ORIGINAL ARTICLE

D-Dimer Testing to Determine the Duration of Anticoagulation Therapy

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ABSTRACT

BACKGROUND

The optimal duration of oral anticoagulation in patients with idiopathic venous thromboembolism is uncertain. Testing of D-dimer levels may play a role in the assessment of the need for prolonged anticoagulation.

METHODS

We performed D-dimer testing 1 month after the discontinuation of anticoagulation in patients with a first unprovoked proximal deep-vein thrombosis or pulmonary embolism who had received a vitamin K antagonist for at least 3 months. Patients with a normal D-dimer level did not resume anticoagulation, whereas those with an abnormal D-dimer level were randomly assigned either to resume or to discontinue treatment. The study outcome was the composite of recurrent venous thromboembolism and major bleeding during an average follow-up of 1.4 years.

RESULTS

The D-dimer assay was abnormal in 223 of 608 patients (36.7%). A total of 18 events occurred among the 120 patients who stopped anticoagulation (15.0%), as compared with 3 events among the 103 patients who resumed anticoagulation (2.9%), for an adjusted hazard ratio of 4.26 (95% confidence interval [CI], 1.23 to 14.6; P=0.02). Thromboembolism recurred in 24 of 385 patients with a normal D-dimer level (6.2%). Among patients who stopped anticoagulation, the adjusted hazard ratio for recurrent thromboembolism among those with an abnormal D-dimer level, as compared with those with a normal D-dimer level, was 2.27 (95% CI, 1.15 to 4.46; P=0.02).

CONCLUSIONS

Patients with an abnormal D-dimer level 1 month after the discontinuation of anticoagulation have a significant incidence of recurrent venous thromboembolism, which is reduced by the resumption of anticoagulation. The optimal course of anticoagulation in patients with a normal D-dimer level has not been clearly established. (ClinicalTrials.gov number, NCT00264277.)

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N Engl J Med 2006;355:1780-9.

Even though long-term treatment with vitamin K antagonists is highly effective in the prevention of a recurrence after a first episode of unprovoked venous thromboembolism, the optimal duration of such therapy is still uncertain.[1-4] Since the risk of recurrence is greatest in the first 6 to 12 months after the initial episode and gradually diminishes thereafter,[5] the benefit of an extended course of anticoagulation may be offset over time by the risk of clinically important bleeding.[1-4,6,7]

Earlier prospective studies involving patients with venous thromboembolism[8-10] showed that the D-dimer level after anticoagulation had a highly predictive value — both positive and negative — for the occurrence of a subsequent episode of venous thromboembolism. These findings suggest that the D-dimer assay may have a role in gauging the appropriate duration of anticoagulation in such patients.

To test this hypothesis, we prospectively investigated patients after a first episode of symptomatic, unprovoked venous thromboembolism who had been treated with vitamin K antagonists for a minimum of 3 months. Patients with a normal D-dimer level did not continue anticoagulation, whereas those with an elevated D-dimer level were randomly assigned either to resume or to discontinue anticoagulation therapy.

METHODS

STUDY PATIENTS

The PROLONG study was a multicenter, prospective study involving patients between the ages of 18 and 85 years who had had a first episode of symptomatic, unprovoked venous thromboembolism, including proximal deep-vein thrombosis of the lower limbs, pulmonary embolism, or both. The protocol specified that deep-vein thrombosis be detected by compression ultrasonography or venography and that pulmonary embolism be diagnosed on the basis of objective algorithms with the use of clinical probability, ventilation–perfusion or helical computed tomography (CT) of the lungs, compression ultrasonography (if indicated), and D-dimer testing. Patients were eligible for the study if they had completed at least 3 months of therapy with a vitamin K antagonist (either warfarin [Coumadin, Bristol-Myers Squibb] or acenocoumarol [Sintrom, Novartis Pharma]), with a target international normalized ratio (INR) of 2.5 (range, 2.0 to 3.0).

Unprovoked venous thromboembolism was defined as an episode not associated with pregnancy or the puerperium, a recent (i.e., within 3 months) fracture or plaster casting of a leg, immobilization with confinement to bed for 3 or more consecutive days, surgery with general anesthesia lasting at least 30 minutes, cancer, the antiphospholipid antibody syndrome, or antithrombin deficiency. Patients who had serious liver disease, renal insufficiency (a plasma creatinine level >2 mg per deciliter [177 μmol per liter]), other indications or contraindications for anticoagulation, or a limited life expectancy or who lived too far from the study center were excluded. The institutional review boards of all participating clinical centers approved the study. All enrolled patients provided written informed consent.

STUDY PROCEDURES

At the end of treatment with vitamin K antagonists, patients underwent a medical examination to assess their eligibility and baseline clinical condition. Patients also underwent compression ultrasonography of the proximal deep veins in both legs to assess the patency of the vessels and to measure the diameter of any residual thrombus in the common femoral, superficial femoral, and popliteal veins.[11] Patients were instructed to stop oral anticoagulation and refrain from taking any other antithrombotic drugs until the next visit, which was scheduled a month later (within 20 to 40 days). Patients with venous thromboembolism that recurred between the time of the discontinuation of therapy with vitamin K antagonists and the follow-up visit were excluded from further analysis.

At the 30-day visit, venous blood was sampled for a D-dimer assay and thrombophilia test. Levels of D-dimer were assessed with the use of the Clearview Simplify D-dimer assay (Inverness Medical Professional Diagnostics), which was donated by Instrumentation Laboratory, Milan. This assay is a qualitative, fast, whole-blood method that was previously shown to perform well in the diagnostic workup for venous thromboembolism.[12] Patients with a normal D-dimer level did not continue anticoagulation, whereas those with an abnormal level were randomly assigned either to resume or to discontinue anticoagulation with

vitamin K antagonists (INR, 2.0 to 3.0) during the subsequent follow-up period of up to 18 months. A different randomization sequence for each study site, with a block size of 10, was generated by computer and encapsulated in a randomization program.

Testing for the presence of the antiphospholipid antibody syndrome[13] and antithrombin deficiency[14] was performed at the enrolling centers. Tests for factor V Leiden[15] and the G20210A mutation in the prothrombin gene[16] were performed at a central laboratory. Patients who were found to have the antiphospholipid antibody syndrome or antithrombin deficiency were excluded from further analysis and resumed anticoagulation. Patients with factor V Leiden or the G20210A mutation continued to participate in the study; the presence of these thrombophilias was taken into account in the multivariate analysis of the study outcome.

STUDY OUTCOMES AND FOLLOW-UP

All patients were followed for a maximum of 18 months after the assignment visit and were seen at the clinical center at intervals of 3 to 6 months. Patients were instructed to contact the clinical center immediately if symptoms developed suggestive of venous thromboembolism or in case of bleeding. The study outcome was the composite of confirmed recurrent venous thromboembolism[9] and major bleeding events.

In cases of a suspected recurrence of deep-vein thrombosis, the results of compression ultrasonography were compared with those of the last available previous examination. A recurrent deep-vein thrombosis was diagnosed if a previously fully compressible segment (contralateral or ipsilateral) was no longer compressible or if an increase of at least 4 mm in the diameter of the residual thrombus during compression was detected.[11] When the diameter of the thrombus changed by 1.1 to 3.9 mm, or in cases of high or moderate clinical probability and normal findings on proximal compression ultrasonography, the examination was repeated 5 to 7 days later.

In patients with suspected pulmonary embolism, the diagnosis of recurrence was based on objective algorithms[17,18] with the use of clinical probability, ventilation–perfusion lung scanning or helical CT, and compression ultrasonography, D-dimer testing, or both if indicated.

Major bleeding events were defined as hemorrhages that were either retroperitoneal or intracranial or were associated with a decrease in hemoglobin of at least 2.0 g per deciliter or that required either transfusion of at least 2 units of blood or surgery or an invasive procedure to stop bleeding.[6]

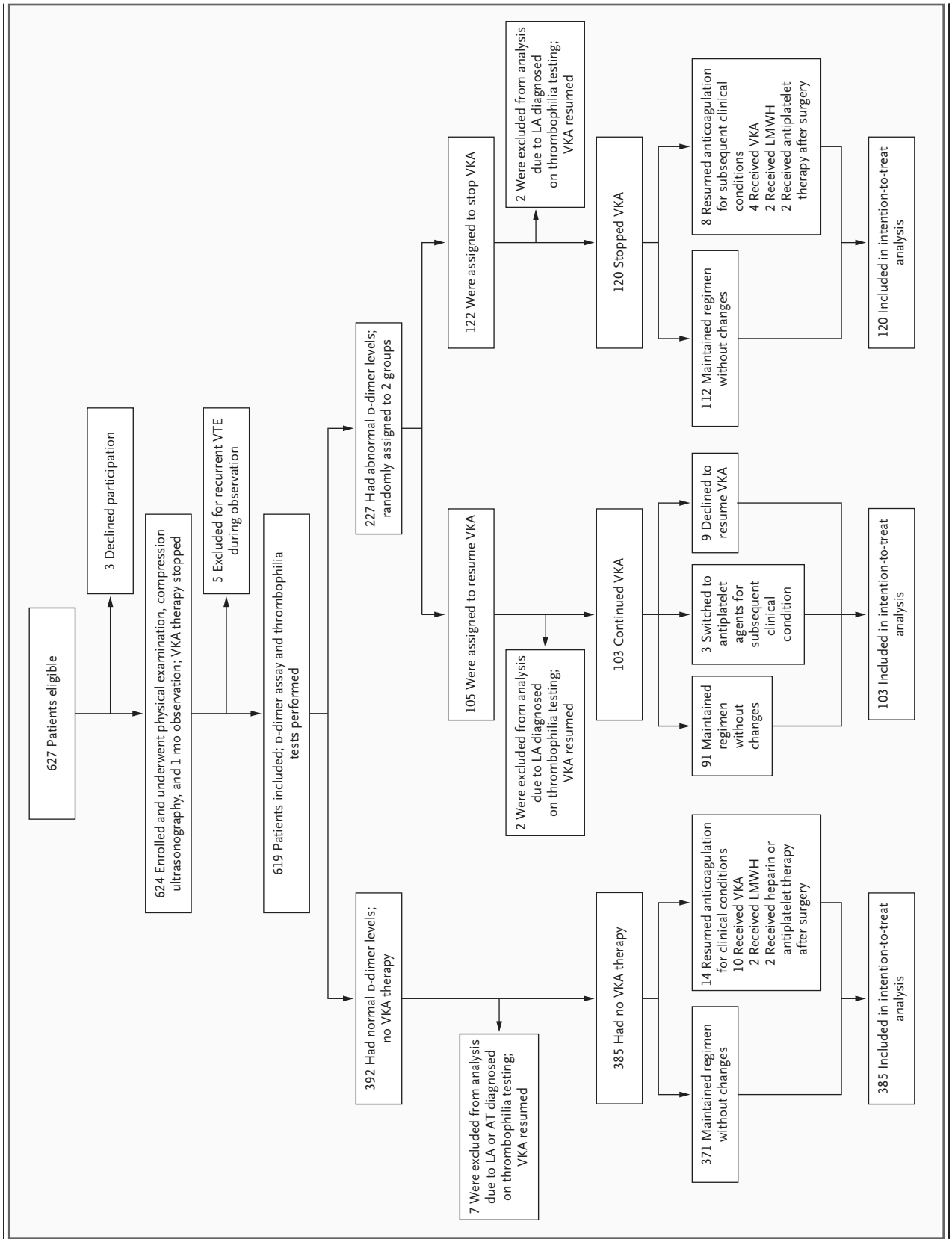
Figure 1 (facing page). Enrollment and Outcomes.
VKA denotes vitamin K antagonist treatment, LA presence of lupus anticoagulant or a high level of antiphospholipid antibody, AT antithrombin deficiency, and LMWH low-molecular-weight heparin.

All suspected outcome events and deaths were evaluated by a central adjudication committee whose members were unaware of the patient's name, the center where the patient had been enrolled, the results of D-dimer and thrombophilia assays, and the group assignment. Committee members also reviewed the results of all clinical investigations without knowing the patient's name, the group assignment, or the center where testing had been performed.

STATISTICAL ANALYSIS

Baseline differences between groups were assessed by the chi-square test with Yates' correction for categorical variables and the t-test or Mann–Whitney test for continuous variables, as appropriate. Data were analyzed according to the intention-to-treat principle. If other important clinical conditions (such as ischemic heart disease, cancer, stroke, and superficial-vein thrombosis) developed and patients changed their assigned treatment, they were regularly followed and were included in the analysis.

Kaplan–Meier survival curves were plotted to estimate the cumulative incidence of symptomatic recurrent venous thromboembolism combined with major bleeding. Hazard ratios and 95% confidence intervals (CIs) were calculated with the use of the Cox proportional-hazards model. Initially, an unadjusted hazard ratio was calculated. Then a multivariate model was constructed, including the patient's age (less than 65 years vs. 65 years or more), the duration of anticoagulation before enrollment (6 months or less vs. more than 6 months), the type of index event (deep-vein thrombosis alone vs. pulmonary embolism with or without deep-vein thrombosis), and the presence or absence of factor V Leiden or the prothrombin gene mutation. Subgroup analyses for each of these baseline variables were also



performed to identify interactions between these factors and the D-dimer results. The data were analyzed with the use of Prism software, version 3.0 (GraphPad Software), and SPSS software, version 11.0 (SPSS).

RESULTS

PATIENTS AND TREATMENT GROUPS

Figure 1 shows a diagram of the entire study population. A total of 627 eligible patients were referred to 30 clinical centers between September 13, 2002, and January 31, 2005. Of these patients, three declined to participate in the study and five were excluded, four because of deep-vein thrombosis and one because of superficial-vein thrombosis during the interval between interruption of anticoagulation and the 1-month visit.

Of the 619 patients who underwent blood sampling for a D-dimer assay and thrombophilia test, 392 (63.3%) had a normal D-dimer level. Of the remaining 227 patients with an abnormal D-dimer level, 105 were randomly assigned to resume anticoagulation and 122 were assigned to discontinue anticoagulation. After randomization, 11 patients were excluded, 9 because of the presence of lupus anticoagulant and 2 because of antithrombin deficiency. The remaining 608

Table 1. Baseline Characteristics of the 608 Study Patients.*

Characteristic	Normal D-Dimer Level (N=385)	Abnormal D-Dimer Level (N=223)	P Value†	Abnormal D-Dimer Level without Anticoagulation (N=120)	Abnormal D-Dimer Level with Anticoagulation (N=103)	P Value†
Female sex — no. (%)	173 (44.9)	118 (52.9)	0.07	70 (58.3)	48 (46.6)	0.11
Age						
Mean — yr	59.3±16.2	69.7±13.0	<0.001‡	68.2±12.5	70.1±13.7	0.07‡
≥65 yr — no. (%)	171 (44.4)	165 (74.0)	<0.001	86 (71.7)	79 (76.7)	0.49
Type of venous thromboembolism — no. (%)						
Proximal deep-vein thrombosis with no pulmonary embolism	241 (62.6)	140 (62.8)	0.97	73 (60.8)	67 (65.0)	0.61
Deep-vein thrombosis plus symptomatic pulmonary embolism	68 (17.7)	41 (18.4)	0.92	25 (20.8)	16 (15.5)	0.41
Isolated pulmonary embolism§	76 (19.7)	42 (18.8)	0.88	22 (18.3)	20 (19.4)	0.99
Congenital thrombophilic alteration — no. (%)						
Total no. evaluated	366	217		118	99	
Factor V Leiden mutation	35 (9.6)	26 (12.0)	0.44	10 (8.5)	16 (16.2)	0.13
Prothrombin mutation	23 (6.3)	16 (7.4)	0.74	10 (8.5)	6 (6.1)	0.68
Combined alterations or homozygous mutation	8 (2.2)	3 (1.4)	0.71	1 (0.8)	2 (2.0)	0.87
Duration of previous anticoagulation — no. (%)						
≤6 mo	65 (16.9)	35 (15.7)	0.79	16 (13.3)	19 (18.4)	0.39
7–12 mo	187 (48.6)	123 (55.2)	0.15	71 (59.2)	52 (50.5)	0.25
>12 mo	133 (34.5)	65 (29.1)	0.20	33 (27.5)	32 (31.1)	0.66
Time from enrollment to assignment to groups — days	32.0±9.4	33.5±7.2	0.008‡	33.5±7.3	33.4±7.2	0.95‡
Total duration of follow-up for all patients — yr	550.2	314.6		165.5	149.1	
Follow-up — yr	1.39±0.35	1.38±0.38		1.31±0.42	1.45±0.32	

* Plus–minus values are means ±SD.
† P values were calculated with the use of the chi-square test unless otherwise specified.
‡ P value was calculated with the use of the Mann–Whitney test.
§ Two patients had isolated distal deep-vein thrombosis.

patients included 385 with normal D-dimer levels and 223 with abnormal D-dimer levels, 103 of whom resumed anticoagulation and 120 who discontinued treatment. Of the group assigned to resume anticoagulation, nine patients declined to do so but were followed with their assigned group for analysis.

The baseline characteristics of the patients in the three groups are reported in Table 1. Overall, 47.9% were women and 55.3% were 65 years of age or older; the mean age was 63 years. As expected, abnormal D-dimer levels were significantly more frequent among older patients.

FOLLOW-UP

All of the study participants had a follow-up of at least 9 months; 421 (69.2%) were followed for 18 months. Three patients (all with normal D-dimer levels) moved to a different town and were lost to follow-up before the conclusion of the study. The mean duration of follow-up was 1.4 years.

During follow-up, 25 patients changed their assigned treatment because of the onset of various clinical conditions: 9 patients had superficial-vein thrombosis, 2 had ischemic heart disease (1 of whom died), 3 had cancer (2 of whom died), 2 had a suspected recurrence of deep-vein thrombosis that was not confirmed by the adjudication committee, 1 had stroke, 1 had isolated distal deep-vein thrombosis, and 7 had other conditions. The specific changes in treatment in each of the study groups are shown in Figure 1. The subsequent follow-up of these patients was included in the analysis according to the originally assigned treatment group.

RECURRENT VENOUS THROMBOEMBOLISM

Of the 120 patients with an abnormal D-dimer level who discontinued anticoagulation, 18 had recurrent venous thromboembolism (15.0%, or 10.9 events per 100 person-years) (Table 2). Of the 103 patients who resumed anticoagulation, 1 had a major bleeding episode and 2 had recurrent venous thromboembolism (2.9%, or 2.0 events per 100 person-years), with one event occurring after anticoagulation was stopped. Of the 385 patients who stopped anticoagulation because they had a normal D-dimer level, 24 (6.2%, or 4.4 events per 100 person-years) presented with recurrent venous thromboembolism.

Event rates were significantly higher among patients with abnormal D-dimer levels who stopped anticoagulation than among those who resumed anticoagulation (adjusted hazard ratio, 4.26; 95% CI, 1.23 to 14.6; P=0.02) or among those with normal D-dimer levels (adjusted hazard ratio, 2.27; 95% CI, 1.15 to 4.46; P=0.02) (Table 3). Event rates did not vary significantly between those patients with a normal D-dimer level and those with an abnormal D-dimer level who resumed anticoagulation, although a trend favoring the latter group was noted. The cumulative probability of recurrent venous thromboembolism in the study groups is shown in Figure 2.

Table 4 shows the hazard ratios for the main outcomes in subgroups according to baseline vari-

Table 2. Main Outcomes (Intention-to-Treat Analysis).

Outcome	Normal D-Dimer Level (N=385)	Abnormal D-Dimer Level without Anticoagulation (N=120)	Abnormal D-Dimer Level with Anticoagulation (N=103)
No. of patients (%)	24 (6.2)	18 (15.0)	3 (2.9)
No. of events/100 person-yr	4.4	10.9	2.0
Type of recurrent venous thromboembolism — no.*			
Deep-vein thrombosis	19	11	1†
Deep-vein thrombosis with pulmonary embolism	3	4	0
Isolated pulmonary embolism	2	3	1
Major bleeding episode	0	0	1

* A total of 21 cases of deep-vein thrombosis occurred in the contralateral leg, and 16 in the ipsilateral leg, 1 case of pulmonary embolism was associated with an isolated distal deep-vein thrombosis in the contralateral leg.
† This thrombotic event occurred during follow-up after the patient had stopped anticoagulation treatment because of repeated episodes of falling.

Table 3. Hazard Ratios for Main Outcomes.

Variable	Unadjusted Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)*	P Value
Abnormal D-dimer level without anticoagulation vs. abnormal D-dimer level with anticoagulation	5.36 (1.58–18.2)	0.007	4.26 (1.23–14.6)	0.02
Abnormal D-dimer level without anticoagulation vs. normal D-dimer level	2.49 (1.35–4.59)	0.003	2.27 (1.15–4.46)	0.02
Normal D-dimer level vs. abnormal D-dimer level with anticoagulation	2.17 (0.66–7.22)	0.20	2.46 (0.71–8.46)	0.15

* Values are adjusted for sex, age, the duration of anticoagulant treatment before enrollment, the type of the index venous thromboembolic event, and the presence or absence of congenital thrombophilia.

ables and the three possible comparisons between groups. No significant interaction was observed between the risk of recurrence in the three comparisons and categories of prespecified baseline variables when the interaction term was included in the Cox proportional-hazards model. The only exception was an interaction of sex as a variable when patients with a normal D-dimer level were compared with those with an abnormal D-dimer level who resumed anticoagulation. However, the number of patients in the study was too small to detect some clinically important interactions.

DEATH

Three deaths occurred during follow-up, two in patients with an abnormal D-dimer level: one patient who resumed anticoagulation died from acute myocardial infarction, and one who stopped anticoagulation died from cancer about a year after randomization. The third patient, who had a normal D-dimer level, died from complications after surgery for cancer diagnosed 8 months after randomization. No deaths from recurrent venous thromboembolism or from bleeding events were recorded.

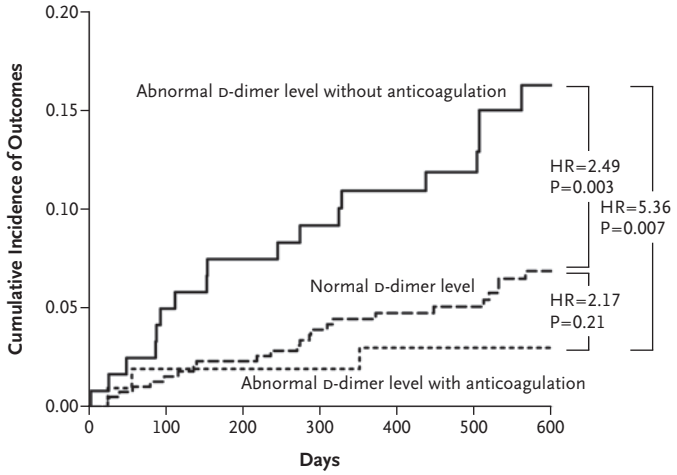


Figure 2. Cumulative Incidence of and Hazard Ratios (HRs) for Main Outcomes.
The graph compares the outcomes among patients who had a normal D-dimer level with those among patients who had an abnormal level and either resumed or stopped anticoagulation therapy.

DISCUSSION

In the PROLONG study, patients with a first episode of documented, unprovoked venous thromboembolism who had completed at least 3 months of treatment with a vitamin K antagonist stopped anticoagulation and underwent D-dimer testing 1 month later. Those with an abnormal D-dimer assay who stopped anticoagulation had a high rate of recurrent venous thromboembolism (15.0%), whereas patients with an abnormal D-dimer level who resumed anticoagulation had a combined rate of recurrent venous thromboembolism and major bleeding of 2.9% (P=0.005). The rate of recurrence in the cohort with a normal D-dimer level was also significantly lower (6.2%, P=0.005) than that in patients with an abnormal D-dimer level who stopped anticoagulation. The rate was not significantly different from that in patients with an abnormal D-dimer level who resumed anticoagulation, although the absolute difference between these two point estimates (6.2% and 2.9%) is large enough to be clinically significant. The risk–benefit relationship of prolonged anticoagulation in patients with a normal D-dimer level is therefore uncertain. In contrast, there was a clear benefit of prolonged treatment with vitamin K antagonists in patients whose D-dimer levels were abnormal a month after the discontinuation of anticoagulation. These results confirm

Table 4. Hazard Ratios for Main Outcome in Subgroups.

Subgroup	Abnormal D-Dimer Level without Anticoagulation vs. Abnormal D-Dimer Level with Anticoagulation		Abnormal D-Dimer Level without Anticoagulation vs. Normal D-Dimer Level		Normal D-Dimer Level vs. Abnormal D-Dimer Level with Anticoagulation	
	Hazard Ratio (95% CI)	P Value*	Hazard Ratio (95% CI)	P Value*	Hazard Ratio (95% CI)	P Value*
Sex						
Male	11.8 (1.51–92.5)	0.21	2.42 (1.11–5.24)	0.20	5.03 (0.67–37.7)	0.04
Female	2.74 (0.58–12.9)		3.44 (1.19–9.91)		0.81 (0.16–4.03)	
Age						
<65 yr	4.28 (0.51–35.6)	0.65	4.40 (1.57–12.4)	0.64	0.98 (0.12–7.74)	0.07
≥65 yr	5.89 (1.32–26.3)		1.62 (0.76–3.46)		3.71 (0.85–16.2)	
Duration of anticoagulation before enrollment						
≤6 mo	3.97 (0.41–38.2)	0.45	3.75 (0.84–16.8)	0.44	1.16 (0.13–10.4)	0.92
>6 mo	6.14 (1.40–26.8)		2.32 (1.19–4.53)		2.67 (0.62–11.4)	
Type of venous thromboembolism						
Deep-vein thrombosis only	4.88 (1.07–22.3)	0.68	1.83 (0.85–3.93)	0.67	2.70 (0.63–11.6)	0.11
Pulmonary embolism with or without deep-vein thrombosis	6.28 (0.79–50.2)		5.10 (1.67–15.6)		1.24 (0.14–10.6)	
Factor V Leiden or prothrombin mutation						
No	4.30 (1.25–14.7)	0.93	2.93 (1.49–5.74)	0.90	1.50 (0.44–5.09)	0.62
Yes	0		0		0	

* P values are calculated for the comparison of the difference in the hazard ratios between the subgroups by entering into the Cox proportional-hazard model a term for the specific subgroup according to the D-dimer interaction.

that the D-dimer assay is correlated with the individual risk of recurrence after a first episode of venous thromboembolism and may be useful in guiding the duration of anticoagulation by helping clinicians select patients who may benefit the most from the prolongation of this demanding and risky treatment.

Patients with an abnormal D-dimer level were significantly older than those with a normal D-dimer level. Although this result is in line with findings of other reports,[19] it also underlines the hypercoagulability and increased risk of venous thromboembolism in the elderly. No significant differences in D-dimer results were detected with regard to sex, the duration of anticoagulation before enrollment, the type of index event, or the presence or absence of inherited thrombophilias.

Unlike previous studies addressing the predictive role of the D-dimer assay for a recurrence of venous thromboembolism,[8-10] our study adopted a qualitative rather than a quantitative method for D-dimer testing. We took this approach because we wished to have a uniform approach across the participating centers for the classification of D-dimer levels as either normal or abnormal. The quantitative D-dimer methods that were routinely used in the clinical laboratories of the participating centers differed, so results would not have been comparable.

Caution is recommended in the evaluation of our results. First, the trial was not blinded, and though committee members who were unaware of the results of the D-dimer tests and treatment assignments assessed recurrent events, bias could not be completely ruled out. However, the rates of events in the treated and untreated patients (both with abnormal and normal D-dimer levels) are in the range of those reported in the literature.

Second, D-dimer testing was performed 30 days after anticoagulation was discontinued. In a previous study,[8] we reported that only 15% of patients had an abnormal D-dimer level at the time of discontinuation of anticoagulation, although the rate increased to 40.3% after 1 month and to 46.2% after 3 months. It has been reported that patients with a high D-dimer level during anti-

coagulation are at increased risk for recurrence during and after an interruption in anticoagulation.[20,21] In this study, five patients had venous thromboembolism during the period between the discontinuation of anticoagulation and D-dimer measurement. Unfortunately, no information is available on their D-dimer levels (or those of the other patients) on the day anticoagulation was stopped. It is therefore impossible to comment on the relationship between D-dimer levels during anticoagulation and the risk of early recurrence after interruption of therapy.

Third, the D-dimer assay was performed only once, with follow-up scheduled to last for the subsequent 18 months. It is possible that during follow-up some patients with originally normal D-dimer levels could have had abnormal results on repeated testing, providing a detectable warning sign of recurrent hypercoagulability and an increased risk of thrombosis. Repeated D-dimer assays in patients with an originally normal level may be useful in detecting a late relapse related to hypercoagulability, but this hypothesis should be assessed in future studies.

Fourth, although the study was large enough to detect significant differences between groups in the frequency of the combined end point of recurrent venous thromboembolism or bleeding, it was not large enough to make a definitive assessment of the relative risk of bleeding, considered alone, with continued anticoagulation. Since the risk of bleeding increases with time and since the clinical consequences of severe bleeding (such as intracranial hemorrhage) may outweigh those of recurrent venous thromboembolism (such as a deep-vein thrombosis that is detected and treated), clinicians should keep this issue in mind when they are treating a patient who is receiving a prolonged course of a vitamin K antagonist.

Finally, we included only patients with a first unprovoked venous thromboembolism, since the optimal duration of anticoagulation is most uncertain in this category of patients. However, a management strategy for all groups of patients, regardless of the nature and number of their previous events, would be of great practical use. These issues remain to be addressed by specifically designed clinical studies.

In conclusion, we evaluated patients with a first documented, unprovoked episode of venous thromboembolism who had been treated with a vitamin K antagonist for at least 3 months. Anticoagulation was discontinued, and qualitative D-dimer testing was performed 1 month later. Patients with an abnormal D-dimer test who resumed anticoagulation had a significantly lower combined incidence of recurrent venous thromboembolism and bleeding than did those who did not resume anticoagulation. Patients with a normal D-dimer level did not resume anticoagulation. The optimal course of therapy for such patients is not clearly established.

Supported by the Italian Federation of Anticoagulation Clinics and by the Department of Angiology and Blood Coagulation of the S. Orsola-Malpighi University Hospital of Bologna, Italy. Instrumentation Laboratory in Milan provided the kits for D-dimer measurement (Clearview Simplify D-dimer assay).

Drs. Palareti, Cosmi, Legnani, Pengo, Testa, and Tripodi report having received lecture fees from Instrumentation Laboratory. No other potential conflict of interest relevant to this article was reported.

APPENDIX

The following were members of the PROLONG study group; all the participating centers are affiliated with the Italian Federation of Anticoagulation Clinics (the numbers of patients who participated in the study appear in parentheses): *Policlinico S. Orsola-Malpighi, Bologna* — G. Palareti, B. Cosmi, C. Legnani, C. Brusi (148); *Azienda Ospedaliera "Istituti Ospitalieri," Cremona* — S. Testa, A. Alatri (79); *Arcispedale Santa Maria Nuova, Reggio Emilia* — A. Ghirarduzzi, A. Iorio (68); *Ospedale S. Bortolo, Vicenza* — A. Tosetto (36); *Ospedale "Ex Busonera," Padua* — V. Pengo, C. Pegoraro, S. Iliceto (27); *Azienda Policlinico Universitario di Palermo, Palermo* — S. Siragusa (27); *Azienda Ospedaliera di Careggi Universita' di Firenze, Florence* — D. Prisco, D. Poli (26); *Ospedale Ca' Granda Niguarda, Milan* — F. Baudo (25); *Policlinico "Le Scotte," Siena* — R. Cappelli (20); *Ospedale San Leopoldo Mandic, Merate* — N. Erba (18); *Ente Ospedaliero di Vimercate, Vimercate* — L. La Rosa (16); *Ospedale Regionale, Parma* — C. Pattacini, R. Quintavalla (15); *Ospedale "S. Cuore di Gesù," Gallipoli* — L. Ria (14); *Presidio Ospedaliero di Faenza, Faenza* — E. Bucherini (12); *Ospedale di Bentivoglio, Bentivoglio* — E. Cerè (11); *Ospedale dell'Annunziata, Cosenza* — V. Rossi (9); *Ospedale degli Infermi, Rimini* — E. Tiraferri (9); *Azienda Ospedaliera Bolognini, Seriate* — C. Agazzi, N. Coffetti (9); *Presidio Ospedaliero S. Maria Incoronata dell'Olmo, Cava dei Tirreni* — C. Villani (8); *Ospedale Valduce, Como* — L. Frigerio (7); *Arcispedale S. Anna, Ferrara* — G. Scapoli (7); *Policlinico Universitario Messina, Messina* — A. Trifiletti (6); *Ospedale Maria Vittoria, Turin* — M. Molinatti (6); *Azienda Ospedaliera "Ospedale Treviglio-Caravaggio," Treviglio* — P. Dori Faccini (5); *Azienda Ospedaliera S. Antonio e Biagio, Alessandria* — R. Santi (5); *Ospedale Regionale di Treviso, Treviso* — G. Scannapieco (4); *Casa Di Cura Villa Serena, Citta' S. Angelo* — G. Lessiani (3); *Ospedale "G. Iazzolino," Vibo Valentia* — V. Scarmozzino (3); *Presidio Ospedaliero S. Leonardo, Castellamare di Stabia* — V. Imbimbo (2); and *Ospedale Galliera, Genoa* — A. Schenone (2). **Executive Committee:** G. Palareti, B. Cosmi, and C. Legnani (Bologna), A. Tosetto (Vicenza), A. Tripodi (Milan), A. Iorio (Perugia), S. Testa (Cremona). **Adjudication Committee:** A. Ghirarduzzi (Reggio Emilia), C. Pattacini (Parma), V. Pengo (Padua).

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