

## WARFARIN SODIUM VERSUS LOW-DOSE HEPARIN IN THE LONG-TERM TREATMENT OF VENOUS THROMBOSIS

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**Abstract** Acute deep-vein thrombosis is usually treated with intravenous heparin for a number of days, then with oral anticoagulants for weeks to months. We have compared adjusted-dose warfarin sodium with fixed low-dose subcutaneous heparin in the prevention of recurrent deep-vein thrombosis. Sixty-eight patients with acute deep-vein thrombosis confirmed by venography were treated with intravenous heparin and then randomized to secondary prophylaxis. Nine of 35 patients receiving subcutaneous heparin, but none of 33 receiving warfarin sodi-

um, had new episodes of objectively documented venous thromboembolism ( $P = 0.001$ ). Seven patients on warfarin sodium experienced bleeding complications (of which four were major), as compared with no patients receiving subcutaneous heparin ( $P < 0.005$ ). Thus, adjusted-dose warfarin sodium is more effective than low-dose subcutaneous heparin in preventing recurrent venous thromboembolism, but its use is accompanied by a significant risk of bleeding. (N Engl J Med 301:855-858, 1979)

HEPARIN is generally accepted as the initial treatment of choice for patients with acute venous thromboembolism. It is common practice to follow the initial course of heparin treatment with oral anticoagulant therapy to prevent delayed recurrence of venous thromboembolism. The evidence that oral anticoagulants are effective for this purpose is limited to one retrospective study<sup>1</sup> in which it was reported that the frequency of recurrence was lower in patients treated with oral anticoagulants than in a group receiving no treatment. However, since both the initial diagnosis of venous thrombosis and the diagnosis of recurrent thrombosis were based on clinical criteria and the patients were not randomized, only limited conclusions can be drawn from this study.

It would be desirable to obtain more definitive information about the value of oral anticoagulant drugs in the prevention of recurrent venous thromboembolism, since their use is associated with bleeding complications in 5 to 10 per cent of patients.<sup>2</sup> In addition, an alternative form of secondary prevention with a lower risk of bleeding would be attractive if it was effective in preventing recurrent venous thromboembolism. Low-dose subcutaneous heparin has proved to be effective in the primary prevention of venous thromboembolism in a number of well defined high-risk groups without inducing major bleeding,<sup>3</sup> and this approach was therefore compared with oral anticoagulant therapy for the secondary prevention of venous thromboembolism. Our study sought to establish the relative effectiveness and safety of these treatments in patients with acute venous thrombosis.

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### METHODS

#### Patients

We studied consecutive patients with venographically demonstrated acute deep-vein thrombosis. Venography was performed because deep-vein thrombosis was suspected or because <sup>125</sup>I-fibrinogen leg scanning or impedance plethysmography (IPG) was positive in patients who were being screened postoperatively. Venography was performed by the method of Rabinov and Paulin,<sup>4</sup> using diagnostic criteria previously described.<sup>5</sup>

Patients were excluded if they were pregnant, had active peptic ulcer disease, had a history of allergy to the dye used in venography or could not be followed as outpatients because of geographic inaccessibility; all exclusions were documented. Patients were stratified according to the site of thrombosis (proximal-vein thrombosis or calf only) and according to history of previous venous thromboembolism.

#### Regimens

All patients were treated for 14 days with continuous intravenous heparin that was adjusted to maintain the activated partial thromboplastin time at 1½ to two times the normal control. Informed consent was obtained, and the patients were allocated at random on Day 10 (by use of a system of sealed envelopes) to receive either warfarin sodium or low-dose heparin. Warfarin sodium treatment began four days before stopping heparin in an initial dose of 10 mg per day. To avoid intervention by study physicians who might keep the warfarin sodium patients under closer supervision, anticoagulant control was monitored weekly with Simplastin (General Diagnostics) by each patient's family physician, who agreed to adjust the warfarin sodium dose to maintain the prothrombin time at 1½ to two times the control value. Fixed, low-dose subcutaneous heparin was begun on Day 14 at a dose of 5000 units every 12 hours. The initial injections were carried out by the nursing staff and then by the patients under direct supervision. Upon discharge from hospital, patients were given a three- to six-week supply of heparin, which was subsequently administered either by the patients themselves or by visiting nurses in the occasional patient who was unable to measure accurately the heparin dose.

Treatment with either warfarin sodium or low-dose heparin continued for 12 weeks in patients who had proximal-vein thrombosis and for six weeks in patients who had calf-vein thrombosis. To avoid contamination, aspirin-containing drugs, sulfipyrazone and dipyridamole were prohibited during the period of trial.

## Compliance

Compliance in patients randomized to warfarin sodium was monitored by the family physicians, who measured prothrombin times weekly. Compliance in patients randomized to heparin was monitored by checking the hospital chart and, after discharge, by heparin vial counts performed at follow-up visits.

## Follow-up

All patients were seen routinely at periodic intervals after randomization and were instructed to report at once if symptoms or signs suggestive of recurrent deep-vein thrombosis, pulmonary embolism or bleeding developed.

All patients with proximal deep-vein thrombosis were seen at a special clinic at three, six and 12 weeks after randomization; patients with calf thrombosis only were seen at three and six weeks. At these visits patients were examined, underwent impedance plethysmography, were injected with  $^{125}\text{I}$ -fibrinogen and scanned 72 hours later. The criteria for positive IPGs and leg scans have been previously described.<sup>6,7</sup>

Venography was performed if either a previously normal IPG became abnormal or a leg scan was positive. To avoid the possibility of bias due to diagnostic suspicion<sup>8</sup> (in which a knowledge of the patient's treatment might influence the intensity of the search for recurrent deep-vein thrombosis) it was decided at the outset to perform venography during routine follow-up only in patients who had positive results with one or both of the screening tests (IPG or leg scan).

Patients were told to report immediately to the clinic if they experienced pain, swelling or discomfort in the leg; venography was performed in all these patients either 72 hours after the injection of  $^{125}\text{I}$ -fibrinogen or earlier if the leg scan or IPG results became abnormal.

## End Points

A diagnosis of recurrent venous thrombosis was made if a constant new intraluminal filling defect was seen in the deep veins at a site not previously involved on the initial venogram. (In the single case in which venography was unsuccessful, the diagnosis was made on the basis of a positive leg scan and the absence of any factor known to cause a falsely positive scan.)

Patients were also instructed to report to the clinic at once if the symptoms of pulmonary embolism developed. Perfusion and ventilation lung scanning was performed routinely on Day 14 before discontinuing intravenous heparin and repeated at the conclusion of secondary prophylaxis (or earlier if pulmonary embolism was suspected). The diagnosis of pulmonary embolism required the presence of a new segmental or lobar defect on perfusion lung scanning in the presence of a normal ventilation scan.

Patients were told to report any bleeding immediately and were also questioned about bleeding at each routine follow-up. Bleeding was classified as major if it was overt and associated with a fall in hemoglobin level of 2 g per deciliter (20 g per liter) or more; or required transfusion of two or more units of blood; if it was retroperitoneal; if it occurred into a major prosthetic joint; or if it was intracranial. Bleeding was defined as minor if it was overt and did not meet the criteria for major bleeding.

Skin bruising was not included as a bleeding complication unless it led to the discontinuation of therapy or withdrawal of the patient from the study.

## Interpretation of Diagnostic Tests

In view of the nature of the treatments, it was not possible to use a double-blind design for the study. To avoid bias due to diagnostic suspicion,<sup>8</sup> the diagnostic tests were interpreted independently without knowledge of other results or of the group to which the patients were randomized.

## Post-study Surveillance

All patients had impedance plethysmography performed three months after stopping secondary prophylaxis and then were kept

under surveillance for an additional time averaging four months. Information was obtained on any hospital admissions for venous thromboembolism, and, in patients who died, the cause of death was documented.

The results were analyzed by use of Fisher's exact test.

## RESULTS

Seventy-four consecutive patients were eligible for entry. Six were excluded before randomization (five of these were geographically inaccessible, and one had a documented gastric ulcer that had bled during the initial course of heparin therapy). Twenty-four had clinically suspected deep-vein thrombosis and 44 had deep-vein thrombosis detected during screening. Thirty-three patients were randomized into the warfarin sodium group and 35 into the subcutaneous heparin group. The groups were comparable (Table 1). All 68 patients were followed up during the study period. During the post-study surveillance period, which lasted an average of seven months, one patient in the group receiving subcutaneous heparin was lost to follow-up.

### Recurrent Venous Thromboembolism

Nine of 35 patients who received subcutaneous heparin (but none of 33 patients on warfarin sodium) had a new episode of venous thromboembolism that was confirmed by objective tests ( $P = 0.001$ ). All nine patients who had recurrent venous thromboembolism had entered the study with proximal-vein thrombosis. Thus, the recurrence rate in the 19 patients with proximal-vein thrombosis who received low-dose heparin was 47 per cent, as compared with no recurrences among 17 patients on warfarin sodium who had entered with proximal-vein thrombosis ( $P < 0.001$ ). No patients in either group who had entered the trial with calf-vein thrombosis experi-

Table 1. Comparability of the Two Groups of Patients.

	SUBCUTANEOUS HEPARIN GROUP (35 PATIENTS)	WARFARIN SODIUM GROUP (33 PATIENTS)
Site of deep-vein thrombosis at entry into study		
Proximal vein	19	17
Calf vein only	16	16
Status on entry		
Deep-vein thrombosis suspected clinically	12	12
Deep-vein thrombosis detected by screening high-risk patients	23	21
Age (<60 yr: ≥60 yr)	11:24	9:24
Sex (M:F)	13:22	16:17
History of previous deep-vein thrombosis	7	5
Hip operation	10	12
Knee operation	9	10
Other operations	5	4
Idiopathic deep-vein thrombosis	5	4
Congestive heart failure	3	4
Cancer	6	7
Paralysis of leg	3	4

enced recurrent venous thromboembolism during the course of the trial. Four of the nine patients who had recurrent thromboembolism during treatment with subcutaneous heparin did so within the first week of treatment, and all but one did so within the first three weeks. Six of the nine patients with recurrent deep-vein thrombosis were still in the hospital at the time of recurrence and had their heparin administered by the nursing staff. Review of the nurses' notes verified that five of the six had received heparin exactly as prescribed and that one had refused an injection on two occasions. The other three were outpatients at the time of recurrence, and a check of their vial counts indicated that they had apparently adhered to their prophylactic regimens. A 10th patient in the subcutaneous heparin group had treatment stopped in error after two weeks of prophylaxis; one week later the patient experienced pleuritic chest pain and had radiologic and lung-scan evidence of pulmonary infarction.

Eight of the nine patients in the subcutaneous heparin group who had recurrent thromboembolism while on therapy had venous thrombosis — the one other patient had symptomatic recurrent pulmonary embolism. A new constant intraluminal filling defect was found by venography in seven of these eight patients, and a positive leg scan was obtained in the calf and thigh in the other patient in whom venography was unsuccessful. Three of the eight patients with recurrent venous thrombosis were identified at routine follow-up because of a positive screening test. All three had a positive leg scan and one also had an abnormal IPG (it had been normal at the previous visit). The other five patients came to the clinic because of acute symptoms or signs of venous thrombosis, and all had either a positive leg scan or a positive IPG result that had been normal at the previous visit. One of these patients had a positive leg scan and an abnormal IPG in the previously uninvolved leg, two had positive IPGs, which had been abnormal at the initial diagnosis and had returned to normal at the previous visit, and the other two had positive scans in the previously involved leg. Two additional patients in the subcutaneous heparin group had a new positive leg scan over an inflamed knee joint at a routine visit. Both had active rheumatoid arthritis, and venography failed to confirm the presence of recurrent venous thrombosis.

The one patient in whom symptomatic pulmonary embolism developed during therapy had a new segmental perfusion defect that ventilated normally. On routine ventilation and perfusion lung scanning at the end of the study, one additional patient in the subcutaneous heparin group had a new lung-scan abnormality. This defect was probably not a pulmonary embolism since it was nonsegmental and the defect on perfusion scan was accompanied by an identical defect on ventilation scan with a normal chest x-ray. No patient in the warfarin sodium group showed a new defect on lung scanning.

### Bleeding Complications

Hemorrhagic complications occurred in seven of the 33 patients who received warfarin sodium therapy and in none of those on low-dose heparin ( $P < 0.005$ ). Four of the hemorrhagic complications were major ( $P = 0.05$ ); all four patients showed a sudden fall in hemoglobin concentration in excess of 2 g per deciliter (20 g per liter) and required transfusion of more than two units of blood. Two of these patients were paraplegics, and extensive hematomas of the thigh developed in both; one of the other two patients suffered severe hemarthrosis seven days after a major operation on the knee, and one had melena due to an occult carcinoma of the colon. The three patients with minor bleeding all had microscopic hematuria, and renal colic developed in one owing to ureteric obstruction by blood clot. In all patients with major bleeding and in two of the three with minor bleeding, the prothrombin time was between 1½ and two times the control value three days or less before bleeding and at the time of bleeding. The remaining patient with minor bleeding and clot colic had a prothrombin time that was more than three times the control value.

### Death during Secondary Prophylaxis

Three patients died during secondary prophylaxis. Two were on warfarin sodium; one died from an acute myocardial infarct (proved by autopsy), and the other from a massive cerebrovascular accident due to a cerebral infarct (coroner's report) that resulted in hemiplegia and death within 48 hours. The third patient was on subcutaneous heparin and died in terminal renal failure associated with disseminated cancer.

### Post-study Surveillance Period

One patient with proximal deep-vein thrombosis at entry had pain and swelling one week after discontinuing 12 weeks of subcutaneous heparin. Leg scanning and venography confirmed the presence of a new intraluminal filling defect. This patient died 12 months later, and autopsy confirmed a massive pulmonary embolism and disseminated cancer.

Two patients with proximal deep-vein thrombosis on entry had documented recurrences of venous thromboembolism after prematurely stopping warfarin sodium at seven weeks on account of bleeding. One, a paraplegic, suffered a pulmonary embolism (confirmed by ventilation and perfusion lung scanning) two months after oral anticoagulants had been stopped. The other, who was bedridden, died from pulmonary embolism two months after prematurely discontinuing warfarin sodium therapy; this patient's pulmonary embolism was established by autopsy. A third patient randomized to warfarin sodium was admitted to another hospital with an unconfirmed clinical diagnosis of recurrent deep-vein thrombosis nine months after stopping three months' warfarin sodium.

Thus, in the combined study period and post-study surveillance period there were 10 confirmed thromboembolisms in the subcutaneous heparin group and two in the warfarin sodium group ( $P < 0.02$ ).

### DISCUSSION

This randomized trial has shown that warfarin sodium therapy, given in doses adjusted according to the prothrombin time, is more effective than subcutaneous heparin given in fixed low doses in preventing recurrent venous thromboembolism. But this increased effectiveness is accompanied by an increased risk of bleeding. Before accepting these findings, it is important to consider whether the observed outcome could be explained by bias, particularly since the trial was not double blind.

The patients in the two groups were at comparable risk for recurrent deep-vein thrombosis at the start of the trial, confirming the absence of biased allocation. Biased determination of recurrent venous thromboembolism was avoided by performing, in all study patients, a repeated series of screening tests for venous thrombosis. Venography was repeated only if the screening tests were positive at the time of routine follow-up or if patients presented at an unscheduled time on an emergency basis with recurrent symptoms of deep-vein thrombosis. Bias due to diagnostic suspicion was further avoided by ensuring that the results of screening tests and the venograms were interpreted independently of each other and without knowledge of the group to which the patients had been randomized. In all cases, the evidence for extension or recurrence was clear-cut and agreed upon by three independent observers. Excessively close supervision of patients receiving warfarin sodium was avoided because anticoagulant monitoring was done by the primary physician; thus patients receiving warfarin sodium attended the special clinic with the same frequency as those on subcutaneous heparin. Our results, therefore, cannot be explained by invoking bias.

Recurrent thromboembolism occurred only in patients with proximal-vein thrombosis at entry, suggesting that these patients were both at high risk of recurrent venous thromboembolism and highly responsive to warfarin sodium. Recurrent venous thrombosis did not occur in either group with calf-vein thrombosis, suggesting that the risk of recurrence in these patients is lower than that in patients with proximal-vein thrombosis. There was a relatively low frequency of recurrent venous thrombosis after anticoagulant therapy was stopped, suggesting that patients with proximal-vein thrombosis do not need to be treated with oral anticoagulants for more than

three months and that patients with calf-vein thrombosis do not require anticoagulant therapy for more than six weeks. The three patients who had recurrent venous thromboembolism after they stopped taking anticoagulants all had continuing risk factors.

The specificity of clinical diagnosis of recurrence was surprisingly high, considering its relatively low specificity in patients presenting for the first time with features of venous thrombosis. However, all five patients who were seen at an emergency visit had florid symptoms and signs, which made the diagnosis much clearer.

Six of the seven patients who bled during warfarin sodium treatment did so when the prothrombin time was not prolonged beyond the drug's therapeutic range. Furthermore, all four patients with major bleeding had predisposing causes. One had recently undergone surgery, two had sustained trauma to an insensitive paralyzed limb, and one had an occult carcinoma. The frequency of recurrent thromboembolism in patients on low-dose heparin was high, and the results clearly indicate that, when used in this way, heparin is an unacceptable form of prophylaxis in patients with prior proximal-vein thrombosis.

Although adjusted-dose warfarin sodium prevented recurrence, its effectiveness was counterbalanced to some degree by the frequency of bleeding associated with its use. It is possible that subcutaneous heparin in higher doses or oral anticoagulants in lower doses than those used in this trial might also be effective in preventing venous thromboembolism without producing the same high risk of bleeding. These possibilities are currently being investigated.

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