

# Treatment of Venous Thromboembolism

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## Abstract

The combination of unfractionated heparin or low molecular weight heparin and oral anticoagulants is currently the treatment of choice for most patients with venous thromboembolism. Oral anticoagulants are started at the same time and heparin is discontinued after at least 5 days when the levels of the International Normalized Ratio reach the therapeutic range between 2.0 and 3.0. Low molecular weight heparin has potential advantages over heparin and is administered in subcutaneous weight-adjusted fixed doses without need for monitoring. This has made the home treatment of a large proportion of patients possible. Randomized clinical trials and several subsequent reports from clinical practice have demonstrated the efficacy and safety of this approach. The results of currently ongoing trials aimed to assess the efficacy and safety of newer compounds for the initial treatment of venous thromboembolism are expected. Oral direct thrombin inhibitors or selective factor-Xa inhibitors have the potential to become the treatment of choice in the next decade. The optimal duration of the secondary prophylaxis with oral anticoagulants is still a matter of debate. The rate of recurrence has been shown to be elevated, particularly in patients with idiopathic venous thromboembolism. A 3-month therapy is therefore currently recommended when a transient risk factor is identified, life-long treatment is recommended for patients with a second episode of venous thromboembolism. The presence of active cancer or a thrombophilic state may require long-term anticoagulation, although not all the congenital hypercoagulable states seem to carry the same level of risk. In all other cases, 6 months are recommended, but a long-term monitoring of the patients is advisable. The use of more aggressive strategies such as thrombolysis is limited to patients presenting with massive pulmonary embolism or signs of right ventricular dysfunction.

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Venous thromboembolism is an important pathology that affects apparently healthy individuals as well as medical or surgical patients. Therapeutic objectives are essentially the prevention of thrombus extension and embolization, the prevention of recurrent episodes of venous thromboembolism to reduce the risk of fatal pulmonary emboli, and the prevention of long term disorders such as the post thrombotic syndrome and secondary pulmonary hypertension. Despite the availability of different treatment strategies, the large majority of patients commonly receive a similar therapeutic approach, and the choice of the treatment is eventually influenced by the severity of the presentation of the disease [1]. The evaluation of the presence and type of risk factors should address the decision on the intensity and duration of the treatment itself.

## 1. Initial Treatment of Venous Thromboembolism

Current recommendations for the treatment of venous

thromboembolism are strongly based on the results of a number of randomized clinical trials. Antithrombotic treatment with unfractionated heparin (UH) or low molecular weight heparin (LMWH) in association with oral anticoagulants is the standard treatment in the initial management of most patients with deep vein thrombosis and pulmonary embolism. In a double blind trial, Brandjes et al [2] compared the association of heparin and oral anticoagulants to oral anticoagulants alone in patients with proximal vein thrombosis and found a significant reduction in the frequency of asymptomatic extension of deep vein thrombosis or pulmonary embolism in favor of the former group (8.2% versus 39.6%). There was also a lower incidence of symptomatic events (6.7% versus 20.0%), and no difference in the rate of bleeding complications (3.0% versus 5.0%) between the treatment groups. These results are likely to be explained by the slower onset of action of the oral anticoagulants as compared to heparin. Oral anticoagulants exert their antithrombotic effect mainly through their ability to

reduce prothrombin levels: prothrombin has a half-life of about 60 hours, and at least 3 to 4 days are therefore required to achieve the effect [3].

UH may be given by continuous intravenous infusion or by subcutaneous injection. In the last decade, LMWH have become an important alternative to UH. Indeed, LMWH have pharmacologic and pharmacokinetic advantages over the parent compound that result in their having greater clinical utility. UH is cleared from the circulation by a saturable mechanism of binding to plasma proteins and to endothelium [4], and has no antithrombotic activity until that binding capacity is overcome. Because the heparin binding proteins are phase-reactant proteins, and they have different concentrations according to the clinical conditions of the patients, the binding capacity for heparin varies from one person to another and depends upon the state of health of the person [5]. LMWH do not bind to the endothelium and have a lower affinity for plasma proteins. This results in a more predictable bioavailability, in a substantially longer half-life and in a stable dose response when injected subcutaneously [6]. Because of their properties, LMWH can be administered for therapeutic purpose subcutaneously in weight-adjusted doses without the need for laboratory monitoring. A number of clinical trials and subsequent meta-analyses have confirmed the efficacy and safety of LMWH in the initial treatment of deep vein thrombosis [7-10]. LMWH have also been successfully evaluated in the treatment of patients presenting with submassive pulmonary embolism, although the number of available studies is still limited. The Sixth Consensus Conference on antithrombotic therapy of the American College of Chest Physicians [1] recommends LMWH, intravenous UH, or adjusted dose subcutaneous UH in the acute stage of deep vein thrombosis or pulmonary embolism.

The practical advantages and the increasing use of LMWH have progressively modified the initial management of venous thromboembolism. Two large trials carried out in the mid-1990s have successfully demonstrated the safety and efficacy of treating out of hospital patients with deep vein thrombosis. In the study by Koopman et al [11], 198 patients were randomized to receive adjusted-dose intravenous UH administered in the hospital and 202 patients to receive fixed dose subcutaneous LMWH administered at home when this was considered possible. The rate of events was comparable in the two groups concerning recurrent venous thromboembolism, major bleeding and death, and the duration of hospitalization was reduced by 67% from 8.1 days in the unfractionated heparin group to 2.7 days in the LMWH group. In the latter group, 75% of the patients were discharged early or even not admitted to the hospital. The second study was carried out in Canada by Levine and colleagues [12] with a similar design and sample size, 253 patients in the intravenous UH group, and 247 patients in the LMWH group. The event rate was comparable to that observed in the Koopman study, with a substantial equivalence between the two compounds. The time spent in the hospital was remarkably

reduced from 6.5 days to 1.1 days, and 120 out of the 247 patients randomized to the LMWH were never admitted to the hospital. The effects of these two studies on clinical practice, at least in some countries, have been impressive. Two Canadian reports from clinical practice subsequently demonstrated that more than 80% of patients with proximal deep vein thrombosis are in fact safely treatable without need for hospitalization [13,14]. In our center in Italy, more than 70% of patients with objectively diagnosed deep vein thrombosis are entirely treated out of hospital [15]. Home treatment of deep vein thrombosis should not be limited to objective diagnosis and prescription of antithrombotic drugs, but requires the availability of qualified, experienced medical staff to accurately select patients and to carefully instruct them. Selected centers are therefore required to provide the appropriate support with a long term follow-up program. Exclusion criteria include active bleeding, renal insufficiency, severe liver disease, concomitant diseases requiring hospital admission, and likelihood of poor compliance [16].

## 2. Alternative Treatment Strategies

There has been an increased interest in the use of thrombolytic agents in the treatment of deep vein thrombosis. Thrombolytic agents have a number of potential advantages over anticoagulants. These advantages include lysis of the thrombi, restoration of the venous circulation to normal and reduction in damage to the venous valves, thus reducing the risk of venous hypertension. Thrombolysis has been shown to be lifesaving when administered in patients with pulmonary embolism causing cardiogenic shock or overt hemodynamic instability. Ongoing studies are evaluating the role for thrombolytic treatment in patients presenting with submassive pulmonary embolism and concomitant echocardiographic signs of right ventricular dysfunction. Thrombolysis is recommended in selected cases with venous thromboembolism: carefully selected young patients with massive iliofemoral vein thrombosis and patients with massive pulmonary embolism [1]. Currently, four thrombolytic agents are available for clinical use: streptokinase, urokinase, recombinant tissue plasminogen activator (rt-PA), and anisoylated plasminogen streptokinase activator complex (APSAC).

The guidelines from the sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy [1] specifically recommend a limited use of the inferior vena caval filters to those patients with contraindications to anticoagulant therapy who are at high risk or have developed a proximal deep vein thrombosis or a pulmonary embolism and to those patients who have had a recurrence despite adequate anticoagulation.

## 3. Oral Anticoagulant Therapy

Oral anticoagulant treatment has been shown to be effective in the prevention of recurrent deep vein throm-

and 3.0) is achieved and maintained for at least 2 consecutive days.

The optimal duration of anticoagulant therapy for venous thromboembolism is still a matter of intense debate. The usual recommendation of 3 months was initially based on the results of a 1973 retrospective study [18], which showed that, in the absence of anticoagulation, the risk of recurrence remained significant for about 12 weeks after the initial event. A number of prospective studies have specifically addressed the duration of anticoagulant therapy. Schulman and associates [19] randomized 897 patients presenting with a first episode of deep vein thrombosis to a 6 weeks or to a 6 months oral anticoagulant treatment period with an INR range between 2.0 and 2.85. Patients were followed-up for a total of 2 years. The incidence of new episodes of venous thromboembolism after 2 years was significantly lower in the group of patients treated for 6 months (9.5%) than in the group of patients treated for 6 weeks (18.1%, odds ratio 2.1) with no difference in mortality or major bleeding complications. The difference between the two groups was achieved during the first 6 months of study, and then maintained with a similar rate of events and a linear increase in the cumulative risk, corresponding to 5-6% annually, from the 7<sup>th</sup> month to the end of follow-up. A subgroup analysis showed a low event rate among patients with a temporary risk factor, whereas the rate of events was much higher in the subgroup of patients with a permanent risk factor, defined as venous insufficiency, systemic lupus erythematosus, and idiopathic venous thromboembolism. In a subsequent study by Kearon and colleagues [20], all patients presenting with a first episode of idiopathic deep vein thrombosis or pulmonary embolism were treated with oral anticoagulants for 3 months with an INR range between 2.0 and 3.0 and were then randomized to receive placebo or to continue the treatment for further 24 months. The study was stopped after an interim analysis of efficacy showed that the rate of recurrent episodes of venous thromboembolism reached 27.4% per patient-year in the placebo group as compared to just 1.3% in the group receiving warfarin. At that time, 162 patients were included in the study and followed for an average of 10 months. The results of the study confirmed a high rate of recurrence when patients with a first episode of idiopathic venous thromboembolism are treated for 3 months, but did not clarify the optimal duration of the treatment, since no data on the event rate after treatment was stopped at 24 months were available. In the WODIT study [21], patients with idiopathic deep vein thrombosis were treated for 3 months with an INR range between 2.0 and 3.0 and were then randomized to stop treatment or to receive oral anticoagulants for 9 additional months. All patients were followed for a total of 2 years. The study was prematurely stopped when 267 patients, 132 randomized to 3 months and 135 to 1 year, were included. At the end of the first year, recurrence of venous thromboembolism was significantly lower in the group of patients still on warfarin (1.5%) than in the group of patients

who stopped treatment at 3 months (7.5%), but at the end of the second year the rate of recurrences was similar between the two groups (11.8% and 14.4%, respectively), and the total number of events, if we include major bleeding episodes, was identical (20 per group). Therefore, the benefit achieved by extending oral anticoagulant treatment was maintained in the Schulman study and lost in the WODIT study. What we have learned from these studies is that a proportion of patients, in particular those with idiopathic deep vein thrombosis do have recurrent episodes of venous thromboembolism after oral anticoagulant treatment is stopped, independently from the duration of the treatment. Strategies to identify patients who should benefit from prolonged treatment are currently under investigation and include screening for thrombophilia [1], assessment of residual prothrombotic activity [22], and ultrasonographic assessment of thrombus regression [23]. Currently, prolonged treatment is indicated for patients with active cancer, antithrombin deficiency and antiphospholipid antibody syndrome [1]. It is recommended to treat patients with idiopathic venous thromboembolism for 6 months and patients with transient risk factors for 3 months [1]. Patients with recurrent venous thromboembolism should be treated indefinitely [1].

#### **4. New Treatment Options**

New antithrombotic drugs are currently undergoing extensive evaluation. In particular, 2 phase III studies assessing the efficacy and safety of fondaparinux, a synthetic pentasaccharide with selective anti-factor Xa activity, in the initial treatment of deep vein thrombosis and submassive pulmonary embolism have just been completed. Fondaparinux has been recently approved both in North America and Europe for prophylaxis of venous thromboembolism in major orthopedic surgery. Ongoing phase III studies are also evaluating a novel direct antithrombin inhibitor, xi-melagatran, for initial and long term treatment of venous thromboembolism. Of great interest, xi-melagatran is administered orally and does not need laboratory monitoring.

#### **5. Conclusions**

A high proportion of patients presenting with deep vein thrombosis or clinically stable pulmonary embolism can now have an early discharge or can be entirely treated at home receiving LMWH. A specialized center should assist these patients who may need to be taught to inject themselves and who will need to be subsequently monitored for the concomitant oral anticoagulant therapy. Patients should also be evaluated to identify risk factors related to the episode of venous thromboembolism. This can be pivotal to determine the optimal duration of oral anticoagulant treatment, which should probably be tailored for every single patient. The significant incidence of recurrent episodes and the high rate of complications such as the post-phlebotic syndrome require in any case a long term follow-up.

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