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A COMPARISON OF THREE MONTHS OF ANTICOAGULATION WITH EXTENDED ANTICOAGULATION FOR A FIRST EPISODE OF IDIOPATHIC VENOUS THROMBOEMBOLISM

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ABSTRACT

Background Patients who have a first episode of venous thromboembolism in the absence of known risk factors for thrombosis (idiopathic thrombosis) are often treated with anticoagulant therapy for three months. Such patients may benefit from longer treatment, however, because they appear to have an increased risk of recurrence after anticoagulant therapy is stopped.

Methods In this double-blind study, we randomly assigned patients who had completed 3 months of anticoagulant therapy for a first episode of idiopathic venous thromboembolism to continue receiving warfarin, with the dose adjusted to achieve an international normalized ratio of 2.0 to 3.0, or to receive placebo for a further 24 months. Our goal was to determine the effects of extended anticoagulant therapy on rates of recurrent symptomatic venous thromboembolism and bleeding.

Results A prespecified interim analysis of efficacy led to the early termination of the trial after 162 patients had been enrolled and followed for an average of 10 months. Of 83 patients assigned to continue to receive placebo, 17 had a recurrent episode of venous thromboembolism (27.4 percent per patient-year), as compared with 1 of 79 patients assigned to receive warfarin (1.3 percent per patient-year, $P < 0.001$). Warfarin resulted in a 95 percent reduction in the risk of recurrent venous thromboembolism (95 percent confidence interval, 63 to 99 percent). Three patients assigned to the warfarin group had nonfatal major bleeding (two had gastrointestinal bleeding and one genitourinary bleeding), as compared with none of those assigned to the placebo group (3.8 percent vs. 0 percent per patient-year, $P = 0.09$).

Conclusions Patients with a first episode of idiopathic venous thromboembolism should be treated with anticoagulant agents for longer than three months. (N Engl J Med 1999;340:901-7.)

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ACUTE venous thromboembolism is usually treated with a five-to-seven-day course of unfractionated or low-molecular-weight heparin, followed by a three-month course of oral anticoagulant therapy.¹ Subgroup analyses of the results of a number of recent studies suggest that, after anticoagulant therapy is stopped, the risk of recurrent venous thromboembolism is greater among patients who have a persistent risk factor for thrombosis and those whose initial episode of thrombosis occurred in the absence of an apparent risk factor than it is among patients in whom thrombosis develops in association with a transient risk factor, such as surgery.²⁻⁵ On the basis of such observations, we hypothesized that patients with a first episode of idiopathic venous thromboembolism would benefit from a course of anticoagulant therapy lasting more than three months.

To test this hypothesis, we performed a double-blind, randomized trial comparing an additional 24 months of warfarin therapy (target international normalized ratio [INR], 2.0 to 3.0) with placebo in pa-

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The institutions that participated in the study are listed in the Appendix.

tients with a first episode of idiopathic venous thromboembolism who had completed three months of initial anticoagulant treatment. We also sought to determine whether the presence of common prothrombotic biochemical abnormalities — namely, factor V Leiden, the G20210A prothrombin-gene mutation, or the presence of antiphospholipid antibodies (lupus anticoagulant or anticardiolipin antibodies) — identified patients with a particularly high risk of recurrent venous thromboembolism.

METHODS

Patients

Consecutive patients with a first episode of idiopathic venous thromboembolism were eligible if they had completed three uninterrupted months of oral anticoagulant therapy after an initial course of treatment with unfractionated or low-molecular-weight heparin. Idiopathic venous thromboembolism was defined as either objectively confirmed,^{6,7} symptomatic, proximal deep-vein thrombosis or as pulmonary embolism that occurred in the absence of a major thrombotic risk factor. Risk factors that precluded classification of the episode as idiopathic thrombosis included fracture or plaster casting of a lower limb, hospitalization with confinement to bed for three consecutive days, or use of general anesthesia, each within the previous three months; a known deficiency of antithrombin, protein C, or protein S; and cancer in the previous five years. Testing for deficiencies of antithrombin, protein C, and protein S was discouraged unless there were additional clinical features that suggested a hereditary hypercoagulable state, such as thrombosis before the age of 40 years or a history of thromboembolism in a first-degree relative. Patients with previous venous thromboembolism were eligible, provided such episodes were secondary to a transient risk factor.

Patients who met the inclusion criteria were ineligible if they had other indications for or a contraindication to long-term anticoagulant therapy; required long-term treatment with nonsteroidal antiinflammatory drugs, ticlopidine, sulfapyrazone, dipyridamole, or more than 160 mg of aspirin per day; had a familial bleeding diathesis; had a major psychiatric disorder, were pregnant or could become pregnant; were allergic to contrast medium; had a life expectancy of less than two years; were initially treated with a nonlicensed preparation of low-molecular-weight heparin; were considered likely to be noncompliant; or were unable to complete follow-up visits because of the distance from their residence to the medical center.

Randomization and Treatment

After the patients gave written informed consent, randomization was performed, with stratification according to whether the patient presented with deep-vein thrombosis alone or with pulmonary embolism and according to clinical center. Patients were provided with consecutively numbered supplies of study drug — either tablets containing 5 mg of warfarin or identical-appearing placebo. A computer algorithm, with a randomly determined block size of two or four within each stratum, had previously determined whether the patient received warfarin or placebo.

The initial dose of study drug was prescribed according to the results of an INR measurement performed on the day of randomization. All subsequent INR results were forwarded to the anticoagulation monitor at each clinical center, who was aware of treatment assignment but not actively involved in the patient's care. For the patients assigned to receive warfarin, the anticoagulation monitor relayed the true INR results to the clinical center. For those assigned to placebo, the anticoagulation monitor substituted a sham INR result from a prepared list and relayed this value to the clinical center. In each case, the dose of study drug was adjusted by the clinical center in response to the INR result

received from the anticoagulation monitor. This process resulted in the patients' receiving either 24 months of warfarin treatment, with the dose adjusted to achieve an INR of 2.0 to 3.0, or 24 months of placebo treatment, with the dose adjusted to achieve a sham INR of 2.0 to 3.0. The study protocol was approved by the institutional review boards of all participating clinical centers.

Follow-up and Outcome Measures

A base-line ventilation–perfusion lung scan, bilateral compression ultrasonography of the proximal leg veins, and (if possible) bilateral impedance plethysmography were performed at the time of randomization in order to increase the accuracy of the diagnosis of recurrent venous thromboembolism. The results of these tests did not influence eligibility. The patients underwent an assessment of symptoms and signs of venous thromboembolism every three months. No surveillance for asymptomatic venous thromboembolism was undertaken. The patients were instructed to report on an emergency basis if symptoms suggesting deep-vein thrombosis or pulmonary embolism developed.

Patients with suspected deep-vein thrombosis underwent compression ultrasonography. Deep-vein thrombosis was diagnosed if the sonogram revealed that a common femoral or popliteal venous segment had become newly noncompressible, as compared with the base-line compression sonogram.⁶ All other findings, including normal results on compression ultrasonography of the proximal veins, were considered nondiagnostic, and ipsilateral ascending venography was performed, supplemented by the findings on serial impedance plethysmography or compression ultrasonography if venography was nondiagnostic (showing areas of nonfilling without an intraluminal filling defect).⁶

Patients with suspected pulmonary embolism underwent ventilation–perfusion lung scanning; the results were supplemented by the findings of compression ultrasonography, bilateral venography, pulmonary angiography, or all three, if the lung scan was nondiagnostic.⁷

Bleeding was defined as major if it was clinically overt and associated with either a fall in the hemoglobin level of at least 2.0 g per deciliter or a need for the transfusion of two or more units of red cells; if it was retroperitoneal or intracranial; or if it warranted the permanent discontinuation of the study drug. Deaths were classified as due to pulmonary embolism (when there was substantive evidence), hemorrhage, or another cause, or as sudden death.

Information on all suspected outcome events and deaths was reviewed and classified by a central adjudication committee whose members were unaware of the treatment assignments.

Laboratory Analysis

Blood was obtained at the time of randomization, when all the patients were receiving warfarin. As previously described by others, assays for factor V Leiden,⁸ the G20210A prothrombin-gene mutation,⁹ anticardiolipin antibodies (IgG or IgM),¹⁰ and lupus anticoagulant^{11–13} were performed at a central laboratory by technicians who were unaware of the patients' treatment assignments and subsequent clinical course. The results of laboratory testing were not made available to the clinical centers or to the members of the central adjudication committee.

Statistical Analysis

The primary analysis of efficacy was a comparison of the rates of recurrent venous thromboembolism according to treatment group during the 24 months after randomization. The final analysis was scheduled for 1 year after the last patient was randomly assigned to treatment, at which time the patients would have completed an average of 1.75 years of follow-up. On the basis of subgroup analyses of two previous studies, we assumed that the rate of recurrent venous thromboembolism would be 10 percent per year in the patients assigned to receive placebo.^{2,14} Warfarin was assumed to produce a 75 percent reduction in the risk of recurrent venous thromboembolism.¹⁵ Given these assump-

tions, 95 patients were needed in each group for us to be able to detect a difference between groups in the frequency of recurrence with a power of 90 percent and with a 5 percent chance of incorrectly concluding that extended warfarin therapy reduced the rate of recurrent venous thromboembolism. One interim analysis was planned after the first 150 patients had been randomized, with the intention of stopping the trial if there was an unequivocal reduction in the rate of recurrent venous thromboembolism in the warfarin group ($P < 0.001$ by one-sided test).

The cumulative incidence of thromboembolic and major bleeding events was described according to the Kaplan–Meier life-table method,¹⁶ and rates were compared with the use of the log-rank test.¹⁷ Univariate and multivariate regression analyses performed with the Cox proportional-hazards model were used to assess the influence of prespecified clinical and laboratory variables on the risk of recurrent venous thromboembolism in the patients randomly assigned to receive placebo.¹⁸ Complete data were not available for all patients in the subgroup analyses (e.g., laboratory tests were not performed or were technically inadequate for some patients); all available data have been included in the analyses. Two-sided P values are reported.

RESULTS

Patients

The recruitment of patients began in October 1994 and was stopped on April 14, 1997, in response to the results of the interim analysis. Follow-up data through April 14, 1997, were included in the analysis for the patients who had already undergone randomization. A total of 327 consecutive patients met the inclusion criteria at the time of diagnosis, among whom 86 also met one or more of the exclusion criteria. Of the remaining 241 patients, 37 met one or more of the exclusion criteria three months later, at the time of the intended randomization. The four

most common reasons for the exclusion of patients at this stage were evidence of cancer since diagnosis (nine patients), inability to make follow-up visits because of geographic inaccessibility (eight patients), the presence of other indications for long-term anticoagulant therapy (five patients), and the presence of a contraindication to long-term anticoagulant therapy (five patients). Of the 204 eligible patients, 162 (79 percent) gave written informed consent and were randomly assigned to receive warfarin (79 patients) or placebo (83 patients) (Table 1).

Treatment and Follow-up

The mean duration of follow-up was 10 months (12 months for the patients assigned to warfarin and 9 months for those assigned to placebo). The mean duration was shorter for the patients assigned to placebo largely because follow-up was discontinued after the diagnosis of recurrent venous thromboembolism, which occurred more frequently in this group. The study drug was permanently discontinued before the completion of follow-up in 14 patients assigned to warfarin, for one or more of the following reasons: 8 patients requested it, 3 patients had a major bleeding complication, indications for long-term anticoagulation developed in 2 patients, and 4 patients discontinued treatment for other reasons. The study drug was permanently discontinued before the completion of follow-up in 13 patients assigned to placebo, for one or more of the following reasons: 7 patients requested it, there was a serious violation

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	PLACEBO (N=83)	WARFARIN (N=79)	TOTAL (N=162)
Age — yr	58±16	59±16	59±16
Weeks of anticoagulation before randomization — no.	15±2	15±2	15±2
Male sex — no./total no. (%)	44/83 (53)	54/79 (68)	98/162 (60)
Previous venous thromboembolism — no./total no. (%)†	3/83 (4)	5/79 (6)	8/162 (5)
Deep-vein thrombosis only at presentation — no./total no. (%)	61/83 (73)	60/79 (76)	121/162 (75)
High probability of pulmonary embolism on ventilation–perfusion scanning‡	5/57 (9)	2/55 (4)	7/112 (6)
Normal ventilation–perfusion scan‡	30/57 (53)	27/55 (49)	57/112 (51)
Normal bilateral compression sonogram‡	29/59 (49)	16/58 (28)	45/117 (38)
Pulmonary embolism at presentation — no./total no. (%)	22/83 (27)	19/79 (24)	41/162 (25)
High probability of pulmonary embolism on ventilation–perfusion scanning‡	0/22	1/19 (5)	1/41 (2)
Normal ventilation–perfusion scan‡	13/22 (59)	12/19 (63)	25/41 (61)
Normal bilateral compression sonogram‡	18/22 (82)	16/19 (84)	34/41 (83)

*Plus–minus values are means ±SD. Complete data were not available for all patients.

†These patients had a previous episode of secondary (nonidiopathic) venous thromboembolism.

‡Results were obtained at the time of randomization, after three months of treatment following the initial diagnosis.

TABLE 2. MAIN OUTCOMES ACCORDING TO TREATMENT GROUP.

OUTCOME	PLACEBO (N=83)	WARFARIN (N=79)	HAZARD RATIO (95% CI)*	P VALUE†
	no. of patients (percent per patient-year)			
Venous thrombo- embolism	17 (27.4)	1 (1.3)	0.05 (0.01–0.37)	<0.001
Type of bleeding				
Major	0	3 (3.8)	—	0.09
Minor	1 (1.4)	6 (7.7)‡	4.0 (0.4–35)	0.18
Total	1 (1.4)	9 (11.5)‡	7.1 (0.9–58)	0.03
Death	3 (4.1)	1 (1.2)	0.25 (0.03–2.5)	0.21

*The hazard ratio is shown for the warfarin group as compared with the placebo group. CI denotes confidence interval.

†Two-sided P values were calculated by the log-rank test.

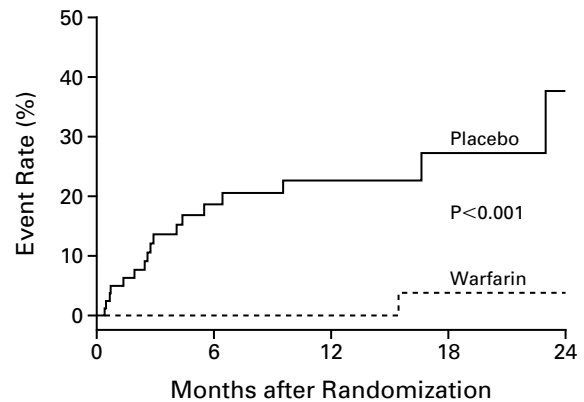
‡One patient receiving warfarin had three minor bleeding episodes (the survival analysis included only the time to the first minor bleeding episode).

of the study protocol in the case of 3 patients, the physician requested it in the case of 3 patients, and 5 patients discontinued treatment for other reasons.

The mean (\pm SD) INR of the patients treated with warfarin was 2.5 ± 1.0 , and the interval between tests was 2.9 ± 2.0 weeks. Using linear interpolation of INR results between tests, we found that the INR was below 2.0 for an average of 22 percent of the time and above 3.0 for 14 percent of the time while the patients were receiving warfarin. Of the 27 patients who permanently discontinued taking the study drug before the scheduled completion of the follow-up period or before recurrent venous thromboembolism developed, 1 of the 13 assigned to placebo and 2 of the 14 assigned to warfarin started warfarin therapy.

Recurrent Venous Thromboembolism

Of the 79 patients assigned to warfarin, 1 had a confirmed episode of recurrent venous thromboembolism (Table 2). This patient, who had a nonfatal pulmonary embolus, had discontinued warfarin treatment 14 months earlier, because of an episode of major upper gastrointestinal bleeding. Of the 83 patients assigned to placebo, 17 had a confirmed episode of recurrent venous thromboembolism (Table 2). Of these episodes, 11 were deep-vein thrombosis, 5 were nonfatal pulmonary embolism, and 1 was fatal pulmonary embolism. The death occurred while the patient was undergoing tests for suspected recurrent pulmonary embolism. The patient had presented with a one-week history of progressive shortness of breath and influenza-like symptoms. A ventilation-perfusion scan showed new defects indicating a high probability of pulmonary embolism, and compression



PATIENTS AT RISK

Placebo	83	44	25	14	4
Warfarin	79	57	36	21	11

Figure 1. Cumulative Probability of Recurrent Venous Thromboembolism in Patients with a First Episode of Idiopathic Thrombosis Who Were Assigned to Warfarin or Placebo after an Initial Three Months of Anticoagulant Therapy.

ultrasonography showed a new proximal deep-vein thrombosis.

The cumulative probability of a recurrent episode of venous thromboembolism in the two groups is shown in Figure 1; the difference between the groups was significant ($P < 0.001$). The rate of recurrent venous thromboembolism was 1.3 percent per patient-year (95 percent confidence interval, 0.0 to 4.7 percent) among the patients assigned to warfarin and 27.4 percent per patient-year (95 percent confidence interval, 14.4 to 40.4 percent) among those assigned to placebo; the absolute difference in these rates was 26.1 percent per patient-year (95 percent confidence interval, 12.9 to 39.4 percent). Warfarin resulted in a 95 percent reduction in the risk of recurrent venous thromboembolism (95 percent confidence interval, 63 to 99 percent). Adjustment for differences in base-line variables did not influence the magnitude of this treatment effect.

Of the 11 patients in the placebo group who had an episode of deep-vein thrombosis during follow-up, 2 initially had pulmonary embolism, 6 initially had ipsilateral deep-vein thrombosis, and 3 initially had contralateral deep-vein thrombosis. Of the six patients in the placebo group who had an episode of pulmonary embolism during follow-up, five initially had pulmonary embolism and one initially had deep-vein thrombosis. All episodes of recurrent venous thromboembolism were idiopathic.

Bleeding Complications

There were three major bleeding episodes among the patients assigned to warfarin (3.8 percent per patient-year; 95 percent confidence interval, 0.0 to 8.1

percent) and no such episodes among those assigned to placebo (95 percent confidence interval, 0.0 to 4.9 percent; $P=0.09$) (Table 2). The INRs at the time of major bleeding were 5.4 and 2.9 for the two episodes of gastrointestinal bleeding and greater than 10 for the one episode of genitourinary bleeding; no bleeding episode was fatal.

Survival

One patient who was assigned to warfarin and three who were assigned to placebo died during the study ($P=0.20$). The patient assigned to warfarin died of pneumonia; the three deaths in the placebo group were due to pulmonary embolism, coronary artery disease, and leukemia.

Biochemical Abnormalities

The prevalence of factor V Leiden was 26 percent, whereas the prevalence of the G20210A prothrombin gene mutation and that of antiphospholipid antibodies were each 5 percent (Table 3). Of the 152 patients for whom at least one of these biochemical assays was performed, 104 (68 percent) had no abnormality.

Risk Factors for Recurrent Venous Thromboembolism

The bivariate association between various clinical and laboratory findings and recurrent venous thromboembolism in the patients who received placebo is shown in Table 3. The presence of a lupus anticoagulant was the only variable significantly associated with recurrent venous thromboembolism ($P=0.03$). Multivariate analyses encompassing all the base-line variables listed in Table 3 and their first-order interactions did not reveal any other factors associated with recurrent venous thromboembolism.

DISCUSSION

We found that patients with a first episode of idiopathic venous thromboembolism have a high rate of recurrence if anticoagulant therapy is stopped after three months and shows that this risk is higher than previously suggested by retrospective analyses.²⁻⁵ Extended warfarin therapy was effective in preventing recurrent venous thromboembolism but was associated with an increased risk of major bleeding; however, the risk of bleeding was small when compared with the benefits of anticoagulant therapy.

Except for those with a lupus anticoagulant, lab-

TABLE 3. RISK OF RECURRENCE OF VENOUS THROMBOEMBOLISM IN THE PLACEBO GROUP, ACCORDING TO SELECTED CHARACTERISTICS.*

CHARACTERISTIC	ALL PATIENTS (N=162)	PLACEBO GROUP (N=83)		HAZARD RATIO (95% CI)†
		PATIENTS WITH RECURRENCE (N=17)	PATIENTS WITHOUT RECURRENCE (N=66)	
		no./total no. (%)		
Age ≥60 yr	86/162 (53)	12/17 (71)	33/66 (50)	2.0 (0.7–5.6)
Male sex	98/162 (60)	6/17 (35)	38/66 (58)	0.5 (0.2–1.3)
Previous venous thromboembolism	8/162 (5)	0/17	3/66 (5)	
Deep-vein thrombosis as qualifying event	121/162 (75)	12/17 (71)	49/66 (74)	0.8 (0.3–2.2)
High probability of pulmonary embolism on ventilation–perfusion scanning	8/153 (5)	2/17 (12)	3/62 (5)	2.2 (0.5–9.9)
Normal ventilation–perfusion scan	82/153 (54)	10/17 (59)	33/62 (53)	1.2 (0.5–3.2)
Normal bilateral compression sonogram	79/158 (50)	9/17 (53)	38/64 (59)	0.8 (0.3–2.2)
Hypercoagulable states				
Factor V Leiden	37/143 (26)	3/16 (19)	17/59 (29)	0.5 (0.1–1.8)
Homozygous	3/143 (2)	1/16 (6)	0/59	
Heterozygous	34/143 (24)	2/16 (13)	17/59 (29)	
Prothrombin gene mutation	7/141 (5)	1/16 (6)	2/59 (3)	2.2 (0.3–17)
Homozygous	2/141 (1)	0/16	0/59	
Heterozygous	5/141 (4)	1/16 (6)	2/59 (3)	
Antiphospholipid antibody	8/150 (5)	4/16 (25)	2/61 (3)	4.0 (1.2–13)
Lupus anticoagulant	4/150 (3)	2/16 (13)	1/61 (2)	6.8 (1.5–31)
Anticardiolipin antibody	4/148 (3)	2/16 (13)	1/61 (2)	2.3 (0.5–11)
Any state	48/150 (32)	7/16 (44)	20/61 (33)	1.4 (0.5–3.8)
Two or more states	4/150 (3)	1/16 (6)	1/61 (2)	2.0 (0.2–16)

*Complete data were not available for all patients.

†The hazard ratio for recurrence is shown for the patients in the placebo group with the specified variable as compared with those without that variable. CI denotes confidence interval.

oratory testing failed to identify subgroups of patients who had either a notably higher or a notably lower risk of recurrent venous thromboembolism after three months of anticoagulant therapy. In particular, the presence of factor V Leiden was not a clinically important risk factor for recurrence, and patients without any of the biochemical abnormalities for which we screened still had a high risk of recurrent venous thromboembolism. Therefore, our findings appear to apply to all patients with a first episode of idiopathic venous thromboembolism. Like others,¹⁹⁻²¹ we found that the continuation of anticoagulant therapy for longer than three months appears to be particularly useful in patients with persistent antiphospholipid antibodies.

The findings of this study are likely to be valid, since extensive precautions were taken to avoid bias, including the use of a double-blind design, central adjudication of outcomes, and a standardized approach to the diagnosis of recurrent venous thromboembolism. However, stopping the study early in response to the findings of an interim analysis could have led to an overestimation of the magnitude of the benefit derived from extended warfarin therapy²²; if such an overestimation did occur, its extent is likely to be small. The most plausible explanation for the higher rate of recurrent venous thromboembolism in the patients receiving placebo in our study than was reported for patients with idiopathic venous thromboembolism in earlier studies^{2,3,5} is that there were differences between the patient populations. In earlier studies, all the patients were retrospectively classified as having "transient" risk factors or "continuous" risk factors (including idiopathic thrombosis). It is likely that some patients were misclassified and that some who did not truly meet the criteria for either clinical category were considered to have had idiopathic thrombosis. However, in our study, the patients had to satisfy prospectively defined inclusion criteria that ensured that all venous thromboembolic events were truly idiopathic.

Although this study has demonstrated that three months of anticoagulant therapy is inadequate for prophylaxis in patients with a first episode of idiopathic venous thromboembolism, how much longer these patients should be treated is not known. Further studies are required to determine when anticoagulant therapy can safely be stopped in this population. In addition, the decision to extend anticoagulant therapy for longer than three months is influenced by a patient's risk of bleeding. Patients with a high risk of bleeding were excluded from this trial, and anticoagulant therapy was closely monitored in those who were studied.

In this study and in a recent study by Schulman and colleagues,²³ no patient who continued to receive anticoagulant therapy with a target INR of about 2.0 to 3.0 for longer than three months had an ep-

isode of recurrent venous thromboembolism during the extended phase of therapy. However, extended anticoagulant therapy was associated with a risk of major bleeding of about 3 percent per year. There is evidence that oral anticoagulation at a lower intensity (i.e., with a target INR of less than 2.0) is effective in preventing venous thromboembolism, particularly when used for primary prophylaxis.^{24,25} Further studies are required to determine whether a lower intensity of anticoagulation is preferable during the extended phase of therapy for patients with idiopathic venous thromboembolism.

Our finding that all episodes of recurrent venous thromboembolism were idiopathic indicates that these events can be prevented only by continuous anticoagulant therapy, not by intermittent prophylaxis limited to times when additional risk factors for thrombosis are present.

We conclude that patients with a first episode of idiopathic venous thromboembolism should be treated with anticoagulants for longer than three months. However, the optimal duration of such therapy has yet to be determined.

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APPENDIX

The following institutions participated in this study: *Canada* — Hamilton Health Sciences Corporation, Henderson, Hamilton General, and McMaster campuses, Hamilton, Ont.; St. Joseph's Hospital, Hamilton, Ont.; London Health Sciences Centre, London, Ont.; Ottawa Civic Hospitals, Ottawa, Ont.; Montreal General Hospital, Montreal; Hôpital Maisonneuve-Rosemont, Montreal; Centre Hospitalier de l'Université de Montréal-Hôtel-Dieu de Montreal, Montreal; Centre Hospitalier de l'Université de Québec-Pavillon Centre Hospitalier de l'Université Laval, Sainte-Foy, Que.; St. Sacrement, Quebec, Que.; Queen Elizabeth II Health Sciences Centre, Halifax, N.S.; St. John Regional Hospital, St. John, N.B.; and *United States* — Rehabilitation Institute of Chicago, Chicago; Scott and White Memorial Hospital, Temple, Tex.

REFERENCES

- Hyers TM, Hull RD, Weg JG. Antithrombotic therapy for venous thromboembolic disease. *Chest* 1995;108:Suppl:335S-351S.
- The Research Committee of the British Thoracic Society. Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. *Lancet* 1992;340:873-6.
- Levine MN, Hirsh J, Gent M, et al. Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. *Thromb Haemostasis* 1995;74:606-11.
- Schulman S, Rhedin A-S, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. *N Engl J Med* 1995;332:1661-5.
- Prandoni P, Lensing AWA, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996;125:1-7.
- Kearon C, Julian JA, Newman TE, Ginsberg JS. Noninvasive diagnosis of deep venous thrombosis. *Ann Intern Med* 1998;128:663-77.
- Kearon C, Hirsh J. The diagnosis of pulmonary embolism. *Haemostasis* 1995;25:72-87.
- Bertina RM, Koeleman BPC, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994;369:64-7.
- Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* 1996;88:3698-703.

10. Loizou S, McCrea JD, Rudge AC, Reynolds R, Boyle CC, Harris EN. Measurement of anti-cardiolipin antibodies by an enzyme-linked immunosorbent assay (ELISA): standardization and quantitation of results. *Clin Exp Immunol* 1985;62:738-45.
11. Proctor RR, Rapaport SI. The partial thromboplastin time with kaolin: a simple screening test for first stage plasma clotting factor deficiencies. *Am J Clin Pathol* 1961;36:212-9.
12. Triplett DA, Barna LK, Unger GA. A hexagonal (II) phase phospholipid neutralization assay for lupus anticoagulant identification. *Thromb Haemost* 1993;70:787-93.
13. Thiagarajan P, Pengo V, Shapiro SS. The use of the dilute Russell viper venom time for the diagnosis of lupus anticoagulants. *Blood* 1986;68:869-74.
14. Prandoni P, Lensing AWA, Büller HR, et al. Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. *N Engl J Med* 1992;327:1128-33.
15. Hull R, Delmore T, Genton E, et al. Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. *N Engl J Med* 1979;301:855-8.
16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
17. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163-70.
18. Hosmer DW Jr, Lemeshow S. *Applied logistic regression*. New York: John Wiley, 1989.
19. Schulman S, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. *Am J Med* 1998;104:332-8.
20. Simioni P, Prandoni P, Zanon E, et al. Deep venous thrombosis and lupus anticoagulant — a case-control study. *Thromb Haemost* 1996;76:187-9.
21. Rance A, Emmerich J, Fiessinger JN. Anticardiolipin antibodies and recurrent thromboembolism. *Thromb Haemost* 1997;77:221-2.
22. Piantadosi S. *Clinical trials: a methodologic perspective*. New York: John Wiley, 1997:250.
23. Schulman S, Granqvist S, Holmström M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *N Engl J Med* 1997;336:393-8.
24. Levine M, Hirsh J, Gent M, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. *Lancet* 1994;343:886-9.
25. Bern MM, Lokich JJ, Wallach SR, et al. Very low doses of warfarin can prevent thrombosis in central venous catheters: a randomized prospective trial. *Ann Intern Med* 1990;112:423-8.

CORRECTION

A Comparison of Three Months of Anticoagulation with Extended Anticoagulation for a First Episode of Idiopathic Venous Thromboembolism

A Comparison of Three Months of Anticoagulation with Extended Anticoagulation for a First Episode of Idiopathic Venous Thromboembolism . On page 904, the sentence that begins 10 lines from the bottom of the right-hand column should have read, "Of the six patients in the placebo group who had an episode of pulmonary embolism during follow-up, *three* initially had pulmonary embolism and *three* initially had deep-vein thrombosis."