REVIEW ARTICLE

Drugs 2004; 64 Suppl. 1: 37-46
0012-6667/04/0001-0037/$34.00/0

Treatment of Venous Thromboembolism and Long-Term Prevention of Recurrence: Present Treatment Options and Ximelagatran

Henry Eriksson

Department of Medicine, Sahlgrenska University Hospital/Östra, Gothenburg, Sweden

Abstract

Despite the effectiveness of anticoagulant therapy for the treatment of acute venous thromboembolism and the prevention of recurrent venous thromboembolism, existing antithrombotic therapies are suboptimal. Unfractionated heparin, low-molecular-weight heparin (LMWH) and warfarin have practical limitations and carry the risk of treatment-related adverse events that restrict their clinical benefits and reduce cost-effectiveness. Efforts to achieve optimal venous thromboembolism prophylaxis by modifying the intensity of oral warfarin treatment have produced equivocal results, and there is a need for new, efficacious antithrombotic drugs providing predictable, well-tolerated oral dosing without the need for coagulation monitoring. Such agents would ideally have no significant food or drug interactions, and be suitable for both short- and long-term treatment. Ximelagatran, the first oral direct thrombin inhibitor, has the potential to fulfill many of the unmet needs in the management of venous thromboembolism.

1. Introduction

Venous thromboembolism, which encompasses deep vein thrombosis (DVT) and pulmonary embolism, is a major cause of morbidity and mortality. Although it is a well-known complication of surgery and various medical illnesses, it also occurs in the general population. In many cases, DVT is asymptomatic and its first manifestation is pulmonary embolism, which can be fatal.[1] Unrecognised or undertreated DVT may also result in long-term morbidity from post-thrombotic syndrome or chronic pulmonary hypertension.[2-4] Although treatments for venous thromboembolism have improved since anticoagulants became available more than 60 years ago, none of the existing therapies are optimal with regard to efficacy, safety and ease of use. Consequently, management of venous thromboembolism remains a major challenge. Short- and long-term morbidity and the social and economic burden associated with venous thromboembolism continue to be high.

This article reviews the results of studies investigating the utility of currently recommended approaches to the short-term treatment and secondary prevention of venous thromboembolism. The specific aims of the various treatment guidelines for venous thromboembolism, the duration of treatment and how these fit into clinical practice will be discussed. Finally, results of recent trials with the new oral direct thrombin inhibitor, ximelagatran, will be outlined.

2. Present Options for Treatment and Secondary Prevention

Venous thromboembolism may be asymptomatic, and its first manifestation can be fatal pulmonary embolism.[1] Consequently, it is important to provide adequate thromboprophylaxis for medical or surgical patients who are at risk for the event. Furthermore, patients with established venous thromboembolism require anticoagulant treatment to prevent thrombus extension, minimise the risk of pulmonary embolism and prevent recurrent thrombosis. The duration of anticoagulant treatment depends on the balance between the risk of recurrence and the risk of bleeding with treatment.[5]

2.1 Short-Term Treatment

The American College of Chest Physicians stated in 2001 that patients with acute DVT or pulmonary embolism should be treated with anticoagulant therapy. Because rapid anticoagulation is needed, these patients require concomitant treatment with a parenteral anticoagulant until a therapeutic anticoagulant response is obtained with an orally active vitamin K antagonist, such as warfarin. Consequently, low-molecular-weight heparin (LMWH) or unfractionated heparin is given for at least 5 days.[6] LMWH is administered subcutaneously, whereas unfractionated heparin is usually given by continuous intravenous infusion.

Less frequently used measures to treat acute venous thromboembolism include thrombectomy, catheter-directed thrombolysis and insertion of intracaval filters. Thrombectomy, which is used infrequently, is generally reserved for massive, life-threatening pulmonary embolism when thrombolytic therapy has failed to stabilise the patient's haemodynamic status.[7] It is also used in some centres, either alone or in conjunction with catheter-directed thrombolytic therapy, for treatment of selected patients with extensive iliofemoral DVT. Another indication for thrombectomy is in patients with chronic large-vessel thromboembolic pulmonary hypertension.[8]

Indications for intracaval filters include patients with acute pulmonary embolism who have a life-threatening haemorrhage while receiving anticoagulant treatment, those with an absolute contraindication to anticoagulation, or those with recurrent pulmonary embolism despite intensive anticoagulation.[9-11] Filters also are used to prevent recurrent pulmonary embolism in patients who have undergone thrombectomy for chronic thromboembolic pulmonary hypertension.

Thrombolytic treatment, the only measure that actively dissolves thrombi, is used in a small proportion of the venous thromboembolism population. This treatment is usually reserved for patients with pulmonary embolism who are haemodynamically unstable or those with submassive pulmonary embolism who have decreased cardiopulmonary function and right ventricular dysfunction. However, the utility of thrombolytic treatment in the latter group remains a matter of debate. In patients with extensive iliofemoral DVT, catheter-directed thrombolytic treatment may be used when the risk of bleeding is low.[5,12]

2.2 Prevention of Recurrence

The most commonly used pharmacological approach for the prevention of recurrent venous thromboembolic events is anticoagulant therapy using warfarin.[5] Warfarin should be overlapped with unfractionated heparin or LMWH for at least 5 days.[5,13] Patients with venous thromboembolism secondary to reversible or temporary risk factors can be treated with warfarin for 3 months.[5,13] In contrast, patients with a first episode of idiopathic DVT should be treated for at least 6 months, whereas those with recurrent venous thromboembolism or ongoing risk factors, such as active cancer, antiphospholipid antibody syndrome, or deficiency of antithrombin, protein C or protein S, require longer treatment.[5]

Graduated compression stockings are often used after DVT to prevent or reduce the symptoms of post-thrombotic syndrome. This disorder, which is characterised by chronic leg pain and swelling, occurs in 20–30% of patients with DVT after

5 years and can be associated with venous ulcers in 5–10%.[14]

The optimal duration of long-term secondary preventive therapy remains a matter of debate and, in clinical practice, the actual duration of long-term secondary preventive treatment is dependent on the balance between the risk of recurrent venous thromboembolism if anticoagulation therapy is stopped and the risk of bleeding with long-term anticoagulation treatment.

3. Challenges for Venous Thromboembolism Management

Patients who have a history of venous thromboembolic events are at increased risk for recurrent events, particularly when they have current risk factors such as malignancy, prolonged immobility or underlying thrombophilic disorders. Decisions regarding the need for initiation or continuation of anticoagulant therapy need to be based upon continuing assessment of the extent of the risk of recurrence of venous thromboembolism for each individual patient, together with the risk of bleeding.

3.1 Balancing the Efficacy and Safety of Heparin-Based Therapy During Acute Treatment

Unfractionated heparin must be administered parenterally. The drug produces an unpredictable anticoagulant response because it binds to a number of plasma proteins, the concentrations of which vary from patient to patient.[12] Consequently, coagulation monitoring is necessary to ensure that a therapeutic response is obtained. The activated partial thromboplastin time (aPTT) is widely used to monitor treatment with unfractionated heparin. Provided that the aPTT is within the therapeutic range, intravenous or subcutaneous injection of unfractionated heparin has proven to be effective in the initial treatment of DVT and pulmonary embolism. Studies have shown that failure to achieve a therapeutic aPTT during initial treatment with heparin is associated with an unacceptably high rate of recurrence.[15] It is important, therefore, to maintain a therapeutic aPTT that corresponds to a plasma heparin concentration of 0.2–0.4 IU/mL by protamine sulphate titration of the thrombin clotting time or 0.3–0.6 IU/mL using an amidolytic anti-factor Xa assay.[5]

Some of the problems associated with the monitoring and dose adjustment of unfractionated heparin treatment are obviated with LMWHs. These agents produce a more predictable dose–response relationship than unfractionated heparin and can be administered subcutaneously for the short-term treatment of venous thromboembolism, without the need for laboratory monitoring and with a lower risk of heparin-induced thrombocytopenia.[5,12] Clinical trial data have shown that LMWH is as effective and well tolerated as intravenous unfractionated heparin for the treatment of DVT[16] and stable pulmonary embolism.[17]

3.2 Assessing the Risk of Long-Term Recurrence

Many factors have to be taken into account when the risk of recurrence is being estimated in patients with venous thromboembolism. The risk of recurrence is lower if the venous thromboembolism developed in association with a reversible risk factor, such as surgery or trauma. In contrast, the risk of recurrence is greater if there is a current risk factor or the venous thromboembolism was unprovoked.[18,19] Thus, in a group of 250 patients with symptomatic, confirmed DVT who received initial oral anticoagulant treatment for 3 months, 24% of patients with idiopathic venous thrombosis had recurrent venous thromboembolism during 2 years of follow-up, compared with 4.8% of patients with a reversible risk factor.[18] A similar observation was reported in a study of 301 patients with DVT who were also treated with warfarin for 3 months.[19] During 9 months of additional follow-up, 12.3% of the 212 patients with continuing risk factors or idiopathic DVT had recurrent venous thromboembolism, compared with none of the 89 patients with transient, reversible risk

factors. Such disparate rates of recurrence underscore the need to tailor the duration of treatment to the perceived level of risk of recurrence of venous thromboembolism. The challenge is to estimate the risk of recurrent venous thromboembolism accurately and then to institute treatment at an appropriate intensity and for an appropriate duration.

The risk of recurrence of venous thromboembolism may also be influenced by the magnitude of the thrombotic burden, the location of the thrombus and failure of resolution of thrombotic obstruction. The observation that evidence of residual, persistent DVT on compression ultrasound is predictive of recurrent thromboembolism in patients with DVT who had initially received heparin-based treatment plus 3 months of warfarin may indicate a need for a longer duration of secondary prevention.[20] The hazard ratio for recurrent thromboembolism over 3 years was 2.4 ($p = 0.004$) for patients with persistent residual thrombosis compared with patients with early vein recanalisation. Further studies are needed to confirm these findings. Furthermore, variables predictive of fibrinolytic activity, such as increased D-dimer concentrations, may also predict an increased risk of recurrent venous thromboembolism.[21] When the risk of recurrence is being assessed, many factors have to be accounted for, including the severity of the initial thromboembolic event, bleeding rates, co-morbidity, compliance, costs and patient preferences.

3.3 The Hazards of Curtailing Long-Term Preventive Treatment

Suboptimal duration of preventive therapy contributes to unnecessarily high rates of recurrence, as illustrated by the finding that the risk of recurrence may be more than doubled in patients treated with 6 weeks rather than 6 months of oral anticoagulant therapy after a first episode of venous thromboembolism.[22] In a trial of patients with idiopathic venous thromboembolism, recurrent venous thromboembolism occurred at a rate of 27.4% per patient-year during an average 10-month period of extended follow-up in patients allocated randomly to groups to receive 3 months of warfarin, compared with a 1.3% per patient-year rate of recurrence for patients who continued to receive warfarin after the initial 3-month period ($p < 0.001$).[23]

Recurrent venous thromboembolism after anticoagulant therapy has been discontinued is a major clinical problem. The cumulative incidence of recurrent DVT gradually increases as time elapses after termination of anticoagulant therapy. This trend was demonstrated in a cohort of 355 patients with first-episode DVT who were initially treated with unfractionated heparin or LMWH and then received oral warfarin for 3 months. The cumulative incidence of recurrent venous thromboembolism was 4.9% at 3 months, increasing gradually to 30.3% after 8 years.[4]

In conclusion, vitamin K antagonists reduce the risk of recurrent venous thromboembolism for as long as they are used. However, the risk for major bleeding remains.[24]

3.4 Balancing the Efficacy and Safety of Warfarin During Preventive Therapy

One of the big challenges for physicians is to achieve optimal long-term prophylaxis of recurrent venous thromboembolism, while minimising the risk of bleeding complications. Currently, the coumarin derivative, warfarin, is the most commonly used oral anticoagulant for the long-term prevention of recurrent venous thromboembolism. Various genetic[25] and environmental factors can affect the dose–response relationship of this vitamin K antagonist,[26] and the greater the intensity of treatment, the greater the risk of bleeding.[27] Food and alcohol can interfere with the activity of warfarin, which also interacts with a range of common prescription and over-the-counter drugs.[28,29] In addition, the delayed onset of action of warfarin makes it unsuitable for use in a situation in which an immediate anticoagulant response is desired. Consequently, warfarin must initially be administered in conjunction with parenterally administered unfractionated heparin or LMWH. The unpredictable pharmacokinetic/

pharmacodynamic profile of warfarin and its narrow therapeutic margin necessitate regular monitoring of the prothrombin time and adjustment of the dose of warfarin to maintain the international normalised ratio (INR) within the recommended therapeutic range. Based on the results of randomised trials, a target INR between 2.0 and 3.0 is recommended for long-term (6 months) treatment with warfarin.[5,26]

Although clinical trials have shown that extended use of warfarin adjusted to achieve an INR between 2.0 and 3.0 is associated with reduced rates of recurrent venous thromboembolism, the risk of bleeding has been highlighted as a limitation of treatment.[23,30,31] The risk of bleeding increases with excessive prolongation of the INR, and numerous regimens have been studied with the aim of maintaining the benefits of long-term treatment with conventional-intensity warfarin, while reducing the risk of bleeding. It has been suggested that it may be possible to decrease the INR range to <2.0 without compromising efficacy,[26] but this is a contentious issue.

The conclusion of the **P**revention of **Re**current **Ven**ous **T**hromboembolism (PREVENT) trial was that long-term (mean follow-up 2.1 years), low-intensity (target INR 1.5–2.0) warfarin provides a highly effective and well-tolerated means of preventing recurrent venous thromboembolism in patients with a previous idiopathic DVT.[32] A total of 508 patients who had completed at least 3 months of conventional-intensity warfarin treatment were randomly assigned to placebo or low-intensity warfarin and followed for recurrent venous thromboembolism, major haemorrhage or death. Low-intensity warfarin reduced the risk of recurrent venous thromboembolism by 64% compared with placebo ($p < 0.001$; figure 1). There was no significant between-group difference in the rate of major haemorrhage. Long-term, low-intensity warfarin halved the risk of the composite study endpoint of recurrent venous thromboembolism, major haemorrhage or death from any cause (hazard ratio 0.52; $p = 0.01$).

In the **E**xtended **L**ow-Intensity **A**nticoagulation for **T**hrombo**E**mbolism (ELATE) study, it was

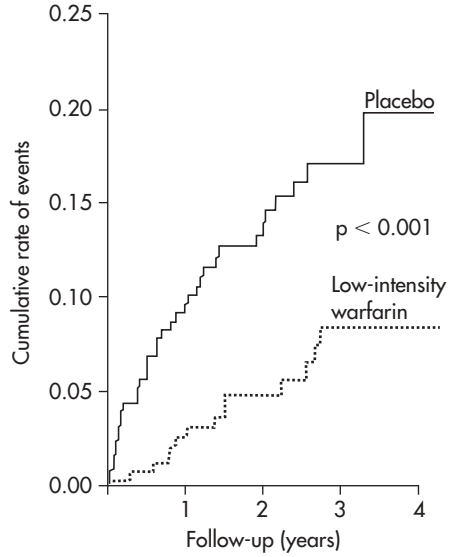

Fig. 1. Cumulative risk of recurrent venous thromboembolism over time in the PREVENT study. (With permission from Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 2003; 348: 1425–34[32])

subsequently found that lower-intensity warfarin is less effective, and not associated with a lower risk of bleeding, than conventional-intensity treatment.[33] In this study, 738 patients with idiopathic venous thromboembolism were allocated randomly to groups to receive treatment with long-term (mean follow-up 2.4 years), low-intensity warfarin (target INR 1.5–1.9) or conventional-intensity warfarin (target INR 2.0–3.0). Patients had completed at least 3 months of oral anticoagulant therapy at the conventional intensity. The incidence of recurrent venous thromboembolism was significantly lower in the conventional-intensity group than in the low-intensity group (0.7 events compared with 1.9 per 100 person-years; hazard ratio 2.8; $p = 0.03$; figure 2), and rates of major bleeding episodes were similar between groups (0.9 compared with 1.1 per 100 patient-years; hazard ratio 1.2; $p = 0.76$). The authors of the ELATE study commented that, with respect to the rate of recurrent venous thromboembolism and the incidence of bleeding with low-intensity

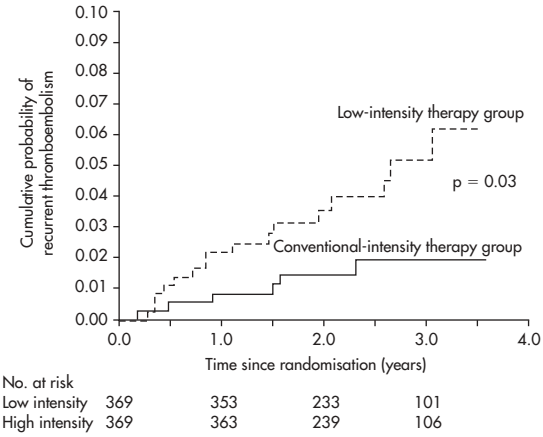

Fig. 2. Cumulative probability of recurrent venous thromboembolism over time in the ELATE study. (With permission from Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003; 349: 631–9[33])

warfarin, their findings were consistent with those of the PREVENT study. However, it should be noted that the extremely low incidence of major bleeding (1.0%) in the group given conventional-intensity oral anticoagulant treatment (INR 2–3) is 3–5 times lower than the incidence of bleeding reported in earlier studies. The authors also stated that, collectively, the results of the ELATE[33] and PREVENT[32] studies, and those of another trial investigating extended treatment of patients with idiopathic venous thromboembolism,[24] suggest that long-term low-intensity warfarin reduces the risk of recurrent thrombosis by about 75%, whereas conventional-intensity warfarin treatment reduces the risk by at least 90%.

4. The Role of Ximelagatran in Venous Thromboembolism

4.1 Characteristics of Ximelagatran

Ximelagatran is a novel oral direct thrombin inhibitor. After oral administration, it is rapidly converted to its active form, melagatran.[34,35] Unlike the indirect thrombin inhibitor heparin, which is able to inhibit only free thrombin, melagatran reversibly inhibits both free- and clot-bound thrombin.[36]

Ximelagatran has a stable and predictable pharmacokinetic profile, and is thus administered as a fixed dose, with no requirement for coagulation monitoring.[37,38] Melagatran has low binding affinity for plasma proteins, and is primarily excreted via the kidneys, so renal function accounts for most of the variability in its pharmacokinetics.[35,37,39-41] The bioconversion of ximelagatran and the elimination of melagatran are not mediated via the cytochrome P450 enzyme system, which means that ximelagatran has a low potential for drug interactions, and there are no known clinically relevant interactions with food or alcohol.[34,37,42]

Several clinical trials have shown that ximelagatran is an effective and well-tolerated agent for the primary prevention of venous thromboembolism after total hip or total knee replacement.[43-47] In addition to these studies in patients undergoing major elective orthopaedic surgery, clinical trials in patients with acute, or at risk of recurrent, venous thromboembolism have verified that ximelagatran holds great promise for both the short-term treatment and long-term secondary prevention of venous thromboembolism.[48–50]

4.2 Ximelagatran for the Treatment of Acute Venous Thromboembolism

The **Thr**ombin **I**nhibitor in **V**enous Thrombo**E**mbolism (THRIVE) I investigators initially explored ximelagatran as an alternative to currently used anticoagulant therapy for initial treatment of DVT in a dose-ranging study that compared ximelagatran with LMWH–warfarin in patients with acute proximal DVT.[48] A total of 350 patients were allocated randomly to groups to receive 2 weeks of treatment with one of four doses of oral ximelagatran between 24mg and 60mg twice daily, or with dalteparin 200 U/kg subcutaneously once daily, followed by conventional-intensity oral warfarin (dose adjusted to achieve a target INR 2.0–3.0), and paired venograms ade-

quate for evaluation were available from 295 patients. Regression in thrombus size occurred in 69% of patients treated with either ximelagatran or dalteparin–warfarin, with no statistically significant difference between any of the treatment groups. The incidence of discontinuation of study drug because of bleeding was low, occurring in 0–1.5% of patients assigned to treatment with ximelagatran and 2.7% of patients receiving dalteparin–warfarin.

Treatment with ximelagatran alone for the duration of a standard 6-month course of treatment has been shown to be as effective as standard treatment with the LMWH, enoxaparin and warfarin in the initial treatment and prevention of recurrent venous thromboembolism.[49] In the Phase III, double-blind THRIVE Treatment study, 2489 patients with acute, symptomatic DVT with or without pulmonary embolism were allocated randomly to groups to receive ximelagatran 36mg orally twice daily, or enoxaparin 1 mg/kg subcutaneously twice daily for at least 5 days, followed by conventional-intensity oral warfarin (target INR between 2.0 and 3.0). No coagulation monitoring was undertaken in the ximelagatran group. The estimated cumulative risk of recurrent venous thromboembolism was similar between the treatment groups (2.1% for ximelagatran and 2.0% for enoxaparin–warfarin). Ximelagatran also seems to have an advantage over enoxaparin–warfarin with respect to the estimated cumulative risk of major bleeding (1.3% for patients treated with ximelagatran, compared with 2.2% for patients receiving enoxaparin–warfarin); however, this difference was not statistically significant.

4.3 Long-Term Ximelagatran for Secondary Prevention of Recurrent Venous Thromboembolism

The results of the THRIVE III clinical trial showed that, after a 6-month period of standard anticoagulation therapy, extended treatment with fixed-dose ximelagatran (24mg twice daily) is highly effective in the prevention of recurrent venous thromboembolism after an initial event.[50] The THRIVE III trial was a Phase III trial in which 1233 patients with previous symptomatic, confirmed venous thromboembolism that had not recurred during an initial 6 months of anticoagulant therapy were allocated randomly to treatment with ximelagatran or placebo for 18 months. The patient population in question was at moderate risk of recurrence. Relative to placebo, there was a continuing reduction in the risk of recurrence with ximelagatran over time (figure 3). The estimated cumulative risk of recurrent venous thromboembolism over the study period was 2.8% in the ximelagatran group and 12.6% in the placebo group ($p < 0.001$). The hazard ratio for recurrence with ximelagatran was 0.16, which is lower than the hazard ratio of 0.36 that was reported with long-term low-intensity warfarin in the placebo-controlled PREVENT trial.[32] No significant between-group difference in the incidence of major bleeding was observed in THRIVE III, the estimated cumulative risk of which was 1.1% for patients treated with ximelagatran and 1.3% for those treated with placebo (hazard ratio 1.16, 95% confidence interval 0.35 to 3.80).

During longer-term use of ximelagatran (more than 35 days), transient, asymptomatic increases in liver enzymes, mainly alanine aminotransferase

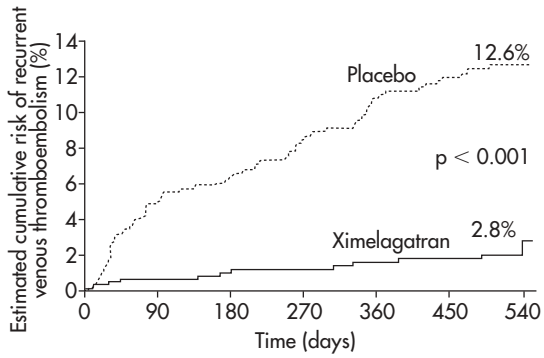

Fig. 3. Estimated cumulative risk of recurrent venous thromboembolism over time in the THRIVE III study. (With permission from Schulman S, Wahlander K, Lundstrom T, et al. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med 2003; 349: 1713-21[50])

(ALT), have been observed in a proportion of patients. In THRIVE III, the incidence of a transient increase in ALT concentration to more than three times the upper limit of normal (figure 4) was 6.0% in the ximelagatran group, as compared with 1.0% in the placebo group ($p < 0.001$).[51] In the THRIVE Treatment study, the incidence of increases in ALT (more than 3-fold higher than the upper limit of normal) was 2% in the enoxaparin–warfarin group and 9.6% in the ximelagatran group.[49] In each case, the increase in incidence of increases in ALT was restricted to the first few months of treatment; it did not result in progressive hepatic dysfunction and ALT concentrations decreased spontaneously whether treatment was continued or discontinued. In addition, it has been recognised that patients will require appropriate evaluation with regard to possible increases in ALT during initial long-term treatment, and patient management strategies are currently being developed.

5. Conclusions

Currently available therapeutic strategies provide effective acute treatment of venous thromboembolism and reduce the risk of recurrence, but the requirements for injections, coagulation monitoring and dose adjustment that are inherent in these strategies are less than ideal. In clinical practice, treatment of venous thromboembolism poses several challenges.

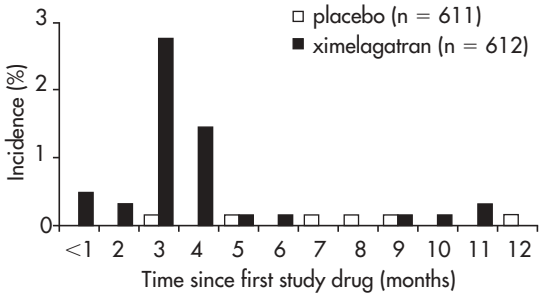

Fig. 4. Incidence of increases in alanine aminotransferase concentrations more than 3-fold higher than the upper limit of normal in patients randomised to ximelagatran or placebo in the THRIVE III trial. (With permission from Eriksson H, Wahlander K, Lundstrom T, et al. Extended secondary prevention with the oral direct thrombin inhibitor ximelagatran in patients with venous thromboembolism [abstract no. OC005]. XIX Congress of The International Society of Thrombosis and Haemostasis; 2003 July 14; Birmingham: vol 1 Suppl. 1[51])

The results of the THRIVE Treatment study have shown that ximelagatran provides an effective and well-tolerated alternative to the currently recommended regimen of heparin followed by 6 months of warfarin therapy in patients requiring treatment after an acute event.

For many patients with venous thromboembolism, secondary prevention with vitamin K antagonists is not extended beyond 6 months, because the risk of recurrence may be outweighed by the risk of major bleeding. The clinician is then faced with the decision of what to do next. One option available to them is to treat the venous thromboembolism as a chronic disease and continue treatment beyond 6 months. In the PREVENT and ELATE trials, long-term low-intensity warfarin reduced the risk of recurrent thrombosis by about 75%, whereas conventional-intensity treatment reduced the risk by at least 90%. However, the long-term use of warfarin for secondary prevention of venous thromboembolism in the setting of clinical practice brings with it a number of problems, including safety and compliance issues (e.g. need for monitoring, bleeding risks, drug–drug interactions and food–alcohol interactions). The results of the THRIVE III trial confirmed the legitimacy of using ximelagatran in the long term for the secondary prevention of venous thromboembolism.

Compared with heparin and warfarin, it could be argued that ximelagatran better fits the optimal treatment profile for an anticoagulant. It provides consistent and effective anticoagulation with low potential for interaction with other drugs and can be administered orally, with no requirement for coagulation monitoring or dose adjustments.

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Correspondence and offprints: *Henry Eriksson*, Department of Medicine, Sahlgrenska University Hospital/Östra, Gothenburg, Sweden.
E-mail: henryeriksson@swipnet.se