Current Issues in Anticoagulation

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Key Words

Venous thromboembolism · Ximelagatran · Melagatran · Stroke · Atrial fibrillation · Orthopaedic surgery · Direct thrombin inhibitors · Heparins · Vitamin K antagonists

Abstract

Anticoagulation therapy with unfractionated heparin, low-molecular-weight heparins and oral vitamin K antagonists is currently the mainstay of treatment and prevention of thromboembolic disorders (such as deep vein thrombosis, pulmonary embolism and stroke prevention in patients with atrial fibrillation). Although these therapies have proven benefits, they also have important limitations that result in their underuse in routine clinical practice. Consequently, many patients identified by guidelines as requiring anticoagulant therapy receive no or inadequate treatment. Heparins require parenteral administration and pose the risk of heparin-induced thrombocytopenia. Vitamin K antagonists have a narrow separation of antithrombotic and haemorrhagic effects and numerous food and drug-drug interactions, and require frequent coagulation monitoring and dose adjustment to ensure effective antithrombotic protection while minimizing the risk of bleeding complications. In response to these limitations, several new anticoagulants have recently been developed, including selective factor Xa inhibitors such as fondaparinux and ximelagatran, the first oral agent in the new class of direct thrombin inhibitors and the first new oral anticoagulant for almost 60 years.

Ximelagatran possesses many of the properties of an ideal agent for anticoagulation therapy. With its oral formulation, consistent and predictable pharmacological profile and no coagulation monitoring, ximelagatran has the potential to increase the use and duration of anticoagulation treatment in thromboembolic disorders and to reduce the burden associated with long-term management.

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Introduction

Anticoagulant agents are central to the treatment and prevention of various thromboembolic disorders, including deep vein thrombosis (DVT), pulmonary embolism and stroke associated with atrial fibrillation (AF) [1, 2]. Currently, the most widely used anticoagulants include the indirect thrombin inhibitors, such as heparin (unfractionated heparin [UFH] and low-molecular-weight heparins [LMWHs]), and vitamin K antagonists (VKAs), in particular warfarin. However, these classes of agents have inherent limitations that result in significant underuse in clinical practice. UFH and LMWHs require parenteral administration, restricting their utility in the outpatient setting, and are associated with the rare but potentially fatal complication of heparin-induced thrombocytopenia [3]. VKAs offer the convenience of oral administration but have a narrow therapeutic index and are subject to numerous food-drug and drug-drug interactions [4], and regular coagulation monitoring and dose adjustments are necessary to ensure adequate antithrombotic protection

Fig. 1. A meta-analysis of trials comparing warfarin with placebo for the prevention of stroke in AF patients. Error bars = 95% CI. Adapted with permission from Hart et al. [9].

while minimizing the risk of bleeding complications. This article considers the clinical implications of these limitations in key indications for anticoagulant therapy, and how they have driven the search for new anticoagulant agents offering an improved profile of efficacy, safety and convenience.

Stroke Prevention in Atrial Fibrillation

AF is the most common cardiac arrhythmia, and the risk of AF increases markedly with age. The prevalence of AF rises from 2.3% in people older than 40 to 5.9% in those older than 65, and the majority of people with AF are aged between 65 and 85 [5]. Although once regarded as a relatively benign condition, AF is now known to be a leading risk factor for stroke [6]. While coronary heart disease and hypertension have been found to increase the risk of stroke by two- and three-fold, respectively, AF is associated with a five-fold increase in stroke risk [7]. Approximately 25% of all strokes in patients aged between 80 and 89 are attributable to AF [7]. Therefore, prophylactic anticoagulant therapy is an important component in the management of patients with AF in order to reduce the burden of stroke-related morbidity and mortality. Such strategies have also been shown to be cost-effective, particularly among elderly patients [8].

Prophylactic anticoagulation therapy with the oral VKA warfarin is proven to be effective in the prevention of AF-associated stroke. A meta-analysis of six trials that compared dose-adjusted warfarin with placebo showed that, in all the trials, warfarin was superior to placebo in reducing the risk of stroke (fig. 1) [9]. The mean risk reduction obtained with warfarin compared with placebo was 62% for stroke and 26% for all-cause mortality [9].

These results provide a strong imperative for prophylactic anticoagulant therapy for patients with AF. However, there is a wealth of data from both Europe and North America showing that many patients with AF who are eligible for prophylaxis according to current guidelines [10] do not receive appropriate treatment. For example, an Italian study of 224 hospital inpatients with AF found that only 21% of eligible patients received oral anticoagulant therapy, and even among the 98 patients with chronic AF only 25% were treated with VKAs. Of all the patients with AF, nearly half received no prophylactic treatment (anticoagulants or antiplatelets) [11]. Similarly, in a study of 3,575 Canadian inpatients with AF, 33% received no prophylaxis, 24% were treated with warfarin alone, 35% received aspirin alone and 8% received both warfarin and aspirin [12]. A US study found that the proportion of outpatients with AF receiving oral anticoagulant treatment with warfarin rose from 13% in 1989 to 40% in 1993. However, between 1993 and 1996 there was

Fig. 2. Percentage of elderly AF patients taking warfarin by age group. Reprinted from [21], copyright 1999, with permission from Excerpta Medica.

no further increase in warfarin use, indicating that the majority of eligible patients continued to not receive appropriate prophylactic therapy [13].

An overview of studies in different healthcare settings indicates that 38–44% of patients discharged from hospital and eligible for oral anticoagulation receive warfarin at the time of discharge [14–16], compared with 20–32% of nursing home patients [17, 18] and 11–32% of patients in the community setting [13, 14, 19]. Taken together, the data clearly demonstrate that prophylaxis with oral anticoagulants is substantially underused and that, despite growing evidence of the importance of stroke prevention in patients with AF and the efficacy of VKAs in this indication, this situation is not changing.

A further important consideration is the use of VKAs according to patient age. Not only is AF more common with advancing age [5], but the risk of stroke associated with AF also increases. For example, data from the Framingham study indicate that in patients with AF, the incidence of stroke per 1,000 patient-years rises from 21 in those aged 60–69 to 49 in those aged 70–79, and reaches 71 in patients aged 80–89 [20]. Despite the increasing risk of stroke with advancing age in patients with AF, the use of prophylaxis actually declines with increasing age. In a US community-based study of patients with AF between 1993 and 1995, the proportion of patients receiving warfarin was 47% for those between the ages of 69 and 79,

falling to 24% for those aged 80–89 and 15% for patients 90 years or older (fig. 2) [21]. Thus, the population at the highest risk of AF-associated stroke is the least likely to receive appropriate prophylaxis with oral anticoagulants.

In summary, prophylaxis with oral VKAs is effective in the prevention of AF-associated stroke, but limitations including a narrow separation of antithrombotic and haemorrhagic effects and the need for frequent coagulation monitoring and dose adjustments reduce its practicality and convenience as chronic therapy. The difficulty in maintaining optimal levels of anticoagulation with warfarin can lead to sub-optimal or over-anticoagulation, which may have serious clinical implications for patients. These safety and convenience issues result in significant underuse, particularly among those elderly patients who are most at risk. Consequently, new anticoagulant agents that are at least as effective as warfarin but are more practical for routine clinical use are needed; these agents have the potential to increase the proportion of eligible patients that receive appropriate therapy. Furthermore, new oral agents without a narrow therapeutic index could help extend the benefits of prophylaxis to those patients at high risk of bleeding complications who may consequently not be prescribed warfarin.

Fig. 3. Cumulative hazard of recurrence of VTE in patients assigned to either 3 months' or 1 year's oral anticoagulant therapy. Adapted with permission from Agnelli et al. [23].

Treatment and Long-Term Secondary Prevention in Venous Thromboembolism

Another indication for anticoagulant therapy is in the treatment and long-term secondary prevention of venous thromboembolism (VTE). Typically, patients with acute VTE are treated for 5–10 days with UFH or LMWH, followed by 3–12 months of VKA therapy dose-adjusted to achieve an international normalized ratio (INR) of 2.0–3.0 [22]. Rates of recurrence during the acute phase are low – approximately 1%. However, although rates of recurrence are low while patients remain on long-term treatment, when treatment is discontinued almost 15% of patients experience recurrence. This was demonstrated in a study from our own group that compared 3 months with 1 year of oral anticoagulant therapy after idiopathic DVT (fig. 3) [23]. The point to note is that the clinical benefit of extending anticoagulant therapy to 1 year was not maintained after therapy was stopped.

These results suggest that more important than debating the optimal duration of oral anticoagulant therapy is considering the various treatment options available after a certain period, say 6 months, of prophylaxis. One option is to accept the risk of recurrence and discontinue treatment in all patients. The benefit of this approach is that it avoids the risk of haemorrhagic complications, but this will come at the cost of an increased rate of recurrent

VTE. Alternatively, anticoagulant therapy might be extended indefinitely in all patients. This should provide extended protection against recurrent VTE but needs to be balanced against the risk of bleeding associated with oral anticoagulant therapy. For example, in a meta-analysis of nine studies of warfarin dose-adjusted to achieve an INR of 2.0–3.0 for the treatment of DVT, the rate of fatal or major haemorrhage was 0.4% per month and the rate of total bleeds was 2.5% per month [24], reinforcing the point that there is a trade-off when using warfarin – efficacy versus an increased risk of bleeding. A third option is to identify those patients at high risk of recurrent VTE based on underlying risk factors, and target these patients with extended prophylaxis. Finally, the availability of new treatment options, such as the oral direct thrombin inhibitor ximelagatran, raises the possibility of extending prophylaxis with new agents. Given the limitations of VKAs, the availability of new oral anticoagulants that are more predictable and practical for chronic use in the out-patient setting should facilitate the use of extended prophylaxis in a greater proportion of patients.

In summary, the risk of recurrence of VTE is critically dependent on underlying risk factors and whether the patient continues treatment with oral anticoagulant therapy. The decision as to whether to continue with prophylaxis needs to take into account the risk of bleeding, and patient compliance and preference, as well as the burden

Fig. 4. Trends in the average length of hospital stay (**A**) and the duration of anticoagulant prophylaxis (**B**) for patients undergoing major orthopaedic surgery. Reproduced with permission from Chest [29].

of management associated with therapy. New treatment options associated with a reduced bleeding risk and greater practicality for patients and physicians compared with VKAs would therefore be expected to shift the balance of benefit and risk to favour long-term prophylaxis in a greater proportion of patients.

Prevention of Thromboembolic Events after Elective Hip or Knee Replacement Surgery

Patients undergoing major elective orthopaedic surgery, such as total hip replacement (THR) or total knee replacement (TKR), are at particularly high risk of VTE

[25]. Data have shown that primary prophylaxis is recommended for all patients undergoing major elective orthopaedic surgery, and a number of agents have been shown to be effective to varying degrees in reducing the risk of VTE [25]. For example, in THR, while aspirin reduced the risk of DVT by 26%, anticoagulant therapy was substantially more effective in the prevention of DVT after THR surgery (mean relative risk reductions of 59% with warfarin, 44% with UFH, 70% with LMWH and 70% with recombinant hirudin) [25]. As well as the very high risk of VTE during and in the days immediately after surgery, in the absence of appropriate prophylaxis, patients continue to be at high risk after discharge from hospital. For example, in the absence of prophylaxis, 10–20% of patients who have undergone THR develop DVT within 4–5 weeks of hospital discharge [26–28].

Two developments in the clinical management of major orthopaedic surgery patients over the last decade are of particular relevance in this regard. First, the average hospital stay for these patients is getting shorter. In a US study, the average length of hospital stay fell from approximately 4.6 days in 1996 to 3.7 days in 2001 (fig. 4A) [29]. Second, over the same 5-year time frame, the proportion of patients receiving prophylaxis for at least 21 days increased by 10% (fig. 4B) [29].

To summarize, anticoagulant therapy is critical to prevent the high rates of VTE associated with major orthopaedic surgery, and needs to be considered within the context of shortening hospital stays and increasing duration of prophylaxis after surgery. Agents that are at least as effective as LMWH or VKAs in the prevention of VTE but are more practical and convenient for use may offer benefits within this changing pattern of clinical management.

Unmet Clinical Needs and New Therapeutic Options

Overall, there is substantial opportunity to improve the status of anticoagulation by using agents that have comparable efficacy to current treatments but increased safety and practicality. In particular, the opportunity exists to:

- simplify the initial and long-term management of vascular diseases;
- increase the proportion of patients with AF who receive appropriate prophylaxis with anticoagulant therapy;

Table 1. Key characteristics of ximelagatran

Fixed oral dosing, twice daily
Rapid absorption and bioconversion to active form, melagatran
Predictable pharmacokinetics
Fast on- and offset of action
Low potential for drug-drug interactions
No interactions with food or alcohol
No heparin-induced thrombocytopenia
No coagulation monitoring

- reduce the burden associated with treatment and long-term secondary prevention after VTE, thus facilitating extended treatment and reducing recurrence rates in the long term;
- reduce the time spent in hospital by patients undergoing major orthopaedic surgery.

The limitations of current anticoagulants have driven the development of new anticoagulants, including selective factor Xa inhibitors such as fondaparinux and idraparinux [30], and inhibitors of tissue factor and factor VIIa [31]. The oral agent that is most advanced in clinical development is ximelagatran, which represents the first new oral anticoagulant since the introduction of the VKAs almost 60 years ago. Ximelagatran was recently approved in Europe for the prevention of VTE in patients undergoing elective hip or knee replacement surgery [32–35] and is being evaluated for use in stroke prevention in AF [36–38] and the treatment [39] and long-term secondary prevention [40] of VTE.

Ximelagatran has a number of characteristics that may help meet the unmet needs in anticoagulant therapy (table 1). Firstly, ximelagatran is the first agent in the new class of direct thrombin inhibitors that can be orally administered. It is rapidly absorbed and bioconverted to its active form, melagatran. Unlike the heparins, melagatran shows low binding to plasma proteins, has predictable pharmacokinetics and is not associated with the risk of heparin-induced thrombocytopenia [41]. In contrast to VKAs, oral administration of ximelagatran has a rapid onset and offset of action, with a $t_{\max}$ for melagatran of 1.5–2 h and a half-life of 4–5 h [42], simplifying clinical management when initiating or discontinuing anticoagulant therapy. Furthermore, unlike VKAs, ximelagatran does not interact with food or alcohol and has a low potential for drug-drug interactions. Finally, ximelagatran does not have a narrow separation of antithrombotic and haemorrhagic effects, unlike warfarin [43], and does not require coagulation monitoring. Elevations in serum

transaminase enzyme levels have been reported to occur in a proportion of patients on ximelagatran during the first 1–6 months of treatment, but were generally transient and without clinical sequelae whether or not treatment was continued [37, 40]. It is likely therefore that regular liver function testing will be required when a patient starts ximelagatran treatment.

Based on its promising profile and the results of clinical trials to date, ximelagatran has the potential to in-

crease the use and duration of anticoagulation therapy for thromboembolic disorders and reduce the burden on physicians and healthcare systems associated with long-term management. Through its positive benefit-risk profile, ximelagatran may also increase the proportion of patients with AF who are eligible for treatment and maximize the potential of anticoagulation in the prevention of stroke.

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