

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 10, 2003

VOL. 348 NO. 15

Long-Term, Low-Intensity Warfarin Therapy for the Prevention of Recurrent Venous Thromboembolism

Paul M Ridker, M.D., Samuel Z. Goldhaber, M.D., Ellie Danielson, M.I.A., Yves Rosenberg, M.D., Charles S. Eby, M.D., Steven R. Deitcher, M.D., Mary Cushman, M.D., Stephan Moll, M.D., Craig M. Kessler, M.D., C. Gregory Elliott, M.D., Rolf Paulson, M.D., Turnly Wong, M.D., Kenneth A. Bauer, M.D., Bruce A. Schwartz, M.D., Joseph P. Miletich, M.D., Henri Bounameaux, M.D., and Robert J. Glynn, Sc.D., for the PREVENT Investigators*

ABSTRACT

BACKGROUND

Standard therapy to prevent recurrent venous thromboembolism includes 3 to 12 months of treatment with full-dose warfarin with a target international normalized ratio (INR) between 2.0 and 3.0. However, for long-term management, no therapeutic agent has shown an acceptable benefit-to-risk ratio.

METHODS

Patients with idiopathic venous thromboembolism who had received full-dose anticoagulation therapy for a median of 6.5 months were randomly assigned to placebo or low-intensity warfarin (target INR, 1.5 to 2.0). Participants were followed for recurrent venous thromboembolism, major hemorrhage, and death.

RESULTS

The trial was terminated early after 508 patients had undergone randomization and had been followed for up to 4.3 years (mean, 2.1). Of 253 patients assigned to placebo, 37 had recurrent venous thromboembolism (7.2 per 100 person-years), as compared with 14 of 255 patients assigned to low-intensity warfarin (2.6 per 100 person-years), a risk reduction of 64 percent (hazard ratio, 0.36 [95 percent confidence interval, 0.19 to 0.67]; $P < 0.001$). Risk reductions were similar for all subgroups, including those with and those without inherited thrombophilia. Major hemorrhage occurred in two patients assigned to placebo and five assigned to low-intensity warfarin ($P = 0.25$). Eight patients in the placebo group and four in the group assigned to low-intensity warfarin died ($P = 0.26$). Low-intensity warfarin was thus associated with a 48 percent reduction in the composite end point of recurrent venous thromboembolism, major hemorrhage, or death. According to per-protocol and as-treated analyses, the reduction in the risk of recurrent venous thromboembolism was between 76 and 81 percent.

CONCLUSIONS

Long-term, low-intensity warfarin therapy is a highly effective method of preventing recurrent venous thromboembolism.

From the Center for Cardiovascular Disease Prevention and the Divisions of Preventive Medicine and Cardiology, Brigham and Women's Hospital and Harvard Medical School, Boston (P.M.R., S.Z.G., E.D., R.J.G.); the National Institutes of Health, Bethesda, Md. (Y.R.); Washington University, St. Louis (C.S.E., J.P.M.); the Cleveland Clinic Foundation, Cleveland (S.R.D.); the University of Vermont, Burlington (M.C.); the University of North Carolina, Chapel Hill (S.M.); Georgetown University Medical Center, Washington, D.C. (C.M.K.); LDS Hospital, Salt Lake City (C.G.E.); Altru Research Clinic, Grand Forks, N.D. (R.P.); St. Boniface General Hospital, Winnipeg, Man., Canada (T.W.); Beth Israel Deaconess Medical Center, Boston (K.A.B.); Midwest Pulmonary Consultants, Kansas City, Mo. (B.A.S.); and the University Hospitals of Geneva, Geneva (H.B.). Address reprint requests to Dr. Ridker at the Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, 900 Commonwealth Ave. E., Boston, MA 02215, or at pridker@partners.org.

*The Prevention of Recurrent Venous Thromboembolism (PREVENT) Investigators are listed in Appendix 1.

This article was published at www.nejm.org on February 24, 2003.

N Engl J Med 2003;348:1425-34.
Copyright © 2003 Massachusetts Medical Society.

THERAPY FOR IDIOPATHIC VENOUS thromboembolism typically includes a 5-to-10-day course of heparin followed by 3 to 12 months of oral anticoagulation therapy with full-dose warfarin, with adjustment of the dose to achieve an international normalized ratio (INR) between 2.0 and 3.0.¹⁻⁴ After cessation of anticoagulation therapy, however, recurrent venous thromboembolism is a major clinical problem, with an estimated rate of 6 to 9 percent annually.^{5,6} Unfortunately, no therapy with an acceptable benefit-to-risk ratio is available for long-term management. In particular, although extended use of full-dose warfarin is associated with reduced rates of recurrent venous thromboembolism,²⁻⁴ community-based studies have consistently found this approach to be associated with substantial risk of major hemorrhage. For example, in observational studies, full-dose warfarin is associated with rates of major bleeding episodes ranging from 5 to 9 percent annually.⁷⁻⁹ Similarly, an annual rate of major hemorrhage of 3.8 percent was observed in a recent trial of full-dose warfarin despite careful on-site monitoring of anticoagulation therapy.³

By contrast, low-intensity warfarin carries a low risk of bleeding when used on a long-term basis, and such therapy may require less frequent monitoring. Furthermore, low-intensity warfarin is effective in reducing biochemical markers of coagulation, such as factor VII activity and levels of prothrombin fragment 1+2.^{10,11} There are, however, no clinical data available on the use of low-intensity warfarin therapy for long-term prophylaxis against venous thrombosis, although this approach has been used successfully for the prevention of a first thrombosis among patients with indwelling central venous catheters and among women with metastatic breast cancer.^{12,13}

The Prevention of Recurrent Venous Thromboembolism (PREVENT) trial was initiated in July 1998 to test the hypothesis that long-term, low-intensity warfarin therapy (target INR, 1.5 to 2.0) might provide a safe and effective method of reducing the risk of recurrent venous thromboembolism among patients who have had a previous idiopathic venous thrombosis.¹⁴ As a secondary aim, the study was designed to test the hypothesis that patients with thrombophilic mutations such as factor V Leiden or the G20210A prothrombin polymorphism might differentially benefit from long-term, low-intensity warfarin prophylaxis.

Designed to enroll 750 patients for an average

follow-up period of four years, our trial was terminated by the independent data and safety monitoring board after 508 patients had undergone randomization, because of the emergence of a large and statistically significant benefit of low-intensity warfarin therapy in the absence of any substantial evidence of harm.

METHODS

STUDY PATIENTS

Men and women 30 years of age or older with documented idiopathic venous thromboembolism were eligible if they had completed at least three uninterrupted months of oral anticoagulation therapy with full-dose warfarin. All index events were confirmed by objective criteria at the central clinical coordinating center on the basis of venography or reports from compression ultrasonography or magnetic resonance imaging (MRI) in the case of deep venous thrombosis and on the basis of ventilation-perfusion scanning, angiography, or computed tomography (CT) of the chest in the case of pulmonary embolism. Idiopathic events were defined as those that did not occur within 90 days after surgery or trauma. Patients were ineligible for the trial if they had a history of metastatic cancer, major gastrointestinal bleeding, hemorrhagic stroke, or a life expectancy of less than three years. Patients who were being treated with dipyridamole, ticlopidine, clopidogrel, heparin, more than 325 mg of aspirin, or drugs that affect the prothrombin time and patients who had known lupus anticoagulant antibodies or antiphospholipid antibodies were excluded.

STUDY DESIGN

Before randomization, eligible patients participated in a 28-day open-label run-in phase designed to ensure that all participants could have their dose of warfarin titrated to a stable level that achieved an INR between 1.5 and 2.0 without exceeding a dose of 10 mg per day. The run-in phase was also used to exclude patients with a level of compliance of less than 85 percent.

During the run-in phase, at randomization, and throughout the follow-up period, all assessments of the INR at each study site were made with the use of specially designed finger-stick devices with an identical thromboplastin (international sensitivity index, 2.0; CoaguChek, Roche Diagnostics). These devices were altered electronically to provide a cod-

ed INR value that was transmitted in a double-blind fashion to the data coordinating center. All dose adjustments were then made according to a simple clinical algorithm (Appendix 2).

Randomization to low-intensity warfarin (Coumadin, provided without charge by Bristol-Myers Squibb; target INR, 1.5 to 2.0) or to matching placebo was performed centrally. Randomization was stratified according to clinical site, time since the index event (≤ 6 months or >6 months), and whether or not the index event was the patient's first venous thromboembolism. All participants were then followed with office visits once every two months that included blinded evaluations of the INR and adjustments of their dose. To ensure blinding, sham dose adjustments were made in the placebo group.

FOLLOW-UP AND STUDY END POINTS

Since the study was designed to evaluate clinically relevant recurrent thromboembolic events, no surveillance for asymptomatic thrombosis was undertaken. Rather, at each visit, clinical events that had occurred since the previous visit were evaluated. All end points were reviewed by a committee of physicians who were unaware of treatment-group assignments. The end point of recurrent deep venous thrombosis was considered to be confirmed if there was a positive venographic study, Doppler compression ultrasonography, or MRI. Events documented by clinical diagnosis alone were not considered to be confirmed. The end point of pulmonary embolism was considered to be confirmed if there was a positive angiogram, a ventilation-perfusion scan that showed at least two segmental defects without ventilation defects, or clear evidence of thrombosis documented by CT or MRI of the chest. In cases of deep venous thrombosis or pulmonary embolism in which the recurrent event occurred in the same leg or lung field as the index event, documentation demonstrating a clear difference between the two events was required. Major hemorrhage was defined as any bleeding episode that led to hospitalization or transfusion.

As an index of net clinical benefit, we defined an a priori composite end point of recurrent venous thromboembolism, major hemorrhage, and death from any cause. New stroke events were also monitored and classified as hemorrhagic or thromboembolic on the basis of clinical records and CT or MRI. So that no event would be counted twice, hemorrhagic strokes were counted as major hemorrhages in analyses of the composite end point.

GENETIC ANALYSES

Blood samples obtained on enrollment underwent DNA extraction and were evaluated in a central laboratory for factor V Leiden and the G20210A prothrombin polymorphism. Genetic data were not made available to the clinical sites or to the end-points committee.

MONITORING OF THE TRIAL

The National Heart, Lung, and Blood Institute appointed an independent data and safety monitoring committee that monitored the primary end point of recurrent venous thromboembolism at an overall alpha level of 0.05 using the O'Brien-Fleming spending function according to the method of Lan and DeMets.¹⁵ Unblinded reviews occurred at least annually or when an additional 20 percent of the expected information was available. At the fourth review (involving approximately 40 percent of the expected information), the committee voted on December 4, 2002, to stop the trial because there was strong evidence of efficacy and the monitoring boundary specified by the Lan-DeMets procedure had been crossed.

STATISTICAL ANALYSIS

For comparisons between treatment groups in the distributions of continuous variables, Wilcoxon rank-sum tests were used; for comparisons of categorical variables, chi-square tests were used. The primary analysis was an intention-to-treat comparison, with a two-sided log-rank test, of the two treatment groups in terms of the time to the first confirmed recurrent venous thromboembolism after randomization. The Kaplan-Meier method was used to estimate the probability of recurrence over time in each treatment group. Estimation of the number of patients who would need to be treated to prevent one recurrent event was based on the rates at three years. We used the proportional-hazards model for estimation of the relative hazard of recurrent events associated with low-intensity warfarin treatment and obtained confidence intervals from this model. The hypothesis of a varying effect of treatment over time was tested in a proportional-hazards model that included a term for the interaction between the treatment group and time. The same methods were used for tests and estimates of the effect of treatment on the composite end point.

The primary prespecified subgroup analysis evaluated the effect of treatment separately in pa-

Table 1. Base-Line Characteristics of the Study Participants.

Characteristic	Placebo Group (N=253)	Warfarin Group (N=255)	P Value
Age (yr)			0.82
Median	53	53	
Interquartile range	47–64	46–65	
Female sex (%)	47.4	47.1	0.93
Race or ethnic group (%)			0.32
Non-Hispanic white	86.6	88.2	
Non-Hispanic black	10.3	9.0	
Hispanic	0.8	2.0	
Other	2.4	0.8	
Body-mass index*			0.89
Median	29.9	29.9	
Interquartile range	26.6–34.3	26.6–34.2	
History of diabetes (%)	8.7	6.7	0.39
≥2 Previous venous thromboembolisms (%)	36.8	40.0	0.45
Family history of venous thromboembolism (%)	31.6	26.3	0.18
Factor V Leiden (%)	26.6	22.0	0.23
Prothrombin mutation (%)	4.8	4.7	0.98
Duration of full-dose warfarin therapy before enrollment (mo)			0.15
Median	6.4	6.7	
Interquartile range	5.7–9.0	5.9–10.8	
Time between cessation of full-dose warfarin therapy and enrollment (mo)			0.57
Median	1.4	2.0	
Interquartile range	0.9–5.1	0.9–4.3	

* The body-mass index is the weight in kilograms divided by the square of the height in meters.

tients with and without either factor V Leiden or the G20210A prothrombin mutation. The hypothesis that the effect of treatment would vary according to genotype was tested by means of a proportional-hazards model that included a term for the interaction between treatment group and the presence or absence of either factor V Leiden or the G20210A prothrombin mutation. The same methods were also used for other comparisons within subgroups.

RESULTS

PATIENTS, THERAPY, AND EVALUATIONS OF THE INR

Between July 6, 1998, and December 4, 2002, 578 patients entered the 28-day run-in phase. At the

time of the early termination of the trial, 13 patients were still in the 28-day run-in phase, and 508 patients had undergone randomization — 253 assigned to placebo and 255 assigned to low-intensity warfarin. The remaining 57 participants did not complete or were not eligible for the trial at the end of the 28-day run-in. The median duration of full-dose anticoagulation therapy before enrollment was 6.5 months. Clinical characteristics and the frequency of known risk factors were similar in the two treatment groups (Table 1).

The mean duration of follow-up after randomization was 2.1 years, with a maximal duration of treatment of 4.3 years. The median INR of patients in the placebo group was 1.0 (interquartile range, 1.0 to 1.1), whereas the median INR in the warfarin group was 1.7 (interquartile range, 1.4 to 2.0). This difference was maintained throughout the study period (Fig. 1). In the warfarin group, the median dose of warfarin was 4 mg (interquartile range, 3 to 6), with a range of 0.5 to 10.0 mg daily.

RECURRENT VENOUS THROMBOEMBOLISM

In total, there were 51 confirmed recurrences of venous thrombosis after randomization. Of these, 39 involved deep venous thrombosis only, and 12 were associated with pulmonary embolism. Eighty-six percent of all recurrent events were idiopathic, and 14 percent were associated with a new diagnosis of cancer, recent surgery, or trauma.

Of the 253 patients assigned to placebo, 37 had confirmed recurrent venous thromboembolism (7.2 per 100 person-years), as compared with 14 of the 255 patients assigned to low-intensity warfarin (2.6 per 100 person-years) — a risk reduction of 64 percent (hazard ratio, 0.36 [95 percent confidence interval, 0.19 to 0.67]; $P < 0.001$) (Table 2). The cumulative risk of recurrent venous thromboembolism is shown in Figure 2. Low-intensity warfarin therapy had similar efficacy in the prevention of early and late recurrent events. On the basis of these rates, 10 patients would need to be treated for three years to prevent one recurrent event.

Of 77 patients with either factor V Leiden or the prothrombin mutation who were assigned to placebo, 14 had recurrent events (8.6 events per 100 person-years), as compared with 3 of 66 such patients who were assigned to low-intensity warfarin (2.2 events per 100 person-years) (Table 3). This 75 percent reduction in risk among those with inherited thrombophilias (hazard ratio, 0.25 [95 percent confidence interval, 0.07 to 0.87]) was not signifi-

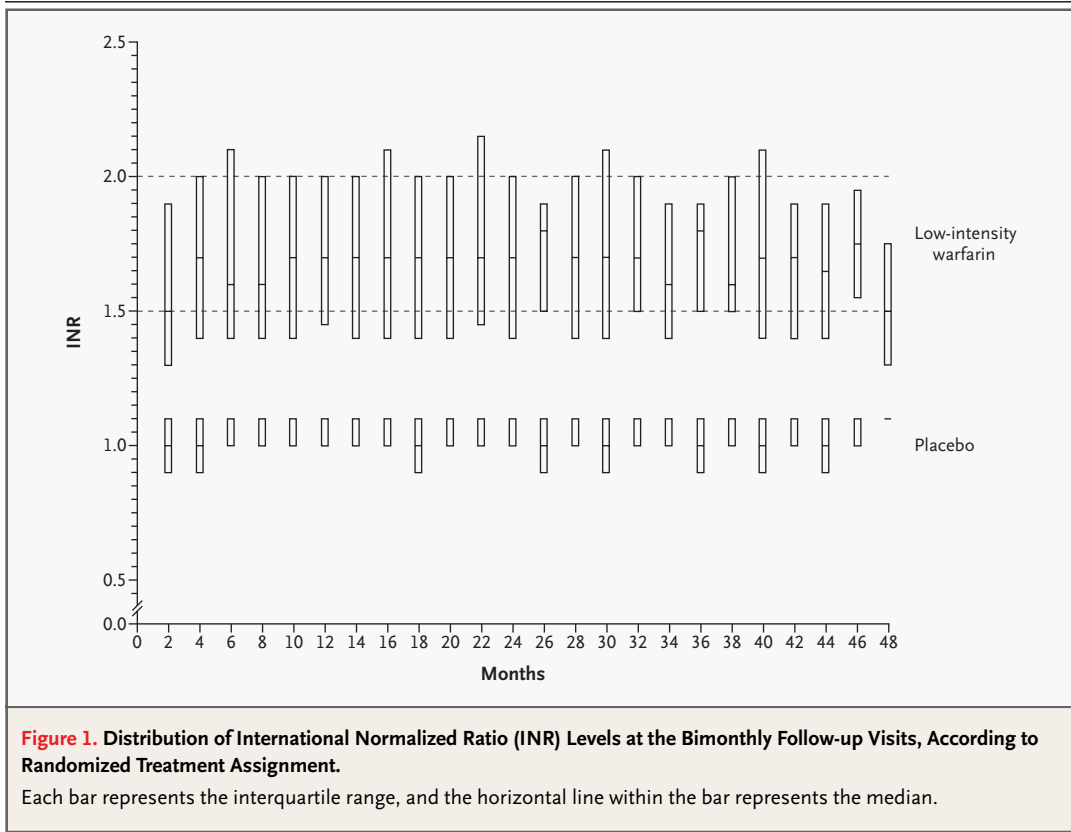


Table 2. Major Study End Points According to Treatment Group.*

Outcome	Placebo Group		Warfarin Group		Hazard Ratio (95% CI)	P Value
	No. of Events	No./100 Person-Yr	No. of Events	No./100 Person-Yr		
Recurrent venous thromboembolism	37	7.2	14	2.6	0.36 (0.19–0.67)	<0.001
Bleeding episode						
Major	2	0.4	5	0.9	2.53 (0.49–13.03)	0.25
Minor	34	6.7	60	12.8	1.92 (1.26–2.93)	0.002
Death	8	1.4	4	0.7	0.50 (0.15–1.68)	0.26
Cancer	9	1.6	4	0.7	0.45 (0.14–1.47)	0.18
Myocardial infarction	2	0.4	3	0.5	1.54 (0.26–9.24)	0.63
Composite end point (recurrent venous thromboembolism, major bleeding episode, or death)	41	8.0	22	4.1	0.52 (0.31–0.87)	0.01

* Major bleeding episodes were defined as episodes resulting in hospitalization, transfusion of packed red cells, or hemorrhagic stroke. CI denotes confidence interval.

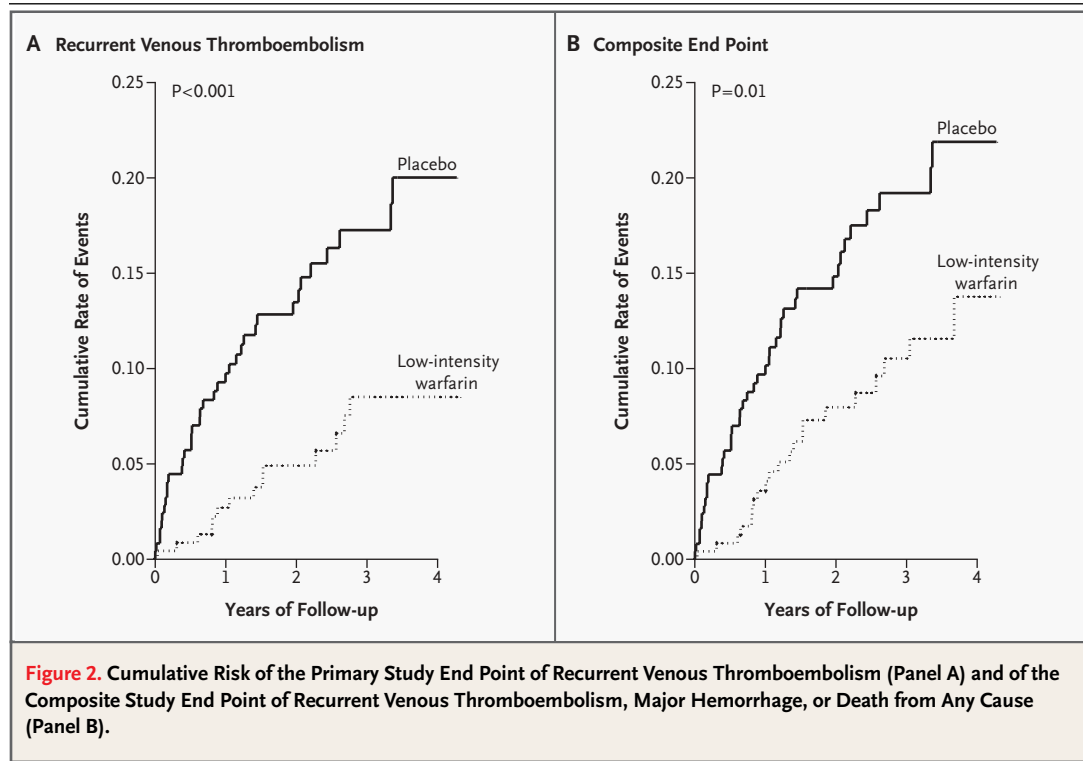


Figure 2. Cumulative Risk of the Primary Study End Point of Recurrent Venous Thromboembolism (Panel A) and of the Composite Study End Point of Recurrent Venous Thromboembolism, Major Hemorrhage, or Death from Any Cause (Panel B).

cantly different from the 58 percent risk reduction among those without factor V Leiden or the prothrombin mutation (hazard ratio, 0.42 [95 percent confidence interval, 0.20 to 0.86]; P for interaction = 0.51).

Risk reductions were of similar magnitude in the other subgroups we evaluated (Table 3). Among women, low-intensity warfarin therapy was associated with an 80 percent reduction in the risk of recurrent venous thromboembolism (hazard ratio, 0.20 [95 percent confidence interval, 0.06 to 0.67]), and a 53 percent reduction was observed among men (hazard ratio, 0.47 [95 percent confidence interval, 0.23 to 0.96]; P for interaction = 0.23). We observed no significant interactions between the magnitude of the reduction in risk and categories of age, time since randomization, time since cessation of full-dose warfarin therapy, or number of previous venous thromboembolic events.

BLEEDING EPISODES

In the placebo group, two patients had bleeding episodes necessitating hospitalization (0.4 per 100 person-years), and in the warfarin group, five patients had such episodes (0.9 per 100 person-years) — a nonsignificant difference ($P = 0.25$). Of the ma-

ior bleeding episodes in the warfarin group, three involved gastrointestinal bleeding, one a hematoma in the leg, and one hematuria associated with the removal of a renal calculus. Only one major hemorrhage necessitated the transfusion of packed red cells; this hemorrhage occurred in a patient in the warfarin group who was receiving full-dose warfarin at the time of the hemorrhage. A total of 34 patients in the placebo group and 60 patients in the warfarin group reported minor bleeding or bruising (hazard ratio, 1.92 [95 percent confidence interval, 1.26 to 2.93]).

DEATH, STROKE, AND OTHER END POINTS

Eight deaths occurred in the placebo group, and four in the warfarin group ($P = 0.26$). Two deaths were due to fatal pulmonary embolism, and one death was due to fatal hemorrhagic stroke; all three of these were in the placebo group.

There were two confirmed strokes in the placebo group and one in the warfarin group. As noted above, one stroke was hemorrhagic and occurred in a patient assigned to placebo. This patient was initially hospitalized for a thromboembolic stroke that became hemorrhagic after the initiation of treatment with heparin and clopidogrel. There were 13

Table 3. Rates and Hazard Ratios for Recurrent Venous Thromboembolism in Clinically Important Subgroups, According to Treatment-Group Assignment.

Characteristic	Placebo Group		Warfarin Group		Hazard Ratio (95% CI)*	P Value for Interaction†
	No. of Events	No./100 Person-Yr	No. of Events	No./100 Person-Yr		
Factor V Leiden or prothrombin mutation						0.51
Present	14	8.6	3	2.2	0.25 (0.07–0.87)	
Absent	23	6.6	11	2.7	0.42 (0.20–0.86)	
Sex						0.23
Male	22	8.6	11	3.9	0.47 (0.23–0.96)	
Female	15	5.9	3	1.1	0.20 (0.06–0.67)	
Age						0.87
30–44 yr	8	7.6	4	3.3	0.45 (0.14–1.51)	
45–64 yr	20	7.3	5	1.7	0.24 (0.09–0.65)	
65–89 yr	9	6.7	5	4.0	0.57 (0.19–1.70)	
No. of previous venous thromboembolic events						0.42
≥2	21	11.4	10	4.8	0.43 (0.20–0.90)	
1	16	4.9	4	1.2	0.25 (0.08–0.74)	
Time since randomization						0.16
≤1 yr	22	10.1	6	2.7	0.27 (0.11–0.66)	
>1 yr	15	5.1	8	2.5	0.49 (0.21–1.16)	
Time since cessation of full-dose warfarin therapy						0.69
>2 mo	14	5.9	7	2.5	0.42 (0.17–1.04)	
≤2 mo	23	8.4	7	2.7	0.33 (0.14–0.76)	

* CI denotes confidence interval.

† The null hypothesis is that there are no differences among subgroups; for age and time since randomization, the interaction tested is between the continuous variable and treatment.

diagnoses of cancer during follow-up: 9 in the placebo group and 4 in the warfarin group (P=0.18).

The rate of the composite end point (recurrent venous thromboembolism, major hemorrhage [including hemorrhagic stroke], or death from any cause) was reduced by 48 percent in the warfarin group (hazard ratio, 0.52 [95 percent confidence interval, 0.31 to 0.87]; P=0.01) (Table 2 and Fig. 2).

PER-PROTOCOL AND AS-TREATED ANALYSES

The study drug was discontinued before the completion of follow-up in 56 patients in the placebo group and 64 patients in the warfarin group (P=0.43). The primary reasons for discontinuation were refusal of treatment by the patient, minor bruising, the development of other medical conditions, or a new indication for anticoagulation therapy. Discontinuation of treatment for each of these reasons, including minor bleeding, occurred with equal frequency in the placebo group and the warfarin group.

Fifteen patients had a recurrent venous thromboembolism after cessation of treatment with the assigned study drug. Of these, eight were in the placebo group and seven were in the warfarin group. Thus, among patients who were documented to be receiving the assigned study drug at the time of the recurrent event, the risk reduction associated with low-intensity warfarin therapy was 76 percent (hazard ratio, 0.24 [95 percent confidence interval, 0.10 to 0.54]).

No patients with recurrent events who had stopped taking the study drug were receiving another form of anticoagulation therapy at the time of the recurrent event. Thus, according to an analysis of the subgroup that was using long-term anticoagulation therapy at the time of the recurrent event, there was an 81 percent reduction in risk in the warfarin group (hazard ratio, 0.19 [95 percent confidence interval, 0.09 to 0.43]).

DISCUSSION

This randomized, double-blind, placebo-controlled trial demonstrates that long-term, low-intensity warfarin therapy given with a target INR of 1.5 to 2.0 results in a large and significant reduction in the risk of recurrent venous thrombosis. This benefit was seen in all the subgroups we evaluated and was achieved with little evidence of any increase in the risk of major hemorrhage or stroke, despite the infrequent monitoring of anticoagulation therapy. Thus, long-term, low-intensity warfarin therapy can be readily implemented in clinical practice.

Previous studies have demonstrated that short-term use of full-dose warfarin is highly effective after a first episode of venous thrombosis, and on the basis of evidence from randomized trials, usual care typically includes full-dose warfarin therapy for up to 12 months.¹⁻⁴ Two completed trials show that the use of full-dose warfarin for longer than one year continues to provide efficacy, in comparison with placebo, in preventing recurrent events,^{2,3} and preliminary data from one trial suggest that there is a greater reduction in the rate of recurrent thrombosis with full-dose warfarin than with low-dose warfarin.¹⁶ However, in the two published trials, rates of major bleeding episodes were high during extended therapy with full-dose warfarin — an observation that supports the widespread concern regarding the net clinical benefit of long-term warfarin therapy with a target INR of 2.0 to 3.0.⁷⁻⁹ One trial comparing an oral thrombin inhibitor with placebo for the prevention of recurrent venous thromboembolism has also recently been described.¹⁷ Direct comparisons will be needed in order to determine whether any of these approaches is truly superior to the others for long-term management.

Our study also addressed the question of whether low-intensity warfarin therapy had differential effects among those with and without inherited

thrombophilias such as factor V Leiden and the G20210A prothrombin polymorphism, each of which is known to increase the risk of a first venous thrombosis.¹⁸⁻²³ Whether these genetic disorders are associated with an increased risk of recurrent venous thromboembolism remains controversial.²⁴⁻²⁹ In our study, patients with factor V Leiden or the G20210A prothrombin polymorphism were not at substantially increased risk of recurrent events as compared with patients without these disorders. Moreover, the relative benefit of low-intensity warfarin therapy in preventing recurrent events was not significantly affected by the patient's genetic status. Thus, it is uncertain whether screening for either of these polymorphisms had important clinical consequences, either in terms of prognosis or in terms of differential therapeutic response. Since our study excluded patients with known antiphospholipid-antibody syndrome, the efficacy of low-intensity warfarin therapy among such patients remains uncertain.

Long-term, low-intensity warfarin therapy is a highly effective method of preventing recurrent venous thromboembolism. Our data reinforce the importance of investigating agents that might be clinically useful but whose status as generic drugs provides little financial incentive for investigation by the pharmaceutical industry.

Supported by grants (HL-57951 and HL-58036) from the National Heart, Lung, and Blood Institute. Study drug and placebo were supplied without fee by Bristol-Myers Squibb. Dr. Ridker receives additional research support from the Leducq Foundation and the Doris Duke Charitable Foundation.

Dr. Ridker reports having received grant support from Bristol-Myers Squibb, AstraZeneca, and Roche Diagnostics, Dr. Goldhaber consulting fees from Aventis and Pharmacia and grant support from Aventis and AstraZeneca, Drs. Cushman and Moll grant support from AstraZeneca, Dr. Kessler consulting and lecture fees from Aventis, Dr. Paulson lecture fees from Aventis, Dr. Bounameaux consulting fees from Aventis and AstraZeneca and lecture fees from Aventis, and Dr. Glynn consulting fees from AstraZeneca and grant support from Bristol-Myers Squibb.

APPENDIX 1

The following persons participated in the Prevention of Recurrent Venous Thromboembolism (PREVENT) Study. Chair: P.M. Ridker (Brigham and Women's Hospital, Boston); Data Coordinating Center: R.J. Glynn (Director), E.M. Danielson, D. Bates, W. Christen, P. DeFonce, W. Griffin, F. Jackson, A. Murray, K. Taylor, K. Johnson, K. McKenna, J. Pierre, B. Holman, F. Dessources, P. Quinn, T. Laurinaitis, J. MacFadyen (Brigham and Women's Hospital, Boston); Laboratory Coordinating Center: C. Eby (Co-Director), J.P. Mileteich (Co-Director), R. Porche-Sorbet (Washington University, St. Louis); Clinical Coordinating Center: S.Z. Goldhaber (Director), R.B. Morrison, R.C. MacDougall, R.M. Morrison (Brigham and Women's Hospital, Boston); Independent Data and Safety Monitoring Board: G. Lamas (Chair), K. Bailey, B. Gersh, E. Pellegrino, M. Rick, D. Vaughan; Scientific Project Officer: Y. Rosenberg (National Heart, Lung, and Blood Institute).

Study sites and investigators (numbers in parentheses are the numbers of patients who underwent randomization): Brigham and Women's Hospital, Boston — S.Z. Goldhaber, R.B. Morrison, R.C. MacDougall, R.M. Morrison (119); Cleveland Clinic Foundation, Cleveland — S.R. Deitcher, J. Olin, S. Sulzer, T. Clark (32); University of Vermont and Fletcher Allen Health Care, Burlington — M. Cushman, R. Cohen (27); University of North Carolina, Chapel Hill — S. Moll, S. Jones (27); Georgetown University Medical Center, Washington, D.C. — C.M. Kessler, A. Lee (18); LDS Hospital, Salt Lake City — C.G. Elliott, N. Kitterman (16); Henry Ford Hospital, Detroit — S. Jaffri, N. Wulbrecht (14); Beth Israel Deaconess Medical Center, Boston — K. Bauer, M. Mahony (13); Altru Research Clinic, Grand Forks, N.D. — R. Paulson, D. Vold (13); St. Boniface General Hospital, Winnipeg, Man., Canada — T.

Wong, S. Erickson-Nesmith (13); University Hospitals of Geneva, Geneva — H. Bounameaux, S. de Lucia, I. Chagnon (12); Midwest Pulmonary Consultants, Kansas City, Mo. — B. Schwartz, R. Thackery, N. Gates (12); Hôtel Dieu de Montréal, Montreal — P. Nguyen, S. Paris, B. LeCours (11); Morristown Memorial Hospital, Morristown, N.J. — M. Oliver, K. Hodapp (11); Northwest Oncology and Hematology, Elk Grove Village, Ill. — G. Grad, B. Bank, J. Rindels, C. Leano (10); University of Nebraska Medical Center, Omaha — W. Haire, D. O'Grady, J. Schneider (10); Fairview University Medical Center, Minneapolis — N. Key, B. Christie (10); Jewish General Hospital, Montreal — M. Blostein, C. Strulovitch (8); Asheville Cardiology Associates, Asheville, N.C. — J. Usedom, D. Oskins (8); Washington University Medical Center, St. Louis — C. Eby, V. Lee, S. Heuerman (7); Vanderbilt University, Nashville — D. Kerins, B. Roberts (7); University of California—Davis, Sacramento — R. White, E. Castro, E. Riddle, M. Ingram (7); University of Massachusetts, Worcester — R.C. Becker, C. Emery (6); Scott and White Memorial Hospital, Temple, Tex. — L. Wong, S. Dent (6); Oklahoma Veterans Affairs Medical Center, Oklahoma City — P. Comp, D. Havarada (5); Research Institute of Kansas, Wichita — J.P. Galichia, L. Terry, S. Waldren (5); University of California—San Francisco, San Francisco — J. Hambleton, J. Roth (5); Foothills Hospital, Calgary, Alta., Canada — G. Pineo, R. Hull, J. Sheldon (5); Lahey Clinic, Burlington, Mass. — N. Tsapatsaris, G. Woodhead, M. Mann (5); Denver Veterans Affairs Medical Center, Denver — C. Welsh, T. Schoch, J. Goldsmith (5); Syracuse Veterans Affairs Medical Center, Syracuse, N.Y. — T. Anthony, J. Walters (4); Evanston Hospital, Evanston, Ill. — J. Caprini, M.L. Maher, K. Medica, S. Rabbitt (4); Akron General Medical Center, Akron, Ohio — J. Finocchio, K. Keaton (4); Group Health Centre, Sault Ste. Marie, Ont., Canada — H. Lee, S. McLean, K. Barban (4); Presbyterian Medical Center, Philadelphia — E. Mohler, E. Medenilla, M. Wolfe, A. deLemos (4); University of Michigan—Ann Arbor, Ann Arbor — M. Rubenfire, S. McDevitt, S. Housholder (4); Cardiza Foundation Hemophilia Center, Philadelphia — J.E. Siegel (4); McGuire Veterans Affairs Medical Center, Richmond, Va. — B. Bradley (3); Boston Veterans Affairs Medical Center, Boston — M. Brophy, C. Reilly (3); Bronx Lebanon Hospital Center, Bronx, N.Y. — E. Brown, A. Valeria, L. Rodriguez (3); Hot Springs Medical Center, Hot Springs, S.D. — A. Kumar, J. Pekron, J. Wagner (3); Saint Louis University Health Sciences Center, St. Louis — J. Richart, J. Jones (3); Geisinger Medical Center, Danville, Pa. — V. Weber, C. Fellin, J. Sim (3); Kansas City Veterans Affairs Medical Center, Kansas City, Mo. — M. Graham, D. Sutton (2); Rhode Island Hospital, Providence — A. Kestin (2); North Idaho Cancer Center, Coeur d'Alene — H. Tezcan, S. Herbst (2); University of Alabama, Birmingham — M. Waldrum, T. Meadows (2); Harvard Vanguard Medical Associates, Boston — W. Carlson, M. Welch-Costantino (1); Wisconsin Heart and Vascular, Milwaukee — J. Gosset, J. Nonnweiler (1); Fort Meade Medical Center, Fort Meade, S.D. — A. Kumar, K. Green (1); Duke University Medical Center, Durham, N.C. — V. Tapson, A. Krichman (1); Toronto General Hospital, Toronto — E. Yeo, S. Boross-Harmer (1).

APPENDIX 2: REGIMEN USED DURING THE BIMONTHLY FOLLOW-UP VISITS FOR THE TITRATION OF THE WARFARIN DOSE

If the international normalized ratio (INR) <1.3 (on blinded measurement), increase current dose by 2 mg per day and repeat blinded measurement of INR in one week.

If INR ≥1.3 and <1.5, increase current dose by 1 mg per day and repeat measurement of INR in eight weeks.

If INR ≥1.5 and ≤2.0, maintain current dose and repeat measurement of INR in eight weeks.

If INR >2.0 and ≤3.0, decrease current dose by 1 mg per day and repeat measurement of INR in eight weeks.

If INR >3.0 and ≤4.0, decrease current dose by 2 mg per day and repeat measurement of INR in one week.

If INR >4.0, stop study drug for three days and repeat measurement of INR. If INR remains >4.0, discontinue therapy. If INR ≤4.0 on repeated measurement, decrease current dose by 2 mg per day and repeat measurement of INR in one week.

REFERENCES

- 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.
- 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.
- Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999;340:901-7. [Erratum, *N Engl J Med* 1999;341:298.]
- Agnelli G, Prandoni P, Santamaria MG, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. *N Engl J Med* 2001;345:165-9.
- Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996;125:1-7.
- Hirsh J. The optimal duration of anticoagulant therapy for venous thrombosis. *N Engl J Med* 1995;332:1710-1.
- Fihn SD, Callahan CM, Martin DC, McDonnell MB, Henikoff JG, White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. *Ann Intern Med* 1996;124:970-9.
- Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med* 1998;105:91-9.
- McMahan DA, Smith DM, Carey MA, Zhou XH. Risk of major hemorrhage for outpatients treated with warfarin. *J Gen Intern Med* 1998;13:311-6.
- Poller I, MacCallum PK, Thomson JM, Kerns W. Reduction of factor VII coagulant activity (VIIc), a risk factor for ischaemic heart disease, by fixed dose warfarin: a double blind crossover study. *Br Heart J* 1990;63:231-3.
- Millenson MM, Bauer KA, Kistler JP, Barzegar S, Tulin L, Rosenberg RD. Monitoring "mini-intensity" anticoagulation with warfarin: comparison of the prothrombin time using a sensitive thromboplastin with prothrombin fragment F1+2 levels. *Blood* 1992;79:2034-8.
- 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.
- 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.
- Ridker PM. Long-term, low-dose warfarin among venous thrombosis patients with and without factor V Leiden mutation: rationale and design for the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial. *Vasc Med* 1998;3:67-73.
- Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:659-63.
- Kearon C, Ginsberg JS, Kovacs M, et al. Low-intensity (INR 1.5-1.9) versus conventional-intensity (INR 2.0-3.0) anticoagulation for extended treatment of unprovoked VTE: a randomized double blind trial. *Blood* 2002;100:150a. abstract.
- Eriksson H, Wähländer K, Lundström T, Clason SB, Schulman S. Extended secondary prevention with the oral direct thrombin inhibitor ximelagatran for 18 months after 6 months of anticoagulation in patients with venous thromboembolism: a randomized, placebo-controlled trial. *Blood* 2002;100:81a. abstract.
- 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.
- Svensson PJ, Dahlbäck B. Resistance to activated protein C as a basis for venous

- thrombosis. *N Engl J Med* 1994;330:517-22.
20. Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. *N Engl J Med* 1995;332:912-7.
21. 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.
22. Price D, Ridker PM. Factor V Leiden mutation and the risk for thromboembolic disease: a clinical perspective. *Ann Intern Med* 1997;127:895-903.
23. Hillarp A, Zoller B, Svensson PJ, Dahlback B. The 20210 A allele of the prothrombin gene is a common risk factor among Swedish outpatients with verified deep venous thrombosis. *Thromb Haemost* 1997;78:990-2.
24. Ridker PM, Miletich JP, Stampfer MJ, Goldhaber SZ, Lindpaintner K, Hennekens CH. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. *Circulation* 1995;92:2800-2.
25. Simioni P, Prandoni P, Lensing AWA, et al. The risk of recurrent venous thromboembolism in patients with an Arg⁵⁰⁶→Gln mutation in the gene for factor V (factor V Leiden). *N Engl J Med* 1997;336:399-403.
26. Miles JS, Miletich JP, Goldhaber SZ, Hennekens CH, Ridker PM. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. *J Am Coll Cardiol* 2001;37:215-8.
27. Eichinger S, Pabinger I, Stumpflen A, et al. The risk of recurrent venous thromboembolism in patients with and without factor V Leiden. *Thromb Haemost* 1997;77:624-8.
28. Lindmarker P, Schulman S, Sten-Linder M, et al. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. *Thromb Haemost* 1999;81:684-9.
29. De Stefano V, Martinelli I, Mannucci PM, et al. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. *N Engl J Med* 1999;341:801-6.

Copyright © 2003 Massachusetts Medical Society.

**RECEIVE IMMEDIATE NOTIFICATION WHEN
A JOURNAL ARTICLE IS RELEASED EARLY**

To be notified when an article is released early on the Web and to receive the table of contents of the *Journal* by e-mail every Wednesday evening, sign up through our Web site at <http://www.nejm.org>