Anticoagulation period in idiopathic venous thromboembolism

How long is enough?

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ABSTRACT

Objective: The period of anticoagulation of a first episode of idiopathic venous thromboembolism has been 6 months. It is unclear if such patients would benefit from longer treatment, as there appears to be an increased risk of recurrence after anticoagulation is stopped.

Methods: In a randomized prospective study of 64 patients admitted to King Hussein Medical city, Amman, Jordan, who developed a first episode of venous thromboembolism, 32 patients were given warfarin for 24-months, while 32 patients stopped anticoagulation after completion of 6-months of therapy. Our goal was to determine the effects of extended anticoagulation on rates of recurrence of symptomatic venous thromboembolism and bleeding. The patients were followed for 12-months after stopping anticoagulation

Results: After 24-months, 7 of the 32 patients (21%) who had standard anticoagulation for 6-months had a recurrent episode of thromboembolism compared to one of the 32 patients who received anticoagulation for 24 months (3%). Extended warfarin therapy for 24-months has resulted in an absolute risk reduction of 0.1% ($p<0.05$). This translates into 8 patients having to be treated for 24-months to avoid one recurrence without increasing the risk of major bleeding. Two patients in each group (6%) had major nonfatal bleeding, all 4 bleeding episodes occurring within the first 3-months of anticoagulation. After 36-months of follow up, the recurrence rate of extended warfarin therapy was only 3 patients (9%), which is a 43% relative reduction in recurrence of thromboembolism compared to standard therapy for 6-months.

Conclusion: Patients with first episodes of idiopathic venous thromboembolism have an increased risk of recurrent venous thromboembolism and should be treated with oral anticoagulants for longer than 6-months, probably 24-months.

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When a patient develops an acute episode of venous thromboembolism, whether it is a deep vein thrombosis or a pulmonary embolism, the patient is usually given unfractionated heparin or low molecular heparin for 5-days as well as warfarin therapy for 6-months.[1] Subgroup analysis of the results of a number of recent studies suggests that after anticoagulation is stopped, the risk of recurrent venous thromboembolism is greater among patients who have a persistent risk factor for thromboembolism (such as previously known thrombophilia) and those whose initial episode of thrombosis has no apparent risk factor than among those patients with a known transient risk factor such as immobilization or surgery.[2-5] Based on these observations, a hypothesis was made that patients with an idiopathic venous thromboembolism would benefit from an extended

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period of anticoagulation therapy longer than 6-months. To evaluate this hypothesis, we performed a randomized prospective study of patients admitted to a tertiary care center with the diagnosis of idiopathic venous thromboembolism and after heparin therapy was then given warfarin for a standard 6-month period or an extended period of 24-months keeping the International Normal Ratio (INR) within the 2.0-3.0 range.

Methods. ***Patient selection.*** Consecutive patients admitted to King Hussein Medical Center, Amman, Jordan and were being followed by the Internal Medicine team A who presented with a first time diagnosis of idiopathic venous thromboembolism from July 1998 through to December 2001 were included in this trial. Idiopathic venous thromboembolism was defined as a symptomatic proximal deep vein thrombosis proven objectively by a doppler flow ultrasonography carried out by an experienced radiologist or a pulmonary embolism proven objectively by spiral chest computerized tomography (CT) scan with intravenous contrast. Risk factors that precluded classification of the episode as idiopathic included fracture or plaster casting of the lower limb, bed confinement for more than 3 days, pregnancy, surgery requiring general anaesthesia, each within a period of 3-months prior to the episode of venous thromboembolism, a known history of thrombophilia (deficiency of protein C, Protein S or antithrombin, the presence of factor V Leiden, anticardiolipin antibodies or lupus anticoagulant), a diagnosis of cancer in the last 5-years. Patients who met these criteria and had no other reason for long-term anticoagulation and had no contraindications for warfarin therapy and were felt to be able to understand the need for compliance with therapy and regular blood tests were included in this trial.

Randomization and treatment protocol. After the patients signed a written consent form, randomization was performed with stratification according to age in decades, sex, smoking history and evidence of pulmonary embolism on presentation using a computer algorithm with a randomly determined block size of 2 or 4 within each stratum. This generated lists in which patients were assigned to either standard warfarin therapy of 6-months or extended warfarin therapy of 24-months. The patients were all initially given unfractionated intravenous heparin to keep the activated partial thromboplastin time 2.5 times the normal level (between 60-90 seconds) or were given low-molecular-weight heparin, for 5-days. Warfarin was started on the first day of therapy and continued for the designated period according to the randomized group. The INR was monitored monthly once the INR was stable between 2.0-3.0 for 2 consecutive weeks on the same dose. The INR was also checked if the patient became ill or was prescribed any new medication. If the INR became out of the required range then the patient would be followed at least weekly until the INR became stable again for 2 consecutive weeks on the same dose. After the first 6 months, the control group was asked to stop taking warfarin and the study group was continued on the same protocol for another 18 months. During that 24-month period, the patients of both groups were asked to report immediately any symptoms that were suggestive of deep vein thrombosis or pulmonary embolism. Any leg pain or swelling suggestive of possible deep vein thrombosis were then evaluated with doppler ultrasonography of the lower limbs, and an enzyme immunoabsorbent assay (ELISA) D-dimer test and if there were any dyspnea, cough, dizziness or chest pain suggestive of possible pulmonary embolism. The patient would undergo arterial blood gas analysis and an ELISA D-dimer test and if positive or there is evidence of new hypoxemia then a spiral CT scan of the chest with intravenous contrast would be carried out. Bleeding was defined as major if it was clinically obvious and associated with either a fall in the hemoglobin of at least 2 gldL or a need for the transfusion of at least 2 units of red blood cells, or if it was intracranial or retroperitoneal bleeding. The patients in each group were followed up after stopping treatment with 4-monthly appointments for 12-months.

Table 1 - Base-line characteristics of patients according to treatment group.

Characteristics	Warfarin for 6-months (N=32)	Warfarin for 6-months (N=32)	Total (N=64)
Age - years	42 ± 14	41 ± 15	**42 ± 15**
Male sex	18/32	20/32	**38/64**
Smoking history	14/32	16/32	**30/64**
Initial presentation of pulmonary embolism	10/32	8/32	**18/64**

Results. The recruitment of patients began in July 1998 and was stopped in December 2001. A total of 92 patients met the inclusion criteria at the time of the diagnosis. Out of those, 28 patients also met the exclusion criteria. The causes for the exclusion of patients were inability to make follow up appointments due to geographic inaccessibility (11 patients), a previous diagnosis of thrombophilia, recent surgery or cancer (9 patients) and lack of

compliance with the medication dose or blood tests (8 patients). Sixty-four patients were finally randomized to the 2 treatment protocols. The baseline characteristics are listed in **Table 1**. There were no statistically significant differences between the 2 groups.

Recurrence of thromboembolism. There were no deaths in either treatment groups. Of the 32 patients assigned to the first group who took warfarin for 6 months, 7 patients (22%) had recurrence of thromboembolism. None of these patients had recurrence during their treatment, but 5 patients had recurrence of deep vein thrombosis (4 patients) and nonfatal pulmonary embolism (one patient) within 6 months of stopping warfarin. Two more patients had recurrence after 6-months of stopping warfarin, one with deep vein thrombosis and one with nonfatal pulmonary embolism. The second group had only one recurrence of pulmonary embolism (3%) that occurred 8-months from starting warfarin. At the time, the INR on presentation was 1.8 as the patient had missed a couple of doses due to traveling unexpectedly without his pills. When comparing the different rates of recurrence of our 2 groups of patients, the absolute risk reduction of 0.1-% using extended warfarin therapy was statistically significant ($p<0.05$). This translate into number need to treat (NNT) of 8, such as 8 patients would have to be treated for 24 months to avoid one recurrence. After stopping the extended warfarin therapy 2 more patients developed recurrent deep vein thrombosis. After a 3-year follow up from starting warfarin therapy the risk of recurrence for extended warfarin therapy was only 9% (3 patients) compared to 22% (7 patients) after the standard 6-months warfarin therapy. This implies that after 36-months there would be a 43 percent relative reduction of recurrence by extending warfarin therapy to 24-months. The odds ratio for extending therapy was 0.115. All episodes of thromboembolism recurrences were also idiopathic.

Bleeding complications. There were 2 major nonfatal bleeding in each group (6%). All 4 episodes of bleeding happened within the first 3 months of warfarin therapy. The INR at the time of presentation of the 3 gastrointestinal bleeding episodes were 3.8, 4.2 and 8.1. In the study group one episode of hematuria occurred at an INR of 8.4. None of the bleeding episodes were fatal.

Discussion. This study demonstrates that patients with a first episode of idiopathic venous thromboembolism have a high rate of recurrence despite anticoagulation for 6-months. These patients were initially anticoagulated for 6-weeks or less but studies have shown that idiopathic venous thromboembolism had a high rate of recurrence with short periods of anticoagulation.[2-5] Consequently, it was recommended to anticoagulate these patients routinely for 6-months. What was not delineated was that the recurrence risk could be made even lower with anticoagulation that extends beyond the 6-month period. The LAFIT study[6] concluded that patients with idiopathic venous thromboembolism should be treated for longer than 3-months but it could not say how much longer that 3-months was required. In the trial by Agnelli et al,[7] 267 patients with a first episode of idiopathic venous thromboembolism who completed 3-months of anticoagulation were randomized to treatment withdrawal or continuation of warfarin for one year. The rate of recurrence was negligible during extended anticoagulation reducing significantly the incidence of recurrence in the one year group. However, after a 3-year follow up, significant reduction in recurrence was not confirmed and the annual incidence of recurrence was identical in the 2 groups (5%). The study suggested that a longer anticoagulation course is recommended for patients with a high risk of recurrence, probably more than one year. In this study, the patients in the second group were anticoagulated for 24-months with a 43% reduction in the accumulative 3-year rate of recurrence. These results need to be confirmed by larger studies to determine exactly how long should these patients be anticoagulated for. The fact that all the bleeding episodes occurred within the first 3-months of anticoagulation shows that prolongation of the anticoagulation period did not incur significantly higher risks of bleeding. Previous studies estimate the risk of major bleeding on anticoagulation is around 3% per year. This was higher than the rate of this study as the second group had no major bleeding episodes in the second year of warfarin therapy. Our findings that all episodes of recurrent venous thromboembolism were idiopathic suggest that these events can only be prevented by continuous anticoagulation and not by intermittent prophylaxis limited to times when additional risk factors for thrombosis are present. Some studies have shown that low intensity warfarin therapy with INR less than 2.0 is effective in preventing venous thromboembolism, particularly when used for primary prophylaxis.[8,9] Further studies are required to determine if lower intensity warfarin therapy is preferable in the extended phase of therapy for patients with idiopathic venous thromboembolism as there are fears that extended warfarin therapy with INR 2.0-3.0 may results in unacceptable risks of bleeding.[10-12] One major study carried out by Ridker et al[13] clearly showed that low intensity warfarin therapy with INR 1.5-2.0, after an initial 6-month therapy at the standard dose of warfarin with INR 2.0-3.0, has lead to a 48% reduction in the composite end point of recurrent venous thromboembolism, major hemorrhage, or

death. Venous thromboembolism should be considered a chronic disease with a continued risk of venous thromboembolism often associated with minor provocation.[14] Although this study has practical implications, it should not be forgotten that as our knowledge of the different possible causes of thrombophilia expand and new tests become readily available the category of patients with idiopathic venous thromboembolism will diminish and hopefully disappear. Some of the patients in this study may have thrombophilia that we did not test for prior to starting treatment. It would be interesting to know whether patients with recurrences are only those who have an occult cause of thrombophilia that we did not test for such as increased fibrinogen level or hyperhomocysteinemia. Meanwhile, while this group of patients with idiopathic venous thromboembolism exists in our daily practice, the treatment protocol should be longer than 6-months. The duration of the treatment is not clear at this time, and a large prospective study should be carried out to answer this question as this study suggests that treatment for a period of 24-months had less recurrence of venous thromboembolism without significantly increasing the rate of major bleeding.

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