

Long-term therapy of pulmonary embolism

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For the majority of patients with pulmonary embolism the recommended therapy consists of a 5 to 7 day treatment with heparin followed by a treatment with oral anticoagulants given for at least 3 months. The currently recommended duration of oral anticoagulant treatment for pulmonary embolism is the result of the balance between the benefit provided by treatment, essentially the prevention of recurrence, and the bleeding risk and inconvenience associated with treatment. Risk of bleeding and inconvenience should be assessed on an individual base. Concerning the risk of recurrence, patients with pulmonary embolism can be classified in three groups: patients with pulmonary embolism associated with temporary risk factors, patients with pulmonary embolism associated with persistent risk factors, patients with pulmonary embolism occurring in the absence of any identifiable temporary or persistent risk factors for venous thromboembolism (idiopathic or unprovoked pulmonary embolism). Due to the limitations of the currently available oral anticoagulant agents, search for the optimal agent to be used in the long-term treatment of pulmonary embolism is still open.

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Therapy currently recommended for the majority of patients with acute pulmonary embolism consists of an initial treatment with heparin, usually for 5 to 7 days, relayed with a treatment with vitamin K antagonists given for at least 3 months¹. A properly conducted long-term treatment with oral anticoagulants is essential in the management of patients with pulmonary embolism. The main aim of this long-term treatment is to prevent recurrence of pulmonary embolism. Most of the information concerning the long-term treatment of patients with venous thromboembolism has been achieved from studies in patients with deep vein thrombosis. Indeed, a relatively small number of patients with pulmonary embolism have been included in studies on the long-term management of venous thromboembolism. Recent findings suggest that patients presenting with pulmonary embolism are at slightly higher risk of death from recurrent pulmonary embolism than patients presenting with deep vein thrombosis^{2,3}. However, this finding does not necessarily imply that patients presenting with pulmonary embolism require a different long-term treatment than patients presenting with deep vein thrombosis.

This paper will focus on the main issues related to the long-term management of patients with pulmonary embolism.

Need for long-term anticoagulant treatment in patients with pulmonary embolism

Patients who suffered an episode of pulmonary embolism have a tendency to have a recurrence in the months or years following the initial episode. If a long-term anticoagulant treatment is not given, 15 to 50% of patients with acute venous thromboembolism experience a symptomatic extension of thrombosis and/or an early recurrence^{4,5}. These figures indicate that a long-term anticoagulant treatment is essential to avoid recurrent episodes of pulmonary embolism. However, this treatment has to be adequate for both efficacy and duration. Concerning the intensity of treatment, a randomized study showed that subcutaneous low-dose unfractionated heparin (5000 U twice daily) is less effective than vitamin K antagonists for the long-term treatment of patients with deep vein thrombosis⁶. Concerning the duration of treatment, randomized trials showed that an anticoagulant treatment < 3 months⁷⁻⁹ is associated with an increased rate of recurrent thromboembolic events.

Oral anticoagulants for long-term treatment of pulmonary embolism

Vitamin K antagonists are the currently recommended agents for the long-term

treatment of patients with pulmonary embolism¹. These agents are given orally. Oral administration is essential to simplify the long-term treatment of venous thromboembolic diseases. However, vitamin K antagonists have a narrow therapeutic window, a number of interactions with food and other drugs and are associated with the risk for bleeding complications. Furthermore, treatment with vitamin K antagonists needs laboratory monitoring for dose adjustment.

The currently recommended intensity of oral anticoagulant treatment for venous thromboembolism is a dose adequate to achieve an international normalized ratio (INR) between 2.0 and 3.0. This INR value was established based on the results of randomized trials that included patients with both deep vein thrombosis and pulmonary embolism¹⁰⁻¹³. To reduce the incidence of bleeding complications and the frequency of monitoring, low-intensity warfarin therapy (target INR < 2.0 and > 1.5) has recently been proposed for the long-term treatment of venous thromboembolism^{12,13}. In one study, patients with idiopathic venous thromboembolism who had received full-dose anticoagulant therapy for a median of 6.5 months were randomly assigned to placebo or low-intensity warfarin (target INR 1.5 to 2.0)¹². The incidence of recurrent venous thromboembolism was 7.2%/year and 2.6%/year in patients assigned to placebo or low-intensity warfarin, respectively (hazard ratio 0.36, 95% confidence interval [CI] 0.19 to 0.67, $p < 0.001$). In another trial, after the completion of at least 3 months of standard-intensity warfarin therapy, patients were randomized in a double-blind fashion to receive low-intensity warfarin therapy (target INR 1.5 to 1.9) or standard-intensity warfarin therapy (INR 2.0 to 3.0)¹³. During an average follow-up of 2.3 years, the incidence of recurrent venous thromboembolism was 1.9%/year in the 370 patients in the low-intensity group, and 0.6%/year in the 369 patients in the standard-intensity group (hazard ratio 3.3, 95% CI 1.2 to 9.1). The incidence of major bleeding was 0.96%/year in the low-intensity group and 0.93%/year in the standard-intensity group. In this study, low-intensity warfarin treatment was less effective than standard-intensity therapy (INR 2.0 to 3.0), without providing a reduction of bleeding complications.

Taken together, these results indicate that although low-intensity warfarin therapy is more effective than placebo, it is less effective than standard-intensity therapy (INR 2.0 to 3.0), and does not reduce the incidence of bleeding complications.

An INR > 3.0 was claimed to be indicated in patients with venous thromboembolism and persistently positive antiphospholipid antibodies. In a recent trial, patients with persistently positive antiphospholipid antibodies and a history of thromboembolism (venous or arterial) were randomized to standard-intensity warfarin therapy (INR 2.0 to 3.0) or high-intensity warfarin therapy (INR 3.1 to 4.0)¹¹. During an average follow-up of 2.7 years, recurrent thromboembolism occurred in

3.4% of patients receiving standard-intensity therapy, compared with 10.7% of patients who received the high-intensity therapy (hazard ratio 3.1, 95% CI 0.6 to 15). Thus, high-intensity warfarin therapy (INR 3.1 to 4.0) did not provide additional antithrombotic protection. The need for monitoring may preclude the use of long-term coumarin therapy to many patients, especially those with estimated high risk of bleeding and old patients.

Low-molecular-weight heparins for long-term treatment of venous thromboembolism

Heparins (unfractionated and low-molecular-weight heparins) are potential alternatives to vitamin K antagonists for the long-term treatment of pulmonary embolism. The main limitation of heparins for chronic indications is the need for parenteral administration. In addition, unfractionated heparin has a narrow therapeutic window and a high interindividual variability that make laboratory monitoring and dose adjustment necessary¹⁴. Low-molecular-weight heparins have a more predictable dose-response and this allows their administration without laboratory monitoring. Moreover, low-molecular-weight heparins are associated with a lower incidence of heparin-induced thrombocytopenia in comparison to unfractionated heparin.

Several trials have compared the efficacy and safety of low-molecular-weight heparins with those of vitamin K antagonists in the long-term treatment of venous thromboembolism¹⁵⁻²³. The majority of patients included in these studies presented with deep vein thrombosis. These trials showed a similar efficacy for the two treatment alternatives. However, the most interesting results with low-molecular-weight heparins for the long term-treatment of venous thromboembolism have been achieved in a study in patients with cancer²³. In this study patients were randomized to receive in a double-blind fashion either the low-molecular-weight heparin dalteparin or warfarin for a period of 6 months. Dalteparin was more effective than warfarin in preventing recurrence without causing an increase in bleeding complications. Based on the results of this study, treatment with low-molecular-weight heparin is currently recommended for the long-term treatment of venous thromboembolism in patients with cancer. Unfortunately, there are no data on the efficacy and safety of dalteparin when given beyond 6 months for the treatment of venous thromboembolism.

Duration of oral anticoagulant treatment for pulmonary embolism

The recommended duration of oral anticoagulant treatment for pulmonary embolism results from a balance between the risks and inconvenience of remaining

on treatment and the risk of recurrent venous thromboembolism once treatment is discontinued. Risk of bleeding and inconvenience should be assessed on an individual base. The risk of recurrence seems to be intrinsic to specific patient populations and could be potentially stratified according to the intrinsic patient features and clinical presentations (Table I).

Recurrent venous thromboembolism: risk stratification. Several studies have shown a particularly high incidence of recurrence in patients with continuing risk factors for venous thromboembolism (such as cancer and molecular thrombophilia), idiopathic presentation at entry, or history of previous venous thromboembolism^{7-9,24}. Recurrent venous thromboembolism is less common among patients with a first episode of venous thromboembolism associated with temporary risk factors. Venous thromboembolism is defined as idiopathic when it occurs in the absence of any identifiable risk factor for venous thromboembolism. The term unprovoked venous thromboembolism has been recently also used to identify these patients.

A prospective cohort study including consecutive patients with a first episode of venous thromboembolism who were followed for up to 8 years showed an incidence of recurrent venous thromboembolism of 18, 25, and 30% at 2, 5, and 8 years from the index event, respectively²⁵. Patients with venous thromboembolism associated with transient risk factors (such as surgery or recent trauma) had a low risk of recurrence. Patients with cancer or molecular thrombophilic abnormalities showed an increased risk of recurrent venous thromboembolism. In a study in patients with a first episode of pulmonary embolism, the incidence of recurrent venous thromboembolism was 12.2% in patients with idiopathic pulmonary embolism and 7.6% in patients with pulmonary embolism associated with temporary risk factors²⁴.

Molecular thrombophilic abnormalities known to predispose to thrombosis can be classified as deficiencies of the naturally occurring inhibitors of coagulation (antithrombin, protein C and protein S), specific gene mutations (factor V Leiden and prothrombin 20210A), elevated levels of coagulation factors (factor VIII), elevated levels of homocysteine²⁶⁻²⁹. Remarkable evidence exists for the risk of recurrent venous throm-

boembolism in patients with venous thromboembolism associated with antiphospholipid antibodies^{30,31}. In a prospective study a 29% incidence of recurrent venous thromboembolism was seen in patients with a first episode of venous thromboembolism associated with anticardiolipin antibodies compared with 14% seen in patients without anticardiolipin antibodies ($p < 0.01$)³⁰.

The optimal duration of oral anticoagulant treatment. The optimal duration of long-term treatment with oral anticoagulants in patients with venous thromboembolism remains a matter of debate. A single study was specifically designed in patients with pulmonary embolism²⁴, while most of the trials included patients with deep vein thrombosis with or without concomitant pulmonary embolism^{7-9,32-34}.

Three studies evaluated the risk-benefit ratio of shortened treatment durations (4 to 6 weeks) in comparison to standard treatment durations (3 to 6 months)⁷⁻⁹. These studies showed a higher incidence of recurrent venous thromboembolism in patients randomized to shortened courses of oral anticoagulant treatment. Therefore, almost no patients should be treated for less than 3 months.

These studies in association with large prospective studies contributed to identify three groups of patients with venous thromboembolism: patients with venous thromboembolism associated with temporary risk factors, patients with venous thromboembolism associated with persistent risk factors, and patients with idiopathic venous thromboembolism. Since then, most of the trials on the optimal duration of oral anticoagulant treatment focused on patients with idiopathic venous thromboembolism.

More recent studies^{12,32,34} evaluated the risk-benefit ratio of extended anticoagulant therapy (1 to 2 years) in comparison to the standard treatment (3 to 6 months) in patients with idiopathic deep vein thrombosis. Two main observations have been achieved from these studies. First, extended treatment with oral anticoagulants is highly effective in reducing the incidence of recurrent venous thromboembolism. Indeed, the incidence of recurrent venous thromboembolism while patients are on anticoagulant treatment is very low, being not higher than 1.0%. The second evidence is that the clinical benefit achieved during extended oral anticoagulant treat-

Table I. Recommended oral anticoagulant treatment duration for patient categories at different risks for recurrent venous thromboembolism.

Risk categories	Recommended treatment duration
Unprovoked PE	At least 6 months – candidates to indefinite treatment
PE associated with temporary risk factors	Three months
PE in patients with active cancer	Indefinite or until cancer is resolved
PE associated with molecular thrombophilia	At least 12 months in patients with at least two molecular abnormalities or antiphospholipid antibodies
Recurrent PE	Indefinite

PE = pulmonary embolism.

ment is not maintained after its discontinuation. This finding was confirmed in a study specifically designed for patients with symptomatic, objectively confirmed pulmonary embolism²⁴. This study showed that extending oral anticoagulant treatment to 12 months in patients with idiopathic pulmonary embolism only delayed the time to recurrence without reducing the risk of recurrence after discontinuation of treatment. Moreover, the benefit of extended treatment is also partially offset by the risk of bleeding. Thus, after a first episode of idiopathic pulmonary embolism it is recommended oral anticoagulant treatment for at least 6 months to 1 year. An indefinite extension of treatment could be considered only in selected patients¹.

Several strategies have been proposed to further stratify patients with idiopathic venous thromboembolism in categories with different risk of recurrence. High D-dimer levels and residual thrombus assessed by compression ultrasonography, both evaluated after discontinuation of oral anticoagulants, have been reported to be associated with an increased risk of recurrent venous thromboembolism^{35,36}. Studies assessing the merit of these observations in terms of treatment management are currently ongoing.

There is no randomized clinical trial supporting the extension of treatment with oral anticoagulants beyond 6 to 12 months after a first episode of venous thromboembolism in patients with molecular thrombophilia. The practice of extending treatment in patients with molecular thrombophilia is essentially based on the results of epidemiology studies that showed a high rate of recurrence in these patients. In patients with venous thromboembolism associated with anticardiolipin antibodies extended anticoagulant regimen has been claimed due to the high mortality rate related to thromboembolic events^{31,37}. Patients with venous thromboembolism associated with anticardiolipin antibodies are potential candidates to indefinite anticoagulant therapy.

In patients with venous thromboembolism and active cancer anticoagulant treatment should be given indefinitely or until cancer is resolved.

Patients with a first episode of venous thromboembolism associated with temporary risk factors should be treated for 3 months.

The risk-benefit ratio of indefinite oral anticoagulant treatment after a second episode of venous thromboembolism has been evaluated in a randomized trial comparing 6 months of treatment with indefinite treatment (average 4 years) in 227 patients presenting with a second episode of venous thromboembolism³⁷. The cumulative incidence of recurrent venous thromboembolism was significantly higher in patients who received 6 months of therapy (20.7%) than in patients who continued anticoagulant treatment (2.6%). The cumulative incidence of major bleeding was 8.6% for the indefinite treatment group compared with 2.7% in the 6-month group corresponding to an absolute risk increase of 5.9%.

For all the patients who are initially addressed to receive indefinite anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed in the individual patient at periodic intervals.

Bleeding complications

The risk of bleeding complications is certainly a hurdle for the long-term anticoagulant treatment. The incidence of bleeding during the administration of vitamin K antagonists for the treatment of venous thromboembolism (target INR 2.0 to 3.0) was assessed by a meta-analysis of 33 prospective studies³⁸. Most of the 10 757 patients included in this meta-analysis received unfractionated heparin or low-molecular-weight heparin in the acute phase followed by oral anticoagulants for 3 months. Overall, 275 major bleeding events were observed: 81% were not intracranial and 13% were fatal most of which being intracranial. This meta-analysis showed that the risk of overall bleeding in patients receiving oral anticoagulants is higher during the first 3 months of treatment. This observation is mainly based on the results of 4 studies that reported higher frequencies of bleeding early in the course of therapy³⁹⁻⁴². One of these studies showed a 3.0% incidence of major bleeding during the first month of outpatient warfarin therapy that decreased to 0.8% per month during the rest of the first year of therapy, and to 0.3% per month thereafter³⁹. On the contrary, the risk of fatal bleeding is constant and does not decrease over time. In general the risk of bleeding is higher in cancer patients.

Novel oral anticoagulants for treatment of venous thromboembolism

The limitations of vitamin K antagonists have promoted the development of new oral anticoagulant agents that have a better safety profile and do not need laboratory monitoring. None of these drugs have been approved for the long-term treatment of venous thromboembolism.

Ximelagatran is the pro-drug of the active site-directed thrombin inhibitor, melagatran. After oral administration, ximelagatran is absorbed from the small intestine. Foods or drugs have not been documented to influence its absorption. After its absorption, ximelagatran rapidly undergoes biotransformation to melagatran via intermediate metabolites⁴³. The plasma half-life of ximelagatran is 3 to 4 hours. Melagatran, the active agent, is eliminated via the kidneys, thus dose adjustments may be needed in the elderly and in patients with renal insufficiency⁴³. Ximelagatran does not need laboratory monitoring of coagulation.

The efficacy of ximelagatran in the treatment of venous thromboembolism was first evaluated in a phase II, dose-ranging study. In this study, 350 patients with

deep vein thrombosis were randomized to receive ximelagatran (dose ranging from 24 to 60 mg twice daily) or subcutaneous dalteparin followed by warfarin⁴⁴. The primary endpoint was the rate of thrombus regression as assessed by venography. The incidence of thrombus regression plus changes in clinical symptoms was similar in the two treatment groups. There was a trend for more thrombus progression with ximelagatran than with dalteparin (8 and 3%, respectively), but this difference was not statistically significant. The incidence of bleeding was similar in the two treatment groups. After this study, efficacy and safety of ximelagatran were tested in a phase III, blind trial with clinical endpoint. In this study, oral ximelagatran (36 mg twice daily) was compared with enoxaparin (1 mg/kg subcutaneously twice daily) followed by warfarin (target INR 2.0 to 3.0); both treatments were given for 6 months⁴⁵. Overall 2489 patients with venous thromboembolism (about 35% affected by pulmonary embolism) were included in the study. Recurrent venous thromboembolism occurred in 2.1 and 2.0% of patients randomized to ximelagatran or enoxaparin/warfarin, respectively. Major bleeding occurred in 1.3 and 2.2% of patients randomized to receive ximelagatran or enoxaparin/warfarin, respectively. These differences were not statistically significant. All-cause mortality occurred in 2.3 and 3.4% of patients randomized to ximelagatran and enoxaparin/warfarin, respectively.

A randomized trial evaluated the long-term efficacy and safety of treatment with fixed-dose oral ximelagatran initiated after 6 months of standard anticoagulant therapy for venous thromboembolism⁴⁶. In this trial 1233 patients who had completed 6 months of anticoagulant therapy were randomized to receive ximelagatran (24 mg twice daily) or placebo for an additional 18 months. Recurrent venous thromboembolism occurred in 12 and 71 patients who had been randomized to receive ximelagatran or placebo, respectively (hazard ratio 0.16, $p = 0.001$). Major bleeding occurred in 6 patients and 5 patients who had been treated with ximelagatran or placebo, respectively. No fatal or intracranial bleeding was observed. Thus, therapy with oral ximelagatran is as effective and safe as conventional anticoagulation therapy with low-molecular-weight heparin followed by warfarin for the initial treatment of patients with venous thromboembolism and more effective than placebo for the extended secondary prophylaxis of venous thromboembolism. Approximately 4 to 10% of patients randomized to receive long-term treatment with ximelagatran in clinical trials developed an increase in alanine aminotransferase levels. This change typically occurred after 6 weeks to 4 months of treatment and was usually asymptomatic and reversible. Although the increase in transaminase levels with ximelagatran therapy appears to be benign, more information is needed. The question is if patients receiving long-term ximelagatran treatment will need to monitor liver enzyme levels during the initial period of therapy.

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