after 2.5 years). This is similar to the rate of recurrence in patients with VTE

Figure 1. Study flow diagram.



VTE = venous thromboembolism.
* Patients could be excluded for >1 reason.
† Anticoagulants were not stopped in 4 patients (1 with chronic deep venous thrombosis on ultrasonography and 3 because of patient preference).
‡ D-Dimer testing was not done in 14 patients (7 who withdrew from the study and 7 who restarted anticoagulant therapy before 1 mo [2 with recurrent VTE adjudicated as study outcomes, 1 with recurrent VTE adjudicated as an isolated calf deep venous thrombosis, 1 with locally diagnosed VTE adjudicated as no recurrent VTE, 1 with superficial venous thrombosis, 1 because of patient preference, and 1 because of physician preference]).
§ Anticoagulants were restarted in 2 patients (reason not given, but no recurrent VTE).
|| Anticoagulants were not restarted in 2 patients (1 because of patient preference and 1 in whom anticoagulant therapy was inappropriately deferred because of infection and then had recurrent VTE).
¶ Unexplained losses to follow-up. These patients were included until the last time they were assessed (mean follow-up, 1.4 y).
** Anticoagulants were restarted during follow-up in 62 patients (41 with recurrent VTE adjudicated as study outcomes, 7 with locally diagnosed VTE adjudicated as no recurrent VTE, 3 with atrial fibrillation, 3 who were pregnant, 2 because of physician preference, 2 with occluded coronary artery stent, 1 with portal venous thrombosis, 1 diagnosed with cancer, and 2 who restarted for new symptoms without recurrent VTE diagnosed by testing).
†† Anticoagulants were stopped in 15 patients before the end of follow-up (6 because of patient preference, 4 because of physician preference, 2 with bleeding, 1 because of fall risk, 1 with severe rash, and 1 with anemia). None had VTE during follow-up.
‡‡ Anticoagulants were stopped in 3 patients before the end of follow-up (2 because of patient preference and 1 because of physician preference).

Table 1. Baseline Patient Characteristics*

Characteristic	All Patients (*n* = 410)	Men (*n* = 231)	Nonestrogen Women (*n* = 109)	Estrogen Women (*n* = 70)
Mean age (SD), *y*	51 (14)	54 (12)	55 (14)	38 (12)
Mean weight (SD), *kg*	93 (23)	99 (22)	89 (25)	83 (19)
Mean body mass index (SD), kg/m^2	31 (7)	30 (6)	33 (8)	30 (7)
Mean duration of anticoagulation (SD), *mo*	5 (1)	5 (1)	5 (1)	5 (1)
Previous provoked VTE, *n (%)*	18 (4)	5 (2)	12 (11)	1 (1)
Qualifying thrombotic event, *n (%)*				
Proximal deep venous thrombosis only	183 (45)	113 (49)	42 (39)	28 (40)
Pulmonary embolism (with or without deep venous thrombosis)	227 (55)	118 (51)	67 (61)	42 (60)
Risk factors for bleeding, *n (%)*†				
0	355 (87)	197 (85)	92 (84)	66 (94)
1	46 (11)	30 (13)	13 (12)	3 (4)
2	7 (2)	4 (2)	2 (2)	1 (1)
3	2 (<1)	0 (0)	2 (2)	0 (0)
Diabetes (requiring medication), *n (%)*	30 (7)	19 (8)	9 (8)	2 (3)
Antiplatelet therapy, *n (%)*‡	28 (7)	19 (8)	9 (8)	0 (0)
Statin therapy, *n (%)*	62 (19)	43 (19)	17 (16)	2 (3)
Compression stockings, *n (%)*	125 (30)	75 (32)	34 (31)	16 (23)
Family history of VTE, *n (%)*§	87 (21)	47 (20)	22 (20)	18 (26)
Hyperpigmentation, edema, or redness, *n (%)*				
No	310 (76)	171 (74)	82 (75)	57 (81)
Yes	100 (24)	60 (26)	27 (25)	13 (19)
1 leg	86 (86)	51 (85)	22 (81)	13 (100)
Both legs	14 (14)	9 (15)	5 (19)	0 (0)
Performance status, *n (%)*‖				
Fully active	372 (91)	213 (92)	96 (88)	63 (90)
Not fully active	38 (9)	18 (8)	13 (12)	7 (10)
CUS of proximal veins¶, *n (%)*				
Not done in either leg	203 (50)	110 (48)	55 (50)	38 (54)
Done in both legs	125 (30)	68 (29)	37 (34)	20 (29)
Done in 1 leg	82 (20)	53 (23)	17 (16)	12 (17)
Fully compressible, *n (% of CUS)*	120 (58)	66 (55)	36 (67)	18 (56)
Not fully compressible, *n (% of CUS)*	87 (42)	55 (45)	18 (33)	14 (44)

CUS = compression ultrasonography; VTE = venous thromboembolism.
* "Estrogen women" and "nonestrogen women" refer to whether the women had the index episode of VTE that qualified them for the study during estrogen therapy.
† Previous stroke, previous peptic ulcer disease, previous gastrointestinal bleeding, previous genitourinary bleeding, known gastrointestinal abnormality associated with bleeding, known genitourinary abnormality associated with bleeding, diabetes requiring medication, or antiplatelet therapy.
‡ Aspirin in all 28 patients.
§ ≥1 parent, sibling, or child.
‖ Assessed by using Eastern Cooperative Oncology Group performance status (0 = fully active; 1 to 4 = restricted strenuous activity to completely disabled).
¶ Common femoral vein, femoral vein, popliteal vein, and calf vein trifurcation.

provoked by a nonsurgical reversible risk factor, a subgroup that is judged to have low enough risk for recurrence that indefinite therapy is not indicated (2, 11). Given an expected recurrence rate of about 4% per patient-year (12), 206 patients were required to exclude a rate of 7% per patient-year with a power of 90% and a 1-sided α of 0.025. We estimated that 85% of patients would have a negative D-dimer result during treatment; 1% of these would have recurrent VTE within the first month of stopping therapy and, of the remainder, 70% would have a second negative D-dimer result 1 month after stopping therapy (12). We also estimated that about 2.5% of patients would be lost to follow-up. Finally, we inflated the sample size by 10% because of uncertainty in our assumptions. This yielded a total sample of 396 patients. Analyses were done by using SAS, version 9.2 (SAS Institute), and Stata 13 (StataCorp).

Role of the Funding Source

This study was funded by the Canadian Institutes of Health Research, which had no role in study design; collection, analysis, or interpretation of data; writing, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

RESULTS

Study Patients and D-Dimer Testing at Enrollment

A total of 675 patients met the inclusion criteria. Of these, 128 met at least 1 exclusion criterion, 56 did not enroll as decided by their physician, and 81 declined to participate (**Figure 1**). Therefore, 410 patients were enrolled and had D-dimer testing during anticoagulant therapy (mean duration, 5.0 months [SD, 1.3]) (**Table 1**). Results were negative in 396 (97%) patients, and 392 of these stopped anticoagulant therapy. Results were positive in 14 (4%) patients, all of whom continued therapy (**Figure 1**). Among the 3 prespecified subgroups, D-dimer results during anticoagulant therapy were positive in 3% (8 of 231) of men, 6% (6 of 109) of nonestrogen women, and 0% (0 of 70) of estrogen women (all of

whom had stopped estrogen therapy before enrollment) (P = 0.141). All patients were scheduled to be followed until 31 May 2013, with an average follow-up of 2.2 years (SD, 1.0). Six patients (1.5%) were unexplained losses to follow-up (Figure 1).

D-Dimer Testing at 1 Month in Patients Who Stopped Anticoagulant Therapy

Among the 392 patients who stopped anticoagulant therapy in response to a negative D-dimer test result at enrollment, 2 had recurrent VTE before they returned for scheduled D-dimer testing at 1 month, 2 were diagnosed with recurrent VTE on the day they returned for scheduled D-dimer testing at 1 month (both had acute symptoms and positive D-dimer results) (Appendix Table 1, available at www.annals.org), 14 did not have scheduled D-dimer testing at 1 month, and 378 had scheduled D-dimer testing at 1 month (including the 2 diagnosed with recurrent VTE at the 1-month assessment) (Figure 1). Of these 378, the D-dimer result at 1 month had converted to positive in 57 (15%) (55 restarted anticoagulant therapy, including the 2 diagnosed with recurrent VTE at 1 month) and remained negative in 321 (85%) (2 restarted anticoagulant therapy) (Figure 1). Among the 3 prespecified subgroups, the result converted to positive at 1 month in 15% (32 of 212) of men, 16% (16 of 98) of nonestrogen women, and 13% (9 of 68) of estrogen women (P = 0.86 for difference).

Recurrent VTE in Patients Who Stopped Anticoagulant Therapy

Among the 319 patients who stopped and did not restart anticoagulant therapy in response to 2 negative D-dimer test results, 42 recurrent episodes of VTE occurred (22 unprovoked, 10 provoked, and 10 not known) during 628 patient-years of follow-up (Appendix Table 1 and Figure 2), corresponding to an overall rate of recurrent VTE of 6.7% (95% CI, 4.8% to 9.0%) per patient-year (Table 2). In the 3 prespecified subgroups, the rate of recurrent VTE was 9.7% (CI, 6.7% to 13.7%) per patient-year in men, 5.4% (CI, 2.5% to 10.2%) per patient-year in nonestrogen women, and 0.0% (CI, 0.0% to 3.0%) per patient-year in estrogen women (P = 0.001 for the 3-group comparison) (Table 2 and Figure 2).

Recurrent VTE in Patients Who Did Not Stop or Who Restarted Anticoagulant Therapy

Among the 69 patients who either did not stop anticoagulant therapy at enrollment because of a positive D-dimer result (14 patients) or stopped at enrollment but restarted anticoagulant therapy because their D-dimer result had converted to positive at 1 month (55 patients, excluding the 2 who had recurrent VTE diagnosed at 1 month), 2 recurrent episodes of VTE occurred during 168 patient-years of follow-up, corresponding to a rate of recurrent VTE of 1.2% per patient-year (Appendix Table 1, Table 2, and Figure 2).

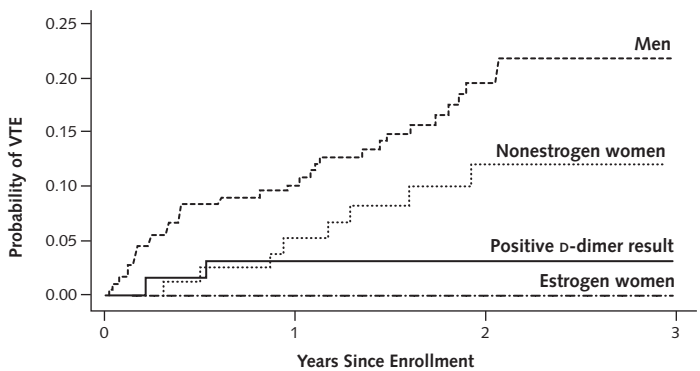
Bleeding During Follow-up

Among all enrolled patients, 7 episodes of major bleeding and 15 episodes of minor bleeding occurred (Appendix Table 1 and Table 2). In patients who used anticoagulants during follow-up, the rate of major bleeding was 2.3% per patient-year (Table 2).

Cancer Diagnosis During Follow-up

Nine patients were diagnosed with cancer during follow-up (Appendix Table 1). The proportions were 7% (1 of 14) for patients with a positive D-dimer result at enrollment, 5% (3 of 55) for those with a negative result at enrollment and a positive result at 1 month, and 2%

Figure 2. Cumulative risk for recurrent VTE during follow-up.



At risk, *n*				
Nonestrogen women	81	65	41	15
Estrogen women	58	51	30	11
Men	180	141	74	32
Positive D-dimer result	67	61	41	28

"Estrogen women" and "nonestrogen women" refer to whether the women had the index episode of VTE that qualified them for the study during estrogen therapy. Men, nonestrogen women, and estrogen women had negative D-dimer test results at baseline and 1 mo after anticoagulant withdrawal and did not restart anticoagulant therapy. Those with a positive D-dimer result were receiving anticoagulant therapy and included men and women who had a positive result at baseline or 1 mo; this group does not include 2 patients who had negative results at baseline and were diagnosed with recurrent VTE at 1 mo. VTE = venous thromboembolism.

Table 2. Rates of Recurrent VTE and Bleeding During Follow-up*

Outcome	Patients, *n*	Events, *n*	Person-Years	Event Rate per 100 Person-Years (95% CI)
Recurrent VTE				
All	410	48	833	5.8 (4.2–7.6)
2 negative D-dimer results				
All	321	42	632	6.6 (4.8–9.0)
All without anticoagulation	319	42	628	6.7 (4.8–9.0)
Men	180	33	339	9.7 (6.7–13.7)
Men without anticoagulation†	180	33	339	9.7 (6.7–13.7)
Nonestrogen women	82	9	171	5.3 (2.4–10.0)
Nonestrogen women without anticoagulation†	81	9	168	5.4 (2.5–10.2)
Estrogen women	59	0	122	0.0 (0.0–3.0)
Estrogen women without anticoagulation†	58	0	121	0.0 (0.0–3.0)
Positive D-dimer result at enrollment or 1 mo				
All	69	2	174	1.1 (0.1–4.1)
All with anticoagulation	67	2	168	1.2 (0.1–4.3)
Major bleeding				
All	410	7	930	0.8 (0.3–1.6)
Positive D-dimer result at enrollment or 1 mo				
All	69	4	172	2.3 (0.9–6.1)
All with anticoagulation	67	4	167	2.4 (0.9–6.3)
Minor bleeding				
All	410	15	913	1.6 (0.9–2.7)
Positive D-dimer result at enrollment or 1 mo				
All	69	8	164	4.9 (2.5–9.6)
All with anticoagulation	67	8	158	5.1 (2.6–9.9)

VTE = venous thromboembolism.
* "Estrogen women" and "nonestrogen women" refer to whether the women had the index episode of VTE that qualified them for the study during estrogen therapy.
† $P = 0.001$ for difference among the 3 groups; $P = 0.072$ for difference between men and nonestrogen women; $P = 0.02$ for difference between nonestrogen women and estrogen women; $P < 0.001$ for difference between men and estrogen women.

(5 of 320) for those with negative results at enrollment and 1 month.

Death During Follow-up

Five patients died during follow-up; causes were ischemic colitis, cardiomyopathy, pulmonary embolism (sudden death without a more likely alternative diagnosis), bleeding, and cancer (Appendix Table 1).

Use of Antiplatelet Therapy, Statins, and Compression Stockings During Follow-up

In patients who had negative D-dimer test results at enrollment and 1 month and did not restart anticoagulant therapy, use of an antiplatelet agent, a statin, or graduated compression stockings was similar in men and nonestrogen women, but use of an antiplatelet agent or a statin was less common in estrogen women than in men or nonestrogen women (Appendix Table 2, available at www.annals.org).

DISCUSSION

We found a higher-than-expected risk for recurrent VTE in patients with a first unprovoked proximal deep venous thrombosis or pulmonary embolism who had a negative D-dimer test result during anticoagulant therapy and 1 month after anticoagulants were withdrawn. Among these patients, and consistent with other reports that emerged during our study (6, 7), we found a higher risk for recurrence in men than in women and a higher risk for recurrence in women with VTE that was not associated with estrogen therapy than in women with estrogen-associated VTE who then stopped therapy. The high risk for recurrence in men accounted for the higher-than-expected overall risk for recurrence in patients with negative D-dimer results.

Although men with unprovoked VTE have long been recognized to have a higher risk for recurrence after stopping anticoagulant therapy than women (13), we did not expect this higher risk to persist when both groups had negative D-dimer results. Instead, we expected that a higher proportion of men would have positive D-dimer results and would therefore need to continue anticoagulant therapy. This was not the case; the proportions of men and women with positive D-dimer results were the same. Therefore, the overall higher risk for recurrence in men did not seem to be expressed as a greater increase in D-dimer levels after anticoagulant therapy was stopped. Retrospective analyses by others (6, 7) have also found that patient sex and whether the initial VTE occurred during estrogen therapy predict the risk for recurrence in patients with a first unprovoked VTE, independent of D-dimer level. When we started the study, we were uncertain whether women who had VTE during estrogen therapy should be considered to have unprovoked VTE. We decided to include them in this study but analyze them as a separate subgroup. Our findings and those of others (7, 14) support categorizing estrogen-associated VTE as provoked thrombosis.

The findings of this study enable better estimation of the risk for recurrent VTE in patients with unprovoked VTE and, therefore, have clinical implications. For example, we conclude that women with estrogen-associated VTE who have completed 3 months of anticoagulant therapy and have stopped estrogen therapy can stop anticoagulant therapy without D-dimer testing. This is because there were no recurrences in women with negative D-dimer results in our study, and other studies have found a low risk for recurrence in women with estrogen-associated VTE regardless of whether the posttreatment D-dimer result was positive or negative (7, 14). Our recommendations for D-dimer testing in other patients are more nuanced. We recommend that a person with unprovoked VTE should have D-dimer testing after completing 3 months of anticoagulant therapy only if that person would restart therapy when the D-dimer result is positive and would not restart therapy when the result is negative. For men, we estimate that the initial recurrence rate is 8% per year with a negative result and 16% per year with a positive result (6, 7). Therefore, men with a first unprovoked proximal deep venous thrombosis or pulmonary embolism should have D-dimer testing only if they would not restart anticoagulant therapy if the recurrence rate was 8% (negative result) and would restart therapy if the recurrence rate was 16% (positive result). D-Dimer testing would not be useful for a man who would continue anticoagulant therapy if his recurrence rate was 8% (negative result) or would stop therapy if his recurrence rate was 16% (positive result). For women, we estimate that the initial recurrence rate is 5% per year with a negative result and 10% per year with a positive result (6, 7). Therefore, women should have D-dimer testing only if they would not restart anticoagulant therapy if the recurrence rate was 5% (negative result) and would restart therapy if the recurrence rate was 10% (positive result). D-Dimer testing would not be useful for a woman who would continue anticoagulant therapy even if her recurrence rate was as low as 5% (negative result) or would stop therapy if her recurrence rate was 10% (positive result). In addition to considering a patient's preferences, the decision to do D-dimer testing is influenced by the patient's risk for bleeding; if the risk is high enough that it precludes indefinite anticoagulant therapy even if D-dimer results are positive, anticoagulant therapy should be stopped without D-dimer testing. We believe that this is generally the case for patients older than 75 years who, therefore, were excluded from our study. In addition, the predictive value of D-dimer testing is expected to be lower in elderly patients because D-dimer levels increase with age.

An alternative study design to test whether a negative D-dimer test result justifies stopping anticoagulant therapy would have been to randomly assign patients with negative results to either stop or continue therapy. If harms of extended therapy outweighed benefits because patients had a low risk for recurrence, stopping therapy would be justified. However, we were reluctant to randomly assign patients to a therapy in order to show lack of benefit or harm.

Important strengths of this study are that patients were managed according to the results of D-dimer testing, patients were enrolled before D-dimer testing was done so that knowledge of results could not influence the decision to enroll, follow-up and diagnostic testing were standardized, few patients were lost to follow-up, and the sex-based subgroups were predefined. Limitations include that the study was not powered to estimate recurrence rates in each of the 3 sex-based subgroups, with resultant imprecision in the female subgroups; the D-dimer assay used in this study is not widely available; and our findings may not be generalizable to other D-dimer assays. A retrospective analysis of individual data from 7 studies suggests that various D-dimer assays can be used to stratify the risk for recurrent VTE in patients with unprovoked VTE (6). A recently published Italian study reported low rates of recurrent VTE in patients younger than 70 years with unprovoked VTE who had negative D-dimer results at 15, 30, 60, and 90 days after stopping therapy (15). Other differences in D-dimer testing between the Italian study and our study were that the former used any of 4 quantitative D-dimer assays, used D-dimer cutoffs to define positive results that were probably lower than the cutoff our qualitative assay uses, and used a lower D-dimer cutoff for men than women. The approach to D-dimer testing in the Italian study resulted in anticoagulant therapy being restarted in about twice as many patients as in our study. Therefore, uncertainty remains about how D-dimer testing should be used to guide decisions about duration of treatment in patients with unprovoked VTE (16). In our study and the Italian study, less than 5% of patients had a positive D-dimer result during anticoagulant therapy, suggesting that it is reasonable to omit this test and just perform D-dimer testing after anticoagulants have been withdrawn. We also note that it is uncertain whether the study's findings apply to patients with an antiphospholipid antibody because some centers excluded such patients and enrolled patients were not routinely tested for these abnormalities.

In conclusion, we found a high risk for recurrence in men with a first unprovoked VTE who had a negative D-dimer test result after withdrawal of anticoagulants, suggesting that a negative result does not justify stopping anticoagulant therapy in men. However, the risk for recurrence in women with a negative D-dimer result seems low enough to justify stopping therapy. Our findings and those of others also suggest that women who have VTE during estrogen therapy should be considered to have thrombosis provoked by a reversible factor and can stop therapy without D-dimer testing.

From McMaster University, Hamilton, Ontario, Canada; University of Limerick, Limerick, Ireland; Addenbrooke's Hospital, Cambridge, United Kingdom; Intermountain Medical Center, Murray, Utah; Hurley Medical Center, Flint, Michigan; Harvard Medical School, Boston, Massachusetts; University of Iowa,

Iowa City, Iowa; Georgetown University, Washington, DC; and University of North Carolina, Chapel Hill, North Carolina.

Note: Dr. Kearon and Mr. Julian had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Parpia and Mr. Julian conducted and are responsible for the data analysis.

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Reproducible Research Statement: *Study protocol:* Available from Dr. Kearon (e-mail, kearonc@mcmaster.ca). *Statistical code:* Not available. *Data set:* Interested parties should contact Dr. Kearon, chair of the study steering committee (e-mail, kearonc@mcmaster.ca), with their request for data access and must include their study proposal, protocol, and analysis plan. Some restrictions may apply.

Requests for Single Reprints: Clive Kearon, MB, PhD, Hamilton Health Sciences, Juravinski Hospital, Room A3-73, 711 Concession Street, Hamilton, Ontario L8V 1C3, Canada.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Kearon: Hamilton Health Sciences, Juravinski Hospital, Room A3-73, 711 Concession Street, Hamilton, Ontario L8V 1C3, Canada.
Dr. Spencer: St. Joseph's Healthcare, Martha Wing Room H319, 50 Charlton Avenue East, Hamilton, Ontario L8N 4A6, Canada.
Dr. O'Keeffe: Graduate Entry Medical School, University of Limerick, University Hospital Limerick, Dooradoyle, Limerick, Ireland.
Dr. Parpia, Ms. Spadafora, and Mr. Julian: Ontario Clinical Oncology Group, 711 Concession Street, Hamilton, Ontario L8V 1C3, Canada.
Dr. Schulman: Hamilton General Hospital, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada.
Dr. Baglin: Box 217, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Treatment Centre, Hills Road, Cambridge CB2 0QQ, United Kingdom.
Dr. Stevens: Intermountain Medical Center, 5169 South Cottonwood Street, Suite 303, Murray, UT 84107.
Dr. Kaatz: Hurley Medical Center, 2W, One Hurley Plaza, Flint, MI 48098.
Dr. Bauer: Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02115.
Dr. Douketis: St. Joseph's Healthcare, Fontbonne Building Room 544, 50 Charlton Avenue East, Hamilton, Ontario L8N 4A6, Canada.
Dr. Lentz: University of Iowa Carver College of Medicine, Department of Internal Medicine, C32 GH, 200 Hawkins Drive, Iowa City, IA 52242.
Dr. Kessler: Podium A, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, 3700 Reservoir Road NW, Washington, DC 20007.
Dr. Moll: University of North Carolina School of Medicine, CB 7035, Chapel Hill, NC 27599.
Dr. Connors: Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.
Dr. Ginsberg: St. Joseph's Healthcare, Martha Wing Room H318, 50 Charlton Avenue East, Hamilton, Ontario L8N 4A6, Canada.

Author Contributions: Conception and design: C. Kearon, T. Baglin, S.M. Stevens, S. Kaatz, K.A. Bauer, S.R. Lentz, C.M. Kessler, J.M. Connors, J.S. Ginsberg, J.A. Julian.
Analysis and interpretation of the data: C. Kearon, F.A. Spencer, S. Parpia, S. Schulman, S.R. Lentz, C.M. Kessler, J.A. Julian.
Drafting of the article: C. Kearon.
Critical revision of the article for important intellectual content: C. Kearon, F.A. Spencer, D. O'Keeffe, S. Parpia, S. Schulman, T. Baglin, S.M. Stevens, S. Kaatz, K.A. Bauer, S.R. Lentz, C.M. Kessler, S. Moll, J.M. Connors, J.S. Ginsberg, J.A. Julian.
Final approval of the article: C. Kearon, F.A. Spencer, D. O'Keeffe, S. Parpia, S. Schulman, T. Baglin, S.M. Stevens, S. Kaatz, K.A. Bauer, S.R. Lentz, C.M. Kessler, S. Moll, J.M. Connors, J.S. Ginsberg, J.A. Julian.
Provision of study materials or patients: C. Kearon, F.A. Spencer, D. O'Keeffe, S. Schulman, S.M. Stevens, K.A. Bauer, S.R. Lentz, C.M. Kessler, J.M. Connors.
Statistical expertise: S. Parpia, J.A. Julian.
Obtaining of funding: C. Kearon, J.A. Julian.
Administrative, technical, or logistic support: C. Kearon, L. Spadafora.
Collection and assembly of data: C. Kearon, F.A. Spencer, D. O'Keeffe, S. Parpia, S. Schulman, T. Baglin, S.M. Stevens, S. Kaatz, K.A. Bauer, J.D. Douketis, S.R. Lentz, C.M. Kessler, S. Moll, J.M. Connors, J.S. Ginsberg, L. Spadafora, J.A. Julian.

Appendix 1: D-Dimer Optimal Duration Study Investigators

Hamilton Health Sciences, McMaster University Medical Centre, Hamilton, Ontario, Canada (70 patients): Laurie Sardo, Pamela Stevens, and Shannon Bates; Hamilton Health Sciences, Juravinski Hospital, Hamilton, Ontario, Canada (56 patients): Sue Smale, Tracy Winkworth, Naomi Bedek, Alla Glushchenko, Peter L. Gross, Lori-Ann Linkins, Martin O'Donnell, and Jeffrey Weitz; University Hospital Limerick, Limerick, Ireland (41 patients): Jane Conway, Mike Watts, Deborah Bourke, and Pat Kiely; Addenbrooke's Hospital, Cambridge, United Kingdom (34 patients): Caroline Baglin; Hamilton Health Sciences, General Hospital, Hamilton, Ontario, Canada (40 patients): Lisa Rudd-Scott, Michelle Zondag, and John Eikelboom; Intermountain Medical Center, Murray, Utah (27 patients): Valerie T. Aston, Greg Elliott, and Scott C. Woller; Henry Ford Hospital, Detroit, Michigan (27 patients): Stacy Ellsworth, Helen Gikas, Syed T. Ahsan, and Vinay Shah; Harvard Medical School, Boston, Massachusetts (24 patients): Marie Mahony, Anita Rodrigues, and Jeffrey I. Zwicker; St. Joseph's Healthcare, Hamilton, Ontario, Canada (23 patients): Rita Betz, Terri Schnurr, Howard Chan, Mark Crowther, and Wendy Lim; University of Iowa Hospitals and Clinics, Iowa City, Iowa (21 patients): Tracy Peters, Mike Lammer, Peter Kaboli, Scott Leaverton, and Donald MacFarlane; Lombardi Cancer Center, Washington, DC (19 patients): Helena Jacobs, Rim Abdallah, and Catherine Broome; University of North Carolina, Chapel Hill, North Carolina (19 patients): Nigel S. Key, Raj S. Kasthuri, Cheryl Jeanneret, and Roberta Kellerman; Brigham and Women's Hospital, Boston, Massachusetts (9 patients): Nivisha Naik, Betty S. Rowe, Lisa Stewart, Rachel Wentz, Nancy Berliner, and Ronald McCaffrey.

Independent Adjudication Committee: Shannon Bates, Jim Douketis, Jack Hirsh, Mark Levine, Sam Schulman, and Jeffrey Weitz.

Data Management and Study Coordination: Clare Stewart, Erin McGean, Beverly Pond, and Donna McCarty (Ontario Clinical Oncology Group, McMaster University, Hamilton, Ontario, Canada).

Data Safety Monitoring Committee: William Geerts (University of Toronto, Toronto, Ontario, Canada) and Robin Roberts (McMaster University, Hamilton, Ontario, Canada).

Appendix 2: Supplemental Information

Definition of Unprovoked VTE

For VTE to be considered unprovoked, there could not have been a major risk factor within 3 months of diagnosis (lower limb fracture, casting or no weight bearing for ≥3 days, bed-bound for 3 days due to acute illness, or surgery with general or spinal anesthesia), a minor risk factor within 2 months of diagnosis (pregnancy, puerperium, or leg trauma with limping for ≥3 days), or active cancer within 2 years of diagnosis.

Study Eligibility Criteria

Patients aged 18 years or older with a first episode of symptomatic unprovoked proximal deep venous thrombosis of the legs or pulmonary embolism who had completed 3 to 7 months of uninterrupted warfarin therapy (therapeutic range of international normalized ratio, 2.0 to 3.0) were potentially eligible.

Patients who met these inclusion criteria were ineligible if they had another indication for long-term anticoagulation (such as atrial fibrillation), had high risk for bleeding (aged >75 years, history of major bleeding without a corrected cause, known platelet count $<120\,000 \times 10^9$ cells/L, creatinine level >150 μmol/L [>1.7 mg/dL], or liver disease with total bilirubin level >25 μmol/L [>1.5 mg/dL]), had active peptic ulcer disease, had poor control of international normalized ratio monitoring during anticoagulant therapy, needed dual-antiplatelet therapy, had a vena cava filter, had D-dimer testing within the past 2 months, had a life expectancy less than 5 years, were unable to attend follow-up visits, or were participating in a competing clinical investigation. Clinical centers had the option of excluding patients with hereditary or acquired thrombophilia or women whose thrombosis occurred during estrogen therapy, provided that this decision was made without D-dimer testing having been done. Patients could have had a previous episode of provoked VTE.

Diagnostic Criteria for Recurrent VTE

Criteria for ultrasonographic diagnosis of recurrent VTE as a proximal deep venous thrombosis were (in descending order of importance) a new noncompressible common femoral or popliteal vein site, an increase of at least 4 mm in compressed thrombus diameter at the common femoral or popliteal site, or clear extension of a thrombus margin (extension of thrombus position by ≥10 cm or, if this measurement was not available, by at least one third of the length of the thigh as drawn on a leg vein diagram).

The criterion for venographic diagnosis of recurrent VTE as a proximal deep venous thrombosis was a new intraluminal filling defect in the proximal veins.

Criteria for diagnosis of recurrent VTE as a segmental or more proximal pulmonary embolism were a new intraluminal filling defect involving a segmental or more proximal pulmonary artery on computed tomography pulmonary angiography, a new high-probability perfusion defect on a ventilation–perfusion scan, or having a nondiagnostic computed tomography pulmonary angiogram or ventilation–perfusion scan but meeting criteria for diagnosis of recurrence as a proximal deep venous thrombosis.

If the aforementioned criteria were not met, adjudicators could diagnosis recurrent VTE if they judged the evidence to be convincing and they described that evidence. For patients who were judged to have had recurrent VTE, the adjudicators assessed whether it was unprovoked or provoked (provoking factor was documented) or whether this was not known.

Deaths were adjudicated as due to pulmonary embolism (including sudden death without a history of cardiac disease or another more likely cause of death), due to bleeding (including those meeting criteria for major bleeding and no more likely cause of death), or not due to pulmonary embolism or bleeding (alternative cause of death was documented).

Criteria for Major and Minor Bleeding

Bleeding was defined as major if it was clinically overt and associated with a decrease in hemoglobin level of at least 20 g/L, required a transfusion of 2 or more units of red blood cells, involved a critical site (such as retroperitoneal or intracranial), or was fatal. Bleeding that was overt and considered abnormal but that did not meet these criteria was categorized as minor.

Data and Safety Monitoring Board Responsibilities

The Data and Safety Monitoring Board met at periodic intervals during the study to:

Review rates of recurrent VTE and their severity in the subgroup of patients who stop anticoagulant therapy in response to negative D-dimer results (primary safety concern) after completion of 150, 300, and 450 patient-years of follow-up. The following served as guidelines for unacceptable rates at these time points: 11% per year at 150 patient-years (16 events), 9% per year at 300 patient-years (27 events), and 7% per year at 450 patient-years (31 events);

Review rates of major bleeding among patients who continued anticoagulant therapy (secondary safety concern);

Review deaths of all enrolled patients; and

Make recommendations to the principal investigator; the steering committee; and, if required, the clinical center research ethics boards concerning continuation, termination, or other modifications of the study.

Appendix Table 1. VTE, Major Bleeding, Cancer Diagnoses, and Deaths During Follow-up*

PID, by Outcome	Type or Site	Time After Enrollment, *d*	D-Dimer Result at Presentation	D-Dimer Result at 1 mo	Subgroup†	Comments
VTE (*n* = 48)‡						
Before 1-mo follow-up (*n* = 2)						
1	Deep venous thrombosis	13	Negative	NA	Nonestrogen women	Not known whether provoked
2	Pulmonary embolism	19	Negative	NA	Men	Unprovoked
At 1-mo follow-up (*n* = 2)						
3	Deep venous thrombosis	28	Negative	Positive	Nonestrogen women	Unprovoked
4	Deep venous thrombosis	32	Negative	Positive	Men	Unprovoked
After 1-mo follow-up (*n* = 44)						
5	Deep venous thrombosis	39	Negative	Negative	Men	Not known whether provoked
6	Pulmonary embolism	42	Negative	Negative	Men	Unprovoked
7	Pulmonary embolism	57	Negative	Negative	Men	Unprovoked
8	Pulmonary embolism	76	Negative	Negative	Men	Unprovoked
9	**Pulmonary embolism**	**80**	**Positive**	**NA**	**Men**	**Unprovoked**
10	Deep venous thrombosis	82	Negative	Negative	Men	Not known whether provoked
11	Deep venous thrombosis	90	Negative	Negative	Men	Unprovoked
12	**Deep venous thrombosis**	**92**	**Negative**	**Negative**	**Men**	**Unprovoked**
13	**Deep venous thrombosis**	**98**	**Negative**	**Negative**	**Men**	**Unprovoked**
14	**Pulmonary embolism**	**121**	**Negative**	**Negative**	**Men**	**Unprovoked**
15	Deep venous thrombosis	128	Negative	Negative	Men	Not known whether provoked
16	Deep venous thrombosis	148	Negative	Negative	Nonestrogen women	Provoked (fall and travel)
17	Pulmonary embolism	149	Negative	Negative	Men	Unprovoked
18	Deep venous thrombosis	150	Negative	Negative	Men	Unprovoked
19	Pulmonary embolism	173	Negative	Negative	Men	Not known whether provoked
20	Pulmonary embolism	179	Negative	Negative	Men	Unprovoked
21	Deep venous thrombosis	182	Negative	Negative	Men	Unprovoked
22	**Deep venous thrombosis**	**214**	**Negative**	**Negative**	**Nonestrogen women**	**Provoked (Crohn disease)**
23	**Pulmonary embolism**	**229**	**Negative**	**Positive**	**Nonestrogen women**	**Provoked (cancer)**
24	Deep venous thrombosis	266	Negative	Negative	Men	Provoked (travel)
25	Pulmonary embolism	330	Negative	Negative	Men	Provoked (surgery)
26	Deep venous thrombosis	346	Negative	Negative	Nonestrogen women	Provoked (long car ride)
27	Deep venous thrombosis	376	Negative	Negative	Nonestrogen women	Not known whether provoked
28	Deep venous thrombosis	382	Negative	Negative	Men	Provoked (surgery)
29	Pulmonary embolism	415	Negative	Negative	Men	Unprovoked
30	Pulmonary embolism	425	Negative	Negative	Men	Not known whether provoked
31	Pulmonary embolism	427	Negative	Negative	Men	Not known whether provoked
32	Deep venous thrombosis	443	Negative	Negative	Men	Unprovoked

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Appendix Table 1–Continued

PID, by Outcome	Type or Site	Time After Enrollment, *d*	D-Dimer Result at Presentation	D-Dimer Result at 1 mo	Subgroup†	Comments
33	Pulmonary embolism	464	Negative	Negative	Nonestrogen women	Unprovoked
34	Deep venous thrombosis	497	Negative	Negative	Nonestrogen women	Provoked (travel)
35	Deep venous thrombosis	525	Negative	Negative	Men	Not known whether provoked
36	Pulmonary embolism	557	Negative	Negative	Men	Unprovoked
37	Deep venous thrombosis	560	Negative	Negative	Men	Not known whether provoked
38	Pulmonary embolism	618	Negative	Negative	Nonestrogen women	Unprovoked
39	Deep venous thrombosis	620	Negative	Negative	Men	Provoked (relative immobility)
40	Pulmonary embolism	674	Negative	Negative	Men	Unprovoked
41	Deep venous thrombosis	698	Negative	Negative	Nonestrogen women	Unprovoked
42	Pulmonary embolism	700	Negative	Negative	Men	Unprovoked
43	Deep venous thrombosis	711	Negative	Negative	Men	Unprovoked
44	Deep venous thrombosis	724	Negative	Negative	Men	Provoked (surgery)
45	Deep venous thrombosis	789	Negative	Negative	Men	Unprovoked
46	Deep venous thrombosis	791	Negative	Negative	Men	Unprovoked
47	Deep venous thrombosis	1223	Negative	Negative	Men	Provoked (travel)
48	**Pulmonary embolism**	**1632**	**Negative**	**Negative**	**Nonestrogen women**	**Not known whether provoked (fatal pulmonary embolism)**
Major bleeding (*n* = 7)						
49	**Gastrointestinal**	**14**	**Positive**	**NA**	**Nonestrogen women**	**–**
50	Menorrhagia	75	Negative	Positive	Nonestrogen women	–
9	**Gastrointestinal**	**140**	**Positive**	**NA**	**Men**	**–**
22	**Gastrointestinal**	**197**	**Negative**	**Negative**	**Nonestrogen women**	**–**
51	**Intracranial**	**204**	**Negative**	**Negative**	**Men**	**Fatal bleeding**
52	Soft tissue	528	Negative	Positive	Men	–
14	Intracranial	727	Negative	Negative	Men	–
Cancer (*n* = 9)						
23	**Rectum**	**14**	**Negative**	**Positive**	**Nonestrogen women**	**Provoked pulmonary embolism at 229 d**
53	Breast	37	Negative	Negative	Nonestrogen women	–
54	Melanoma	177	Negative	Positive	Men	–
55	Prostate	225	Negative	Positive	Men	–
56	Prostate	397	Positive	NA	Men	–
57	Hematologic	466	Negative	Negative	Nonestrogen women	–
58	Basel cell (eyelid)	512	Negative	Negative	Men	–
12	**Melanoma**	**917**	**Negative**	**Negative**	**Men**	**Unprovoked deep venous thrombosis at 92 d**
13	**Prostate**	**1115**	**Negative**	**Negative**	**Men**	**–**

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Appendix Table 1–Continued

PID, by Outcome	Type or Site	Time After Enrollment, *d*	D-Dimer Result at Presentation	D-Dimer Result at 1 mo	Subgroup†	Comments
Death (*n* = 5)						
49	**Ischemic colitis**	**62**	**Positive**	**NA**	**Nonestrogen women**	**–**
59	Cardiomyopathy	164	Negative	Negative	Nonestrogen women	–
51	**Bleeding**	**204**	**Negative**	**Negative**	**Men**	**–**
60	Cancer	377	Negative	Negative	Men	–
48	**Cannot rule out pulmonary embolism**	**1632**	**Negative**	**Negative**	**Nonestrogen women**	**–**

NA = not applicable; PID = patient identifier; VTE = venous thromboembolism.
* Events in boldface occurred in patients who had >1 type of event.
† "Nonestrogen women" denotes those not receiving estrogen therapy when the episode of VTE occurred that qualified them for the study.
‡ Recurrent VTE had to involve the proximal deep veins or be a segmental or more proximal pulmonary embolism to be counted as a study outcome. The independent adjudication committee judged that an additional patient had an isolated calf deep venous thrombosis during follow-up (no patient was diagnosed with subsegmental pulmonary embolism). The patient was a man who had a negative D-dimer test result at enrollment, had stopped anticoagulant therapy, and was diagnosed with an unprovoked calf deep venous thrombosis at 27 d (in addition to ultrasonographic findings, nonstudy D-dimer result was noted to be positive at that time).

Appendix Table 2. Patients Reporting Use of Antiplatelet Agent, Statin, or Graduated Compression Stockings* for ≥50% of Follow-up†

Variable	All Patients	Men	Nonestrogen Women	Estrogen Women	*P* Value for Difference Among Subgroups
Enrollment to 1-mo follow-up					
Negative D-dimer result at enrollment	396	223	103	70	
Antiplatelet agent	52 (13)	36 (16)	14 (14)	2 (3)	0.02
Statin	52 (13)	38 (17)	13 (13)	1 (1)	<0.01
Graduated compression stockings	134 (34)	76 (34)	41 (40)	17 (24)	0.11
Positive D-dimer result at enrollment	14	8	6	0	
Antiplatelet agent	4 (29)	1 (13)	3 (50)	0 (0)	–
Statin	7 (50)	3 (38)	4 (67)	0 (0)	–
Graduated compression stockings	4 (29)	3 (37)	1 (17)	0 (0)	–
All patients	410	231	109	70	
Antiplatelet agent	56 (14)	37 (16)	17 (16)	2 (3)	0.02
Statin	59 (14)	41 (18)	17 (16)	1 (1)	<0.01
Graduated compression stockings	138 (34)	79 (34)	42 (30)	17 (24)	0.14
1 mo to end of follow-up					
Negative D-dimer results at enrollment and 1 mo and stopped anticoagulants	319	180	81	58	
Antiplatelet agent	51 (16)	34 (19)	14 (17)	3 (5)	0.04
Statin	38 (12)	29 (16)	9 (11)	0 (0)	<0.01
Graduated compression stockings	69 (22)	42 (23)	19 (24)	8 (14)	0.28
All patients	410	231	109	70	
Antiplatelet agent	64 (16)	45 (20)	16 (15)	3 (4)	<0.01
Statin	58 (14)	40 (17)	17 (16)	1 (1)	<0.01
Graduated compression stockings	90 (22)	57 (25)	25 (23)	8 (11)	0.06
Enrollment to end of follow-up					
All patients	410	231	109	70	
Antiplatelet agent	65 (16)‡	44 (19)	18 (17)	3 (4)	0.01
Statin	61 (15)	42 (18)	18 (17)	1 (1)	<0.01
Graduated compression stockings	94 (23)	59 (26)	27 (25)	8 (11)	0.04

* 1 or both legs.
† Data are numbers (percentages). "Estrogen women" and "nonestrogen women" refer to whether the women had the index episode of VTE that qualified them for the study during estrogen therapy.
‡ Among patients who reported antiplatelet use at a follow-up assessment, 91% reported using aspirin and 9% reported using aspirin and clopidogrel.