

THREE MONTHS VERSUS ONE YEAR OF ORAL ANTICOAGULANT THERAPY FOR IDIOPATHIC DEEP VENOUS THROMBOSIS

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ABSTRACT

Background In patients with idiopathic deep venous thrombosis, continuing anticoagulant therapy beyond three months is associated with a reduced incidence of recurrent thrombosis during the period of therapy. Whether this benefit persists after anticoagulant therapy is discontinued is controversial.

Methods Patients with a first episode of idiopathic proximal deep venous thrombosis who had completed three months of oral anticoagulant therapy were randomly assigned to the discontinuation of oral anticoagulants or to their continuation for nine additional months. The primary study outcome was recurrence of symptomatic, objectively confirmed venous thromboembolism during at least two years of follow-up.

Results The primary intention-to-treat analysis showed that of 134 patients assigned to continued oral anticoagulant therapy, 21 had a recurrence of venous thromboembolism (15.7 percent; average follow-up, 37.8 months), as compared with 21 of 133 patients assigned to the discontinuation of oral anticoagulant therapy (15.8 percent; average follow-up, 37.2 months), resulting in a relative risk of 0.99 (95 percent confidence interval, 0.57 to 1.73). During the initial nine months after randomization (after all patients received three months of therapy), 1 patient had a recurrence while receiving oral anticoagulant therapy (0.7 percent), as compared with 11 of the patients assigned to the discontinuation of oral anticoagulant therapy (8.3 percent, $P=0.003$). The incidence of recurrence after the discontinuation of treatment was 5.1 percent per patient-year in patients in whom oral anticoagulant therapy was discontinued after 3 months and 5.0 percent per patient-year in patients who received an additional 9 months of oral anticoagulant therapy. None of the recurrences were fatal. Four patients had nonfatal major bleeding during the extended period of anticoagulant therapy (3.0 percent).

Conclusions In patients with idiopathic deep venous thrombosis, the clinical benefit associated with extending the duration of anticoagulant therapy to one year is not maintained after the therapy is discontinued. (N Engl J Med 2001;345:165-9.)

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THE optimal duration of treatment with oral anticoagulant agents after deep venous thrombosis reflects a balance between the risk of recurrence when treatment is discontinued and the risk of bleeding resulting from continued anticoagulant therapy.¹⁻³ The risk of recurrent thromboembolism after the discontinuation of anticoagulant therapy is highly dependent on patient-specific risk factors.⁴⁻⁷ Patients who have thrombosis in the absence of known risk factors (i.e., who have idiopathic venous thrombosis) or in association with persistent risk factors (such as cancer and thrombophilia) are at higher risk of recurrence than patients with thrombosis associated with time-limited, reversible risk factors.⁴⁻⁷ In this last group of patients, oral anticoagulant therapy can be limited to three months after the elimination of the risk factor. More prolonged courses of anticoagulant therapy are recommended for patients in whom thrombosis is associated with persistent risk factors²; in addition, on the basis of the results of two recent, adequately designed studies, longer therapy should be considered for patients with idiopathic thrombosis.^{5,8}

In the more recent of the two studies, Kearon et al. randomly assigned patients with idiopathic venous thromboembolism who had received three months of oral anticoagulant therapy to the discontinuation of anticoagulant therapy or its continuation for two additional years.⁸ The study was terminated early be-

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cause of the impressive reduction in the risk of recurrence of thromboembolic events during therapy in the group of patients assigned to continued anticoagulant therapy. Whether the advantage observed in patients in whom therapy is continued for an extended period is maintained after that therapy has been stopped remains unclear.

We conducted a multicenter, randomized trial to evaluate the long-term clinical benefit of extending to one year the three-month course of oral anticoagulant therapy after a first episode of idiopathic proximal deep venous thrombosis. The primary outcome of the study was the symptomatic, objectively confirmed recurrence of venous thromboembolism during at least two years of follow-up.

METHODS

Patients

Consecutive patients ranging from 15 to 85 years old with a first episode of symptomatic idiopathic proximal deep venous thrombosis, as demonstrated on compression ultrasonography or venography, were eligible for the study, provided that they had completed three uninterrupted months of oral anticoagulant therapy without having a recurrence of thromboembolism or bleeding. Idiopathic deep venous thrombosis was defined as thrombosis occurring in the absence of known cancer, known thrombophilia, prolonged immobilization (i.e., lasting more than seven days) from any cause, recent trauma or surgery (i.e., within the previous three months), pregnancy, recent childbirth, or the use of oral contraceptives. Systematic screening for occult cancer or thrombophilia was not performed before patients were enrolled in the study. Patients who required prolonged anticoagulant therapy for reasons other than venous thromboembolism were excluded from the study, as were patients with major psychiatric disorders, patients with a life expectancy shorter than two years, those who could not return for the follow-up visits, and those who declined to participate. The study protocol was approved by the institutional review boards of the participating hospitals; all patients gave written informed consent.

Study Design and Interventions

The Warfarin Optimal Duration Italian Trial was a randomized, multicenter, open trial with independent, blinded assessment of the outcome events. The study was designed to evaluate the clinical benefit of extending to one year the three-month course of oral anticoagulant therapy after a first episode of idiopathic proximal deep venous thrombosis. After three months of therapy with warfarin (in 97 percent of the cases) or acenocoumarol, patients were randomly assigned to discontinue oral anticoagulant therapy or to continue it for nine additional months.

The dose of warfarin or other oral anticoagulant was adjusted to achieve a target international normalized ratio (INR) between 2.0 and 3.0. The therapy was monitored in anticoagulant clinics associated with the 10 study centers, all in Italy.

Outcome Measures

The primary outcome of the study was the recurrence of symptomatic, objectively confirmed deep venous thromboembolism during a follow-up period of at least two years. The criteria for the diagnosis of recurrent deep venous thrombosis were positive results on compression ultrasonography or venography in the contralateral leg; an intraluminal filling defect in the ipsilateral leg that was visible on a venogram; or the finding on ultrasonography of a newly non-compressible venous segment in the ipsilateral leg. The criteria for the diagnosis of pulmonary embolism were a diagnostic pulmonary angiogram, a ventilation-perfusion lung scan indicating a high probability of pulmonary embolism, or an indeterminate lung scan

with a high degree of clinical suspicion of pulmonary embolism in a patient with an objectively diagnosed asymptomatic recurrence of deep venous thrombosis.

Bleeding was defined as major if it was clinically overt and associated with either a decrease in the hemoglobin level of at least 2 g per deciliter or the need for the transfusion of 2 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 the result of pulmonary embolism, bleeding, or another identifiable cause or as unexplained.

All suspected outcome events (recurrent thromboembolism and bleeding episodes) and all deaths were reviewed centrally, for both the interim and final analyses, by an independent, external adjudication committee whose members were unaware of the treatment-group assignments.

Follow-up

Patients were instructed to return for follow-up visits at 3, 6, and 12 months after randomization and every 6 months thereafter until the completion of the study. Patients were asked to return to the study center immediately if symptoms developed that were suggestive of recurrent venous thromboembolism or bleeding. For all patients who died during the follow-up period, the date and cause of death were documented. We attempted to gain permission for autopsies of all patients in whom a pulmonary embolism could not be excluded as the cause of death.

Statistical Analysis

The primary analysis of efficacy was a comparison of the rates of symptomatic, objectively confirmed recurrence of venous thromboembolism in the two treatment groups during a follow-up period of at least two years after randomization. The primary analysis was performed on an intention-to-treat basis. However, since some patients discontinued oral anticoagulant therapy before its scheduled completion, continued to use the anticoagulant after its scheduled completion, or resumed its use after the scheduled interruption, a per-protocol analysis including only the patients who completed treatment according to the study protocol was also performed.

On the basis of the results of previous studies, it was assumed that the rate of recurrence of venous thromboembolism would be 15 percent over two years of postrandomization follow-up in patients assigned to the discontinuation of oral anticoagulant therapy.^{5,6} We also assumed that the prolongation of oral anticoagulant therapy by nine months would produce a 50 percent reduction in the risk of recurrence. Given these assumptions, we needed 246 patients in each group to detect a difference of this magnitude between groups with a power of 80 percent and a type I error rate of 5 percent. In order to avoid the exposure of the study patients to an ineffective or dangerous therapeutic regimen, one prespecified interim analysis of efficacy and safety was planned after the randomization of the first 246 patients. The following criteria for stopping the trial were defined a priori: an overall rate of recurrence of thromboembolic events lower than 7.5 percent; an unequivocal reduction in the rate of recurrent venous thromboembolism in the patients assigned to continued therapy ($P < 0.001$ by a one-sided test); a risk of recurrence in the continued-therapy group that was less than 25 percent lower than that in the group assigned to discontinue therapy, in the presence of the expected rate of events (15 ± 2.5 percent) in the latter group; or a rate of major bleeding higher than 5 percent in the continued-therapy group.

The cumulative hazard of recurrent venous thromboembolism was calculated according to the Kaplan-Meier life-table method.⁹ Rates of recurrence in the two groups were compared with the use of the log-rank test.¹⁰

RESULTS

Patients

The recruitment of patients began in January 1995 and was stopped in June 1998 after the inclusion of

267 patients, when the results of the interim analysis were available and showed a difference of less than 25 percent in the risk of recurrence. At that time, thromboembolic events had recurred in 16 of the 123 patients assigned to the discontinuation of oral anticoagulant therapy (13.0 percent) and in 15 of the 123 patients assigned to the continuation of oral anticoagulant therapy (12.2 percent), corresponding to a difference in risk of 6.2 percent. Follow-up was continued until the last enrolled patient completed two years of follow-up.

At the time of randomization, 290 consecutive patients met the criteria for inclusion, among whom 23 also met one of the criteria for exclusion. The reasons for the exclusion of patients were contraindications to long-term anticoagulant therapy (in eight patients), other indications for long-term anticoagulant therapy (in six patients), declining to give consent (in six patients), and inability to return for follow-up visits (in three patients). Therefore, 267 patients were enrolled in the study, 133 in the group assigned to discontinue oral anticoagulant therapy and 134 in the group assigned to continue therapy.

The base-line characteristics of the patients in the two treatment groups were similar. The average age was 67.7 ± 7.3 years among the patients assigned to discontinue therapy and 66.8 ± 6.7 years among those assigned to continue therapy; men accounted for 61.2 percent of the patients assigned to discontinue therapy and 54.5 percent of those assigned to continue therapy. Approximately 20 percent of patients in both groups received low-molecular-weight heparin as an initial treatment; the remaining patients received intravenous unfractionated heparin. Four patients declined to continue oral anticoagulant therapy after randomization. Oral anticoagulant therapy was prematurely and permanently discontinued in nine patients assigned to the continuation of therapy. Oral anticoagulant therapy was prolonged beyond its scheduled cessation in two patients assigned to discontinue therapy and was resumed after the scheduled cessation in five patients assigned to discontinue therapy. On the basis of the linear interpolation of INR results between tests, we estimate that the INR was between 2.0 and 3.0 for an average of 81 percent of the time during the nine months of extended anticoagulant therapy. During the follow-up period, cancer was newly diagnosed in five patients — three assigned to continue therapy and two to discontinue therapy (1.9 percent of the total cohort; lung cancer in two patients and bladder cancer, breast cancer, and prostate cancer in one patient each).

Recurrent Venous Thromboembolism

The primary intention-to-treat analysis showed that of the 134 patients assigned to continue therapy, 21 had recurrent venous thromboembolism (15.7 percent; average follow-up, 37.8 months), as did 21 of the

133 patients assigned to discontinue therapy (15.8 percent; average follow-up, 37.2 months), resulting in a relative risk of 0.99 (95 percent confidence interval, 0.57 to 1.73). The features of the recurrences are shown in Table 1. All episodes of recurrent venous thromboembolism were idiopathic, and none were fatal. The average time to recurrence was 11.2 months from randomization in the patients assigned to discontinue therapy and 16.0 months from randomization in those assigned to continue therapy. The cumulative hazard of recurrent venous thromboembolism in the two groups according to the intention-to-treat analysis is shown in Figure 1 (log-rank statistic = 0.02, P = 0.88). Of the 115 patients assigned to continue therapy who were included in the per-protocol analysis, 18 had a recurrence of venous thromboembolism (15.7 percent), as compared with 21 of the 126 patients assigned to discontinue therapy who were included in this analysis (16.7 percent), resulting in a

TABLE 1. RECURRENCES OF THROMBOEMBOLIC EVENTS ACCORDING TO TREATMENT GROUP.

TYPE OF EVENT	DISCONTINUATION OF ORAL ANTICOAGULANT (N=133)	CONTINUATION OF ORAL ANTICOAGULANT (N=134)
	no. of events	
Deep venous thrombosis		
Ipsilateral	7	4
Contralateral	11	10
Bilateral	0	2
Nonfatal pulmonary embolism	3	5
Total	21	21

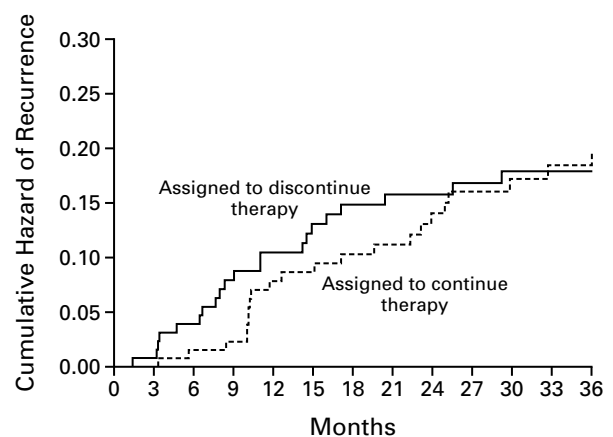


Figure 1. Cumulative Hazard of Recurrent Venous Thromboembolism in Patients Assigned to Discontinue Oral Anticoagulant Therapy and Those Assigned to Continue Oral Anticoagulant Therapy (Intention-to-Treat Population).

relative risk of 0.94 (95 percent confidence interval, 0.54 to 1.67).

An intention-to-treat analysis showed that the risk of recurrence during the first nine months of follow-up was lower among the patients assigned to continue therapy (4 patients; 3.0 percent; 4.6 percent per patient-year) than in those assigned to discontinue therapy (11 patients; 8.3 percent; 12.3 percent per patient-year; relative risk, as compared with patients assigned to discontinue therapy, 0.36; 95 percent confidence interval, 0.12 to 1.11). Three patients assigned to continue therapy who had recurrent thromboembolism during the initial nine-month study period had prematurely interrupted oral anticoagulant therapy (two voluntarily and one because of major bleeding). Thus, only one patient had a recurrence while receiving active oral anticoagulant therapy (0.7 percent; 1.2 percent per patient-year; relative risk as compared with patients assigned to discontinue therapy, 0.09; 95 percent confidence interval, 0.02 to 0.69; $P=0.003$).

The incidence of recurrence after the discontinuation of therapy was 5.1 percent per patient-year among the patients assigned to discontinue therapy (95 percent confidence interval, 3.2 to 7.5 percent; 21 events; average interval since discontinuation, 37.2 months) and 5.0 percent per patient-year in those assigned to continue therapy (95 percent confidence interval, 3.1 to 7.8 percent; 17 events; average interval since discontinuation, 29.4 months).

Bleeding Complications

Four patients (3.0 percent) assigned to continue therapy had nonfatal episodes of major bleeding while receiving oral anticoagulant therapy (melena in three patients and menorrhagia in one patient). None of these patients had an INR above the therapeutic range at the time of the episode. Two fatal episodes of bleeding occurred in patients assigned to discontinue therapy (1.5 percent) — one intracranial, 1 month after the discontinuation of oral anticoagulant therapy, and the other gastrointestinal, 12 months after discontinuation.

Deaths

Fourteen patients (5.2 percent) died during the study period. Seven patients assigned to discontinue therapy died — three from myocardial infarction, two from heart failure, one from intracranial bleeding, and one from gastrointestinal bleeding. Seven patients assigned to continue therapy died — three from myocardial infarction, three from cancer, and one from respiratory failure.

Cumulative Adverse Outcomes

A total of 28 patients assigned to discontinue therapy (21.1 percent) had at least one adverse outcome (a symptomatic, objectively confirmed recurrence of venous thromboembolism, major bleeding, or death),

TABLE 2. ADVERSE OUTCOMES ACCORDING TO TREATMENT GROUP.

OUTCOME	DISCONTINUATION OF ORAL ANTICOAGULANT (N=133)	CONTINUATION OF ORAL ANTICOAGULANT (N=134)
	no. of patients (%)	
Venous thromboembolism	21 (15.8)	21 (15.7)
Major bleeding	2 (1.5)	4 (3.0)
Death	7 (5.3)	7 (5.2)
At least one adverse event	28 (21.1)	31 (23.1)

as compared with 31 patients assigned to continue therapy (23.1 percent) (Table 2). No adverse events occurred in patients in whom therapy was extended or resumed after its scheduled interruption or in any of the four patients who declined to continue therapy after randomization.

DISCUSSION

Kearon et al.⁸ showed that the rate of recurrence of venous thromboembolism in patients with idiopathic deep venous thrombosis who were assigned to receive extended anticoagulant therapy was lower while they were receiving that therapy than the rate of recurrence in patients assigned to discontinue anticoagulant therapy. The results of our study show that the clinical benefit achieved during therapy when the three-month course of oral anticoagulant therapy is extended to one year is not maintained after the discontinuation of therapy. Approximately two thirds of the recurrences of thromboembolic events in both treatment groups occurred during the first year after the discontinuation of oral anticoagulant therapy. These findings suggest that prolonging anticoagulant therapy beyond three months in patients with idiopathic deep venous thrombosis simply delays recurrence until anticoagulant therapy is stopped, rather than reducing the risk of recurrence.

Despite the fact that patients with a high risk of bleeding were excluded from this study and that oral anticoagulant therapy was monitored closely, 3 percent of patients had major bleeding during the nine months of extended oral anticoagulant therapy, a percentage consistent with the rate of bleeding events in previous studies.^{5,8}

The results of this study apply only to patients with idiopathic deep venous thrombosis as defined by the study protocol. Patients with known permanent or temporary risk factors were excluded from this study, but systematic screening for thrombophilia and cancer was not performed. Our findings are likely to apply to the large majority of patients with a first episode of apparently spontaneous deep venous thrombosis, since

they are currently not systematically screened for occult cancer and thrombophilia. Differences in the definition of idiopathic venous thromboembolism and in the duration of anticoagulant therapy could help explain the differences between the outcome in our study and those in other studies.^{5,8}

As in some previous studies, all recurrent thromboembolic events were idiopathic,⁸ and more than half involved the initially unaffected leg.¹¹ The idiopathic nature of the recurrences suggests that these events could be prevented by continuous anticoagulant therapy, but not by intermittent prophylaxis limited to the times when temporary risk factors for deep vein thrombosis are present. The recurrences in the contralateral leg suggest that a persistent underlying hypercoagulable state, rather than residual anatomical changes, accounts for the high risk of recurrence in patients with idiopathic venous thrombosis who have stopped oral anticoagulant therapy.¹²

Our study was not a double-blind trial. However, its findings are likely to be valid, since a number of measures were taken to avoid bias. These were the enrollment of consecutive patients, central randomization, follow-up of all patients who underwent randomization, the central adjudication of all outcome events by a committee unaware of the treatment assignments, the assessment of recurrences of venous thromboembolism and bleeding events on the basis of predetermined objective criteria, and the inclusion in the study analysis of all patients randomly assigned to treatment groups.

With respect to the primary a priori hypothesis, this study shows that 15 percent of patients with presumed idiopathic proximal deep vein thrombosis will probably have a recurrence in the first two to three years after the discontinuation of anticoagulant therapy. We confirmed that during extended oral anticoagulant therapy, the rate of recurrence is negligible in patients who actually continue therapy. The administration of oral anticoagulants indefinitely could extend the initial benefit, but such therapy carries the risk of bleeding and is inconvenient. Anticoagulant therapy of indefinite duration could be made safer by reducing the doses of oral anticoagulants after an initial period of treatment with the full dose. The development of oral antithrombotic agents that have an improved safety profile and do not require laboratory monitoring

could certainly pave the way toward extending therapy indefinitely. Patients with presumed idiopathic deep vein thrombosis could be further categorized in order to identify those at high risk for recurrence after the discontinuation of anticoagulant therapy.

Studies assessing both the strategy of extending low-dose anticoagulant therapy indefinitely and that of improving risk stratification among patients with idiopathic venous thromboembolism have recently begun or been planned. The results of these studies will probably define the optimal long-term treatment for patients with idiopathic deep vein thrombosis.

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