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## THE DURATION OF ORAL ANTICOAGULANT THERAPY AFTER A SECOND EPISODE OF VENOUS THROMBOEMBOLISM

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### ABSTRACT

**Background** A consensus has not been reached about the optimal duration of oral anticoagulant therapy after a second episode of venous thromboembolism.

**Methods** In a multicenter trial, we compared six months of oral anticoagulant therapy with anticoagulant therapy continued indefinitely in patients who had had a second episode of venous thromboembolism. Of 227 patients enrolled, 111 were randomly assigned to six months of anticoagulation and 116 were assigned to receive anticoagulant therapy indefinitely; for both groups, the target international normalized ratio was 2.0 to 2.85. The initial episodes of deep-vein thrombosis (n=193) and pulmonary embolism (n=34), as well as recurrent episodes, were all objectively confirmed.

**Results** After four years of follow-up, there were 26 recurrences of venous thromboembolism that fulfilled the diagnostic criteria, 23 in the group assigned to six months of therapy (20.7 percent) and 3 in the group assigned to continuing therapy (2.6 percent). The relative risk of recurrence in the group assigned to six months of therapy, as compared with the group assigned to therapy of indefinite duration, was 8.0 (95 percent confidence interval, 2.5 to 25.9). There were 13 major hemorrhages, 3 in the six-month group (2.7 percent) and 10 in the indefinite-treatment group (8.6 percent). The relative risk of major hemorrhage in the six-month group, as compared with the indefinite-treatment group, was 0.3 (95 percent confidence interval, 0.1 to 1.1). There was no difference in mortality between the two groups.

**Conclusions** Prophylactic oral anticoagulation that was continued for an indefinite period after a second episode of venous thromboembolism was associated with a much lower rate of recurrence during four years of follow-up than treatment for six months. However, there was a trend toward a higher risk of major hemorrhage when anticoagulation was continued indefinitely. (N Engl J Med 1997;336:393-8.)

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ORAL anticoagulant therapy is routinely given to most patients who have had episodes of venous thromboembolism. Two recent multicenter trials have demonstrated that if the duration of treatment after a first episode of thromboembolism is extended to three to six months, instead of four to six weeks, the rate of recurrence can be reduced, especially among patients with permanent risk factors such as thromboembolism that was idiopathic in nature and venous insufficiency.<sup>1,2</sup> The optimal duration of secondary prophylaxis after a second episode of venous thromboembolism is unknown. In one study, patients were stratified according to whether the episode of venous thromboembolism was their first or second, but the number of patients with second episodes was small and no conclusions could be drawn.<sup>3</sup> In the absence of data, it has been assumed that the risk of recurrence is greater after a second episode than after a first. Sixty percent of Swedish hospitals recommend that patients with second episodes of venous thromboembolism receive oral anticoagulant

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\*The investigators and institutions participating in the Duration of Anticoagulation (DURAC II) Trial Study Group are listed in the Appendix.

therapy for three to six months or even longer; some centers recommend continuing therapy for more than two years.<sup>4</sup> It has also been suggested that oral anticoagulation be continued indefinitely after recurrent venous thromboembolism.<sup>5</sup>

We undertook this trial to compare six months of oral anticoagulant therapy after a second occurrence of deep-vein thrombosis or pulmonary embolism with the same treatment continued indefinitely. The end points were recurrent thromboembolism, major hemorrhagic complications, and death during four years of follow-up.

## METHODS

### Study Design

The portion of the Duration of Anticoagulation (DURAC) trial that we describe here was a randomized, open trial of anticoagulant therapy in patients with second episodes of venous thromboembolism, in which 16 medical centers in central Sweden participated. It was conducted in parallel with a study of anticoagulation after a first episode of venous thromboembolism,<sup>2</sup> and followed the same protocol except for the duration of treatment. Consecutive patients at least 15 years of age who had acute pulmonary embolism or deep-vein thrombosis in the leg, the iliac veins, or both were included.

The diagnostic procedures have been described previously.<sup>2</sup> Briefly, objective diagnosis based on the results of venography in the case of deep-vein thrombosis and on the results of angiography or the combination of chest radiography and ventilation-perfusion lung scanning in the case of pulmonary embolism was required. The exclusion criteria were identical to those in the study of patients with the first episode of venous thromboembolism.<sup>2</sup> Oral informed consent was obtained from all patients before enrollment.

Randomization, which was stratified only according to medical center, took place at the end of hospitalization and was performed centrally. A computer-generated allocation schedule was used to assign patients, in blocks of 10, to receive oral anticoagulant therapy either for six months or indefinitely; the duration of therapy was counted from the date when stable prothrombin times within the target range were achieved.

### Anticoagulant Therapy

The initial treatment of the venous thromboembolism consisted of unfractionated or low-molecular-weight heparin administered intravenously or subcutaneously for at least five days (until the prothrombin time had been within the target range for two days). If the treating physician thought it was indicated, thrombolytic therapy could be given at the start of the study. Patients with deep-vein thrombosis were provided with a graduated-compression stocking and instructed to wear it during the day for at least one year.

Oral anticoagulation with warfarin sodium or dicumarol was usually begun at the same time as heparin therapy; the target chosen for the international normalized ratio (INR) was 2.0 to 2.85, partly because a pilot study showed an excess of hemorrhagic complications when the INR exceeded that range.<sup>6</sup> The analysis of prothrombin times was performed as previously described,<sup>2</sup> with use of thromboplastin reagents with international sensitivity indexes of 0.86 to 1.00. When a stable prothrombin time within the target range had been achieved, the test was repeated weekly for the first three weeks and then at least once every four weeks. Oral anticoagulant therapy was discontinued after six months, without tapering, in the patients randomly assigned to six months of therapy, usually at the time of the six-month visit.

Before anticoagulant therapy was initiated, we obtained plasma

samples from patients who were less than 50 years old and those with a family history of venous thromboembolism for measurement of antithrombin, protein C, and protein S, as previously described.<sup>2</sup>

The patients were instructed to abstain from taking analgesic agents containing aspirin and, if antiinflammatory treatment was required, to use only ibuprofen. All the patients were informed about the symptoms of deep-vein thrombosis and pulmonary embolism. They were told to report immediately to the emergency room if any such symptoms occurred, and patients receiving oral anticoagulant therapy were also asked to report all hemorrhagic complications. Follow-up evaluations by one of the investigators or by a specially trained nurse or physiotherapist were scheduled for 1.5, 3, 6, 9, 12, 24, 36, and 48 months after randomization. At each visit, the patients were asked about new symptoms of venous thromboembolism and, if they were still receiving an anticoagulant drug, about possible hemorrhage. They were also reminded of the symptoms of deep-vein thrombosis and pulmonary embolism and reminded to come to the emergency room if such symptoms occurred and to report bleeding episodes.

### End Points

The principal end points of the study were major hemorrhage, recurrent venous thromboembolism, and death during the four-year period. Major hemorrhages were defined as episodes of bleeding that resulted in death or required hospitalization, treatment with blood products or vitamin K, or any combination of these outcomes.

Recurrent thromboembolic events were objectively verified by the same methods as the index events. In addition, to be considered confirmed, a recurrent deep-vein thrombosis had to be characterized by one of the following: thrombus in the contralateral leg; thrombus in another deep vein of the same leg as the original thrombus; or thrombus in the same vein as the original event, with proximal extension of at least 5 cm if the upper limit of the original thrombus had been visualized or, if the upper limit of the original thrombus had not been determined, the presence of a constant filling defect surrounded by contrast medium. Recurrent pulmonary embolism had to be confirmed by defects in previously perfused areas, unless another scan during the intervening period had shown resolution of the original defects. Fatal pulmonary embolism had to be confirmed by autopsy. Initial and subsequent venograms in patients with confirmed and unconfirmed recurrences of deep-vein thrombosis and lung scans in patients with pulmonary embolism were reviewed by an independent radiologist who was blinded to the patients' treatment assignments and the order of the examinations.

Patients who were lost to follow-up were repeatedly cross-checked against data in the national Death Registry; no deaths have been missed. Names were also checked against the registry of hospitalizations. The ascertainment of recurrences or major hemorrhages is almost certainly complete.

An independent safety committee reviewed the number of patients included and the number of major end points twice during the study. The committee was instructed to stop the study in case of a significant difference between the treatment groups in the rate of major hemorrhages.

### Statistical Analysis

For the calculation of the required number of patients in each treatment group, we assumed an annual rate of recurrence of 1 percent among patients receiving oral anticoagulation and 5 percent among those not receiving such treatment, or a cumulative incidence after four years of 4 percent and 18 percent, respectively. With an alpha error of 5 percent and a beta error of 20 percent (two-tailed), we needed 88 patients per group; since we estimated that 20 percent would be lost to follow-up, recruitment of 110 patients per group was required.

All statistical analyses were performed on an intention-to-treat basis, although some patients in both groups received oral anti-

coagulation for shorter or longer periods than called for in the protocol, and some were discovered after randomization to have cancer. For statistical analysis, we used Wilcoxon's rank-sum test and the log-rank test (the Lifetest procedure in the SAS software system) and Fisher's exact test for two groups. Patients were lost to follow-up for a total of 442 months (4 percent of the total); these person-months were accounted for in the log-rank test. The group in this study that was assigned to six months of therapy has also been compared with a group of patients in another portion of the DURAC trial who had a first episode of venous thromboembolism and were treated with oral anticoagulant drugs for six months.<sup>2</sup> The latter group has also completed four years of follow-up and was recruited during the same period. The protocols for these two groups have in all respects been identical. Ninety-five percent confidence intervals are shown for all results. The study was approved by the regional and local ethics committees.

RESULTS

Enrollment took place from April 12, 1988, through April 18, 1991; during this period, 227 patients were randomly assigned to treatment groups. Two patients assigned to indefinite anticoagulation had suspected congenital protein C deficiency, but because of the difficulties of confirming this diagnosis during treatment they were not withdrawn from the study. No congenital protein S or antithrombin deficiency was detected.

According to the logbooks, which were available from 12 of the 16 medical centers, corresponding to 84 percent of all patients (191 of 227), 63 percent of patients evaluated were enrolled (191 of 301). The patients from the centers with missing logbooks were equally divided between the two treatment groups. Five eligible patients were not enrolled because the investigators did not have time to enroll them.

Of the 227 patients recruited for the study, 111 were randomly assigned to six months of treatment and 116 to indefinite treatment. The treatment groups were similar at entry (Table 1). In the six-month group, 10 patients received treatment for a longer period than intended (1 to 42 months longer); as a result, the mean duration of anticoagulation was actually 7.7 months. In the group assigned to indefinite treatment, 26 patients had shorter periods of treatment (1 to 43 months shorter), resulting in a mean duration of treatment of 42.7 months during the 4 years of follow-up. The main cause for these deviations was a refusal by the patient to adhere to the protocol. The percentages of patients who complied with the instructions for the use of compression stockings were 95 percent in the six-month group and 94 percent in the indefinite-treatment group at 3 months; 82 percent and 77 percent, respectively, at 12 months; 55 percent and 43 percent at 24 months; and 38 percent and 37 percent at 48 months (there were no significant differences in these rates between the groups).

During the four years of follow-up, 26 patients died and 14 dropped out. The principal end points

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT ENROLLMENT, ACCORDING TO THE DURATION OF ASSIGNED TREATMENT.

CHARACTERISTIC	6 Mo (N=111)	INDEFINITE (N=116)
	mean ±SD	
Age (yr)	65.0±12.4	64.0±12.5
Years since previous thromboembolic event	8.1±11.8	6.4±7.2
	no. (%)	
Male sex	70 (63)	68 (59)
Type of index event		
Pulmonary embolism	17 (15)	17 (15)
Deep-vein thrombosis	94 (85)	99 (85)
Proximal thrombosis	68 (72)	65 (66)
Site of previous deep-vein thrombosis*		
Ipsilateral leg	54 (59)	45 (47)
Contralateral leg	37 (41)	50 (53)
Temporary risk factor†	22 (20)	21 (18)
Subsequent cancer	8 (7)	8 (7)
Family history of venous thromboembolism	24 (22)	22 (19)
Thrombolytic therapy	4 (4)	4 (3)
Therapy with low-molecular-weight heparin	3 (3)	8 (7)

\*Of the patients with deep-vein thrombosis as the index event, three in the six-month group and four in the indefinite-treatment group had previously had pulmonary embolism.

†Temporary risk factors were surgery, trauma, temporary immobilization, travel, the receipt of estrogen, infection, Baker's cyst, and pregnancy; permanent risk factors were idiopathic venous thromboembolism and venous insufficiency.

are shown in Table 2. There was no statistically significant difference in mortality between the two treatment groups. No cases of fatal pulmonary embolism could be confirmed, although it was suspected in a patient in the six-month group who died suddenly at 27 months.

There was a trend toward more major hemorrhages in the group assigned to indefinite anticoagulation. In the six-month group, only one of the three major hemorrhages occurred during anticoagulant therapy (an episode of vaginal bleeding, triggered by an occult cancer). The remaining two episodes, both of which were cerebral hemorrhages, occurred 14.5 and 18 months after the discontinuation of therapy; one was fatal. In the group receiving anticoagulation for an indefinite period, there were a fatal subarachnoid hemorrhage, a case of fatal hemorrhagic pancreatitis, an episode of severe epistaxis requiring hospitalization, three gastrointestinal hemorrhages (two of which required transfusions), two episodes of hematuria requiring hospitalization (one of which occurred after cystoscopy), a post-traumatic subcutaneous hematoma requiring hospitalization, and an episode of intraabdominal bleeding treated with transfusions. In five of the patients with hemorrhagic complications, the intensity of anticoagulation was greater than the target range at the time of admission (INR, 3.7 to 6.7). None of the patients with

hemorrhage received vitamin K alone without hospitalization.

The difference in the rate of recurrent venous thromboembolic events between the six-month group (20.7 percent; 95 percent confidence interval, 13.1 to 28.3 percent) and the group receiving therapy indefinitely (2.6 percent; 95 percent confidence interval, 1.1 to 4.1 percent) was significant ( $P < 0.001$ ) after four years of follow-up.

The cumulative probability of a recurrent event is shown in Figure 1. In the six-month group there was a progressive accumulation of recurrent events, dis-

tributed over the three and a half years after the discontinuation of anticoagulation. In the group assigned to indefinite anticoagulation, there were only three recurrent thromboembolic events (at months 26, 29, and 42), all of which occurred 1 to 10 months after the premature discontinuation of anticoagulant therapy. There was thus no recurrence during anticoagulant therapy in any group. One of the three events was fatal: a mesenteric-vein thrombosis, verified by laparotomy, in a patient with diabetes mellitus and cirrhosis of the liver, in whom the anticoagulant therapy was discontinued prematurely after 28 months, 1 month before the event occurred. The remaining recurrences consisted of eight cases of pulmonary embolism and eight cases of deep-vein thrombosis in the same leg as the index event and nine in the contralateral leg. None of the recurrences occurred in a high-risk situation (e.g., after surgery or while the patient was immobilized).

Three of the recurrences (all in the six-month group) were detected at a follow-up visit and the remainder when the patients came to the emergency room because they had new symptoms. In six patients in the six-month group and two in the group assigned to therapy of indefinite duration who came to the emergency room because of new symptoms, venograms or lung scans did not demonstrate a recurrence. Four additional patients (all in the six-month group) were hospitalized because of new symptoms and filling defects on the venogram (two patients) or perfusion defects on the lung scan (two patients). On subsequent review, these abnormalities did not meet the criteria for a recurrence, however, and they are not included in the statistical analysis. Sixty-two percent of the prothrombin times were within the target range for oral anticoagulant therapy (INR, 2.0 to 2.85).

The group assigned to six months of therapy in this study was also compared with a group of patients treated for the same length of time and according to the same protocol who had had only one episode of venous thromboembolism at the time of enrollment. The difference after three and four years of follow-up did not reach statistical significance, either by the chi-square test ( $P = 0.2$  for both time points) or by the log-rank test ( $P = 0.2$ ), which gives more weight to late events.

The patients with recurrences did not differ significantly from the rest with respect to age, sex, whether the index event was a pulmonary embolism or deep-vein thrombosis, whether the index thrombus was proximal or distal, whether the factor triggering the index thrombus was temporary or permanent, the length of time between the first thromboembolic event and the index episode, and the presence or absence of a family history of venous thromboembolism. The numbers in these subgroups were too small, however, for reliable analyses.

**TABLE 2.** FREQUENCY OF PRINCIPAL END POINTS AFTER FOUR YEARS, ACCORDING TO THE DURATION OF ASSIGNED TREATMENT.

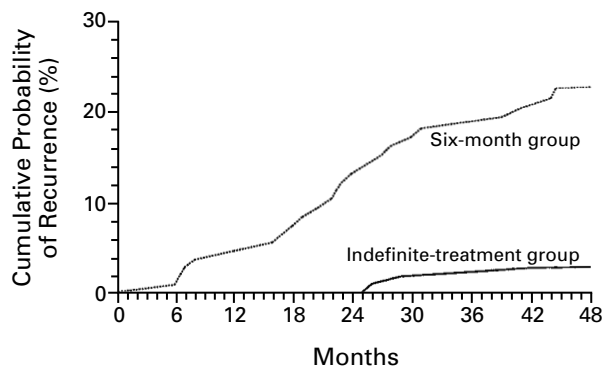
END POINT	6 Mo (N = 111) no. (%)	INDEFINITE (N = 116) no. (%)	RELATIVE RISK (95% CI)*	P VALUE
Major hemorrhage	3 (2.7)†	10 (8.6)	0.3 (0.1–1.1)	0.084
Recurrence	23 (20.7)	3 (2.6)‡	8.0 (2.5–25.9)	<0.001
In hospitals with logbooks§	21 (22.1)	3 (3.1)	7.1 (2.2–22.9)	<0.001
Death	16 (14.4)	10 (8.6)	1.7 (0.8–3.5)	0.21

\*Relative risks are expressed as the ratio of the number of patients with the specified end point to the total number of patients in the six-month group, divided by the corresponding ratio in the indefinite-treatment group. CI denotes confidence interval.

†Two of the hemorrhages occurred after the discontinuation of oral anticoagulation.

‡All recurrences in this group occurred after the premature discontinuation of anticoagulation.

§There were 95 patients in the six-month group and 96 in the indefinite-treatment group at these 12 hospitals.



**Figure 1.** Cumulative Probability of Recurrent Venous Thromboembolism in Patients with a Second Episode, According to the Duration of Assigned Anticoagulant Therapy.

## DISCUSSION

Because little is known about anticoagulant therapy in patients with second episodes of venous thromboembolism, we studied such patients in a separate trial. The demonstration of a difference or equivalence in outcome between two groups of such patients after random assignment to different, limited periods of anticoagulation — for example, six months as compared with one year — would require many more patients than were included in this trial. Although long-term anticoagulation has been recommended after recurrent venous thromboembolism,<sup>5</sup> there is a justified fear that major hemorrhagic complications will result. With an intensity of anticoagulation corresponding to an INR of 2.0 to 3.0, the incidence of major or fatal bleeding is 0.6 to 0.7 percent per month.<sup>1,7</sup> With the target intensity used in our trial (INR, 2.0 to 2.85), six major hemorrhages occurred in patients who had had a first episode of venous thromboembolism during 3399 person-months (incidence, 0.18 percent per month).<sup>2</sup> In the present study the actual total duration of anticoagulation during four years of follow-up was 5561 person-months; there were 11 major hemorrhages during treatment, for a monthly incidence of 0.20 percent. Any comparison with the results of previous studies must be made with great caution, because of slight differences in the definitions of major hemorrhage. When we took into account the serious hemorrhages, which occurred even without anticoagulation, the difference in the incidence of major hemorrhages between the two study groups amounted only to a statistical trend. There is also a possibility of bias resulting from underestimation of the incidence of hemorrhage in the six-month group, since these patients were not actively questioned about hemorrhages after the discontinuation of anticoagulant therapy.

The risk of recurrent thromboembolism was, on the other hand, significantly reduced when the oral anticoagulant therapy was continued indefinitely. We tried to minimize the risk of bias due to the unblinded study design by having the venograms and lung scans reviewed by an independent, blinded radiologist. Furthermore, all but three of the recurrences were detected by physicians who were not involved in the study, and the number of negative examinations of possible recurrences was small in both groups, indicating that there was probably no tendency to overdiagnose recurrences in the six-month group. Except for the effects of any remaining bias, the intensity of anticoagulation we used (target INR, 2.0 to 2.85) proved effective, since no patient actually receiving anticoagulant therapy had a confirmed recurrence. Our results therefore suggest that long-term secondary prophylaxis is effective in patients with recurrent venous thromboembolism and that it does not entail a high risk of hemorrhagic complications.

Nonetheless, the occurrence of hemorrhages in patients receiving anticoagulant therapy cannot be disregarded. Our results indicate that if 100 patients were treated indefinitely instead of for only six months, 0.43 episode of recurrent thromboembolism would be averted per month, at a cost of 0.20 major hemorrhage per month (albeit not caused exclusively by anticoagulant therapy). It would thus be of value to investigate whether a reduction in the intensity of anticoagulation — to a target INR of 1.5 to 2.0 after, for example, one year — could eliminate the risk of bleeding while still offering the same protective effect.

Our results do not indicate which subgroups of patients may have a special need for prolonged anticoagulation, partly because of the limited numbers of patients in the study. It is possible that most patients who have second thromboembolic episodes are at such a high risk for further recurrences that a division into subgroups would yield little information. We were unable to demonstrate an increased risk of recurrence after a second episode, as compared with the risk after a first episode, among patients treated for six months according to identical protocols. This failure may reflect an insufficient number of patients with second thromboembolic episodes, or it may mean that no difference exists.

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## APPENDIX

The DURAC II Trial Study Group consisted of the following investigators: *Danderyd Hospital, Danderyd* — A. Carlsson, C. Gustafsson, and A. Gröndahl; *Huddinge Hospital, Huddinge* — A.-S. Rhedin, E. Törnebohm, M. Holmström, and D. Lockner; *Karolinska Hospital, Stockholm* — S. Schulman, P. Lindmarker, and H. Johnsson; *Köping Hospital, Köping* — P. Nicol, J. Kobosko, B. Malmros, N. Arcini, and J. Saaw; *Nacka Hospital, Stockholm* — E. Loogna and R. Stig; *Norrköping Hospital, Norrtälje* — S. Viering; *Nyköping Hospital, Nyköping* — B. Ljungberg, S. Wilhelmsson, and Å. Ohlsson; *Sabbatsberg Hospital, Stockholm* — H. Walter, K. Malmqvist, and F. Al-Khalili; *St. Göran Hospital, Stockholm* — B. Leijd and A. Petrescu; *Södersjukhuset, Stockholm* — J. Brohult, G. Lärffars, and J. Hulting; *Södertälje Hospital, Södertälje* — S.-G. Eklund, E. Svensson, and L. Dahlin; *Uppsala Academic Hospital, Uppsala* — J. Boberg; *Västerås Central Hospital, Västerås* — S. Nordlander and B. Marjanovics; *Örebro Regional Hospital, Örebro* — O. Linder; *Linköping Regional Hospital, Linköping* — K.-Å. Jönsson and C. Malm; *Lidköping Hospital, Lidköping* — M. Hjorth and A. Lindgren; *Safety Committee* — B. Fagrell, Karolinska Hospital, and M. Kallner, Löwenströmska Hospital; *Radiologic Assessment* — S. Granqvist, Ersta Hospital; *Steering Committee* — J. Boberg, J. Brohult, S.-G. Eklund, B. Fagrell, H. Johnsson, B. Ljungberg, D. Lockner, P. Nicol,

S. Schulman (chair and coordinator), S. Wilhelmsson, and B. Wadman, Örebro Regional Hospital; *Statistical Analysis* — M. Snyder, Tadiran Information Systems, Givat Shmuel, Israel.

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