Review Article

New Oral Anticoagulants: Should They Replace Heparins and Warfarin?

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Thromboembolic diseases are a major problem of public health. They have a great impact on mortality in both the general population and hospitalised patients. Heparins – unfractionated heparin (UFH) and low molecular weight heparins (LMWH) – and vitamin K antagonists (VKAs) have formed the cornerstone of antithrombotic treatment and prophylaxis for the last 60 years.[1-3] Heparins are rapidly acting parenteral anticoagulants. They are widely used for the prevention and initial short-term treatment of venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE).[2] VKAs are currently widely used for VTE treatment and prophylaxis in medical and surgical patients.[2] Both heparins and VKAs are used for the long-term prevention of stroke and systemic thromboembolism in patients with valvular and non-valvular atrial fibrillation (AF), for the secondary prevention and treatment of patients with acute coronary syndromes and whenever inhibition of intravascular clot formation is needed.[2]

Although UFH has been used for decades, during the last 20 years LMWH have almost replaced UFH, since their use offers significant advantages.[1,2] LMWH are considered effective, safe and more convenient alternatives for the treatment and prevention of VTE, as they are administered subcutaneously, once or twice daily, in doses defined relative to the body weight.[1,2] In the majority of patients there is no need to monitor efficacy.[1,2] Their anticoagulant effect should be tested only in patients with severe kidney disease, in the elderly, in the over- and under-weighted and during pregnancy.[1,2] Heparin-induced thrombocytopenia, osteoporosis and alopecia are rarely observed in patients following the use of LMWH.[1,2] Nevertheless, one concern regarding their use is the need for parenteral administration.[1,2]

To date, VKAs are the only available oral anticoagulants approved for the prevention and long-term treatment of arterial and venous thromboembolism in medical and surgical patients.[3] Commonly used VKAs are warfarin, acenocoumarol and phenindione.[3] They have similar pharmacokinetic properties and side effects.[3] However, their use has a number of limitations. They have a slow onset of action and a correspondingly slow reversion time to normal.[3] When immediate anticoagulant effect is needed, administration of parenteral fast-acting anticoagulants (UFH or LMWHs) is necessary.[3] Moreover, oral anticoagulants have a narrow therapeutic range and their effect needs frequent monitoring with determination of the international normalised ratio

(INR).[3] Metabolism of oral anticoagulants is affected by genetic factors.[3] Cytochrome P450 plays a critical role in this process.[3] It has been determined that polymorphisms in the CYP2C9 enzyme of this cytochrome alter the clearance of VKAs and affect dose and efficacy.[3] Another variant of cytochrome P450, CYP4F2, is also associated with warfarin dosage.[3] The enzyme VKORC1 converts oxidised vitamin K to its active form required for the carboxylation of coagulation factors. This enzyme is the target of the oral anticoagulants. It has been identified that polymorphisms in VKORC1 affect the response to warfarin and other VKAs.[3]

Additionally, VKAs have multiple interactions with drugs that are metabolised in cytochrome P450. Diet may also affect warfarin metabolism, especially when foods contain substantial amounts of vitamin K, as do green leafy vegetables. For these reasons, patients who are permanently anticoagulated should have frequent and close monitoring of the anticoagulant effect of VKAs.[3] Monitoring should be closer during the initiation of treatment. In particular, during the first three months after the initiation of treatment, patients are vulnerable to serious haemorrhagic episodes and show an increased recurrence rate of the thrombotic event. [3]

Necessity for new drugs

Although heparins are safe and effective agents for the rapid initiation of treatment in acute thrombotic events and VKAs remain a reliable and inexpensive treatment option when long-term anticoagulation treatment is indicated, there are several limitations to their use.[3,4] Parenteral administration for heparins, the need for frequent monitoring, and the risk of haemorrhagic complications for both groups are major concerns in their administration. Furthermore, the population requiring long-term anticoagulation is large and expanding and the need for new orally administered anticoagulants with improved characteristics is essential.[3,4]

During the last decades, excessive research has been carried out into the pathogenesis of thrombotic diseases. This has led to major efforts to produce orally administered anticoagulants with improved characteristics that probably will replace the older antithrombotic agents.[4] The "ideal" anticoagulant should be as effective as heparin and VKAs in preventing thrombus formation and at least equally safe with regard to the bleeding risk.[4]

In addition, an improved oral anticoagulant should also have some other desired properties. It should be administered orally once or at most twice daily and must have good bioavailability. The therapeutic effect should be obtained soon after oral administration, so there will be no need for "bridging" therapy with UFH or LMWHs.[4] The currently used anticoagulants, and especially VKAs, act against multiple coagulation factors. An ideal new anticoagulant should preferably target a specific coagulation factor, e.g. activated factor X (FXa) or thrombin.[4] The "ideal" anticoagulant should also be free of interactions with other drugs and food. It must have a wide therapeutic range, so the risk of haemorrhagic complications or recurrent thrombosis will be eliminated. The anticoagulant response should be predictable and related to the administered dose.[4] This will allow use without the need for monitoring the anticoagulant effect or dose titration.[4] Furthermore, the anticoagulant effect of an improved drug should be reversible by a specific antidote.[4] An "ideal" anticoagulant should not have unexpected toxicities unrelated to the anti-haemostatic activity—as recently occurred with ximelagatran, which was associated with unacceptable liver toxicity and deaths and was withdrawn from use soon after its initial introduction, without being approved by the US Food and Drug Administration.[4] A laboratory test ensuring efficacy and adherence to treatment should be also available and, finally, the cost should be reasonable and at least comparable with that of the widely used older drugs.[4]

Nowadays, there are agents that fulfil some of these criteria for the "ideal" oral anticoagulant. The first group includes rivaroxaban, apixaban, betrixaban, and edoxaban, and targets FXa. Another new oral anticoagulant, dabigatran, belonging to the class of the orally administered direct thrombin inhibitors, is also currently available.[4] There is substantial evidence coming from phase II and III studies that these drugs are safe and effective for the treatment of thromboembolic disease. Probably some ongoing trials will better establish their efficacy in several categories of patients and support their widespread use.[4]

The role of factor Xa and thrombin in the coagulation system

Anticoagulant administration aims to reduce or prevent intravascular blood clotting.[1-4] The process of thrombus formation is the final step in the activation of two different pathways, the contact pathway (in-

trinsic pathway) and the tissue factor pathway (extrinsic pathway).[5] These two pathways initiate coagulation and lead to the formation of FXa. The role of FXa is significant in the process of coagulation, because it leads to the transformation of prothrombin to thrombin and activation of the final common pathway of the coagulation cascade. In turn, the final common pathway leads to clot formation by transforming fibrinogen to insoluble fibrin (Figure1).[5]

When vascular damage occurs, tissue factor (TF) is exposed to other circulating coagulation components and forms complexes with FVIIa.[5] The TF-FVIIa complex activates FX. Additionally, the intrinsic coagulation cascade pathway is simultaneously triggered by vascular damage. Coagulation factors XII, XI, IX are activated and subsequently enhance factor X activation. Factors Xa, Va and VIIIa, form the prothrombinase complex which catalyses the transformation of prothrombin to thrombin.[5]

Thrombin generation plays a critical role in clot formation; it catalyses the transformation of fibrinogen to insoluble fibrin.[5] Thrombin also exerts additional thrombogenic properties.[5] It promotes activation of factors V, XI and VIII. Activated FVIII in turn contributes to thrombus stabilisation. Moreover, thrombin is one of the more potent platelet "agonists" and may also express additional prothrombotic potential because of an inhibitory effect on the endogenous fibrinolytic activity.[5]

Mode of action of UFH and LMWHs

UFH is an heterogeneous mixture of polysaccharide chains with variable molecular weight ranging from 3,000 to 30,000.[1,2] LMWHs are glycosaminoglycans consisting of chains of alternating residues of D-glycosamine and either glycuronic or iduronic acid. They are fragments of UFH produced by depolymerisation and their mean molecular weight is about 5,000.[1,2]

The anticoagulant effect of both UFH and LMWHs is exerted by antithrombin activation.[1,2] Pentasaccharide sequences are randomly distributed along the molecules of UFH and LMWHs and interact with endogenous antithrombin.[1,2] LMWHs contain significantly less pentasaccharide sequences than UFH.[1,2] Pentasaccharide binding to antithrombin leads to conformational changes in the antithrombin molecule and accelerates interaction with thrombin and FXa. The main difference between UFH and LMWHs is in their inhibitory action against FXa and thrombin. Most of the UFH chains contain at least 18 saccharides and form ternary complexes with both antithrombin and thrombin. Few chains of LMWHs have this length of saccharide sequences and subsequently the potency to bind both antithrombin and thrombin. In contrast to UFH, the complex of LMWHs and antithrombin binds FXa and catalyses its inactivation. Thus, LMWHs express higher activity against FXa than against FIIa, whereas UFH inactivates both

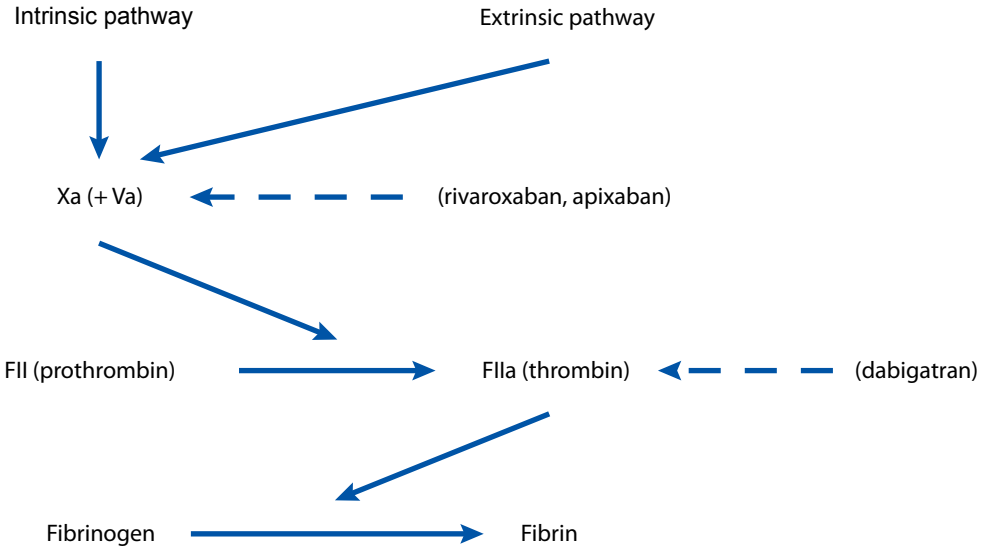

Figure 1. Coagulation cascade and sites of action of the novel anticoagulants.

thrombin and FXa.[2] Moreover, both UFH and LMWHs trigger the release of tissue factor pathway inhibitor from the damaged endothelium, enhance its inhibitory effect on FXa and FVIIa and contribute to the endogenous anticoagulant activity.[5]

The anticoagulant activity of UFH begins soon after subcutaneous and bolus or continuous intravenous infusion.[1] The anticoagulant activity of UFH is monitored by the determination of activated partial thromboplastin time (aPTT). Activated PTT is a reliable and generally accepted test for the laboratory monitoring of UFH activity.[1] However, in some situations aPTT is resistant to the effect of sufficient doses of UFH. This occurs when FVIIIa or fibrinogen levels are high, in cases of acute inflammation or extended thrombosis. In these circumstances, despite infusion of adequate amounts of UFH to achieve therapeutic anti-Xa levels, aPTT remains sub-therapeutic.[6] In these cases there is an "apparent heparin resistance"; therefore, it is preferred that anti-Xa activity be used for monitoring in order to avoid the administration of excessive UFH amounts, which can lead to extremely high and dangerous heparin plasma levels.[6] Protamine sulphate is a specific antidote that effectively reverses the anticoagulant effect of UFH and may be used in cases of severe haemorrhagic complications or excessive dosage.[1,2]

LMWHs are administered subcutaneously once or twice daily.[1] They produce a more predictable anticoagulant effect than that of UFH and they have a longer half-life and better bioavailability, related with their reduced binding to plasma proteins, endothelium and macrophages.[1] Their clearance is dose dependent. In this context there is no need for laboratory monitoring, except in patients with renal insufficiency and those with very high or low body weight.[1] Moreover, LMWHs bind to the platelets to a lesser extent than does UFH, and they express a lower affinity with endothelial cells and high molecular weight multimers of von Willebrand factor.[1] Because of these properties, LMWHs have less interference with platelets and vessel wall and cause less bleeding compared to UFH. Although the majority of patients treated with LMWHs do not need monitoring, plasma anti-Xa activity should be assessed in selected patients (elderly, pregnant, obese and those with severe kidney disease).[1] Anti-Xa activity is commonly monitored using a commercially available chromogenic assay. However, there is no clear relationship between anti-Xa levels and clinical outcome or bleeding in many patients.[1,2]

Anti-Xa activity determination may not accurately reflect the anticoagulant effect of LMWHs, because they also inhibit thrombin (FIIa).[1,2,7] The anti-IIa / anti-Xa activity of several categories of LMWHs depends on the length of saccharides and consequently on their molecular weight.[7] The anti-Xa activity requires the presence of the pentasaccharide sequence, whereas the anti-IIa activity requires a chain length of at least 18 saccharides. Therefore, it is necessary for some LMWH preparations that the anti-IIa activity also be monitored.[7] Although LMWHs are administered in fixed doses according to the total body weight and exhibit predictable anticoagulant properties, in rare cases, haemorrhagic complications may occur.[8,9] Protamine sulphate effectively reverses the anticoagulant effect of UFH; however, it only partially reverts the effect of LMWH. Approximately 60% (mainly the anti-Xa activity) of LMWH action is neutralised by protamine sulphate.[8,9] Therefore, in some cases of severe haemorrhage, protamine sulphate may not be sufficient to stop bleeding.[7] Additionally, in high doses protamine sulphate may also exhibit anticoagulant properties in its own right.[8,9] Consequently, protamine sulphate infusion should not exceed a maximum dose of 50 mg. Repeated doses of protamine sulphate should be considered when bleeding continues, and not on the basis of plasma anti-Xa results, or prolonged aPTT levels.[8,9] Moreover, discrepancy in the neutralisation of LMWHs depends on the molecular size of each preparation, the total sulphate content per saccharide unit, and consequently on the different anti-IIa and anti-Xa activity of each preparation.[8,9]

Fresh frozen plasma (FFP) and/or recombinant activated FVII (NovoSeven®) are effective in reversing the anticoagulant effect of LMWHs and should be administered in unstable patients with severe haemorrhage or postoperative bleeding.[1,9]

Indications for use

UFH and LMWHs are indicated as initial therapy for DVT and PE.[1,2] UFH is administered as an intravenous continuous infusion. LMWHs are administered subcutaneously, without laboratory monitoring and this set the basis for outpatient management of VTE in stable patients.[1,2] LMWHs have been proven as safe and effective as UFH and they have nearly replaced UFH administration.[1,2] LMWHs have been also proven equally effective and safe as UFH for the treatment of unstable angina and the other acute cor-

onary syndromes, in combination with the antiplatelet agents.[1,2] LMWH administration is more convenient than that of UFH because they are administered subcutaneously and there is no need for laboratory monitoring.[1,2]

Low-dose UFH or LMWHs are also indicated and widely used for the prevention of DVT and PE in patients after general surgery, total hip and knee replacement and other orthopaedic interventions that have a high risk of developing VTE. Thromboprophylaxis with LMWHs or UFH is also indicated in medical patients.[1,2] Moreover, LMWHs may be used for the long-term prevention and treatment of VTE and PE in patients with active cancer. There are indications that LMWH administration in cancer patients offers an advantage in survival, relative to other anticoagulant treatments.[1]

VKAs mode of action - indications for use

Coumarins act as vitamin K antagonists and have been the cornerstone of oral antithrombotic therapy for more than 60 years.[3] They are used for the long-term prevention and treatment of DVT and PE, as prophylaxis against recurrent myocardial infarction, and for the lifelong prevention of cerebrovascular and peripheral embolic episodes in patients with mechanical heart valves and chronic non-valvular atrial fibrillation.[3]

VKAs inhibit vitamin K epoxide reductase (VKORC1) and the carboxylation of vitamin K-dependent coagulation factors II, VII, IX and X in the liver.[3] Subsequently, partially carboxylated coagulation factors exert a reduced coagulant potential. In addition, VKAs inhibit the carboxylation of the endogenous anticoagulant proteins C and S.[3]

The most commonly used VKAs in Europe and the US are warfarin and acenocoumarol. Following oral administration, they are rapidly absorbed by the gastrointestinal system and bind to plasma proteins.[3] They have high bioavailability and reach maximum concentrations soon after their administration. They have a long half-life. VKAs accumulate in the liver and are metabolised by the CYP2C9 enzyme of the cytochrome P450.[3]

The efficacy of anticoagulation treatment is monitored via the determination of INR.[3] This is a simple, not time-consuming and relatively inexpensive test, which does not need specialised personnel or equipment. It mirrors the patients' compliance and is very well related to the administered dose and the intensity of treatment.[3] Anticoagulation treatment is effective when the INR ranges between 2 and 3.[3] For patients with a prosthetic mitral valve or recurrent thrombotic events INR should be prolonged to 3.5.[3]

The major adverse event following VKA administration is haemorrhagic tendency.[3] It has been reported that patients with cerebrovascular ischaemic episodes on anticoagulant therapy with VKAs have a bleeding risk ranging from 2-13%. The risk ranges from 1-8.3% in patients with mechanical heart valves, whereas in patients with VTE the risk ranges from 0-16.7%. Patients with ischaemic heart disease have a bleeding risk up to 19.3%. In contrast, in patients with atrial fibrillation the risk ranges between 0% and 6.6%. This variation in the incidence of haemorrhagic complications is probably associated with several factors, such as patient characteristics and the length and the intensity of therapy.[9]

Bleeding episodes are more common in patients who have a prolonged INR and are receiving concomitant treatment with aspirin, clopidogrel and non-steroidal anti-inflammatory drugs.[9] Patients with comorbidities (chronic liver failure and severe renal disease) and the elderly may exhibit haemorrhagic complications more commonly.[9] Rare side effects of coumarins are skin necrosis and blue toe syndrome.[3] Patients under long-term treatment may exhibit osteoporosis.

Vitamin K is a specific antidote for VKAs and can reverse their anticoagulant effect in cases of bleeding or when INR is prolonged.[3] Patients who have a high INR without active bleeding require the withholding of VKAs alone, or the simultaneous administration of vitamin K, orally, intravenously or subcutaneously. This strategy allows the INR to fall quickly into a therapeutic range.[10] In patients who bleed or require rapid reversal of the anticoagulant effect of VKAs, management depends on the severity and location of the haemorrhage, and on the INR value.[10] VKAs should be withheld and intravenous vitamin K and coagulation factors must be administered.[10] The fall in INR begins within two hours and normalisation occurs within 24 hours in the absence of comorbid states, which may cause delay in reversal.[10] FFP transfusion provides sufficient amounts of the factors II, VII, IX, X and rapidly reverses prolonged VKA-related coagulopathy; it is the most commonly used strategy for effective and urgent reversal of VKAs.[9,10] Prothrombin complex concentrate (PCC) is a purified plasma product containing factors II, VII, IX, X and has been used for rapid reversal of the anticoagulant

effect of VKAs in emergency cases with severe haemorrhage, or that need surgery.[10] Recombinant activated FVII (Novo Seven®) may be also administered in cases with prolonged INR and severe bleeding; however, there are few data to demonstrate safety and efficacy. When PCC or FVIIa are administered, it is important to simultaneously infuse adequate amounts of vitamin K, because both PCC and activated FVII have a short half-life relative to warfarin and coagulopathy may recur.[10]

New oral anticoagulants

The new oral anticoagulants act directly against thrombin (FIIa) or activated factor FXa.[4] Both FXa and thrombin are important in thrombus formation and propagation.[5] There is considerable discussion about the superiority of drugs with anti-Xa action versus drugs with antithrombin action in preventing and treating thromboembolic diseases. Both thrombin and FXa have a central, key role in the coagulation cascade. Up to the present, there is no answer to this question; probably, comparative trials between the two groups are warranted to determine the superiority of one group of drugs over the other, if any.[4,5]

Orally administered direct thrombin inhibitors

Drugs acting as direct thrombin inhibitors are already used for the treatment of selected patients with thrombotic episodes. These drugs are hirudin, bivalirudin, lepirudin and argatroban.[4] They are administered intravenously. Lepirudin is indicated for antithrombotic prophylaxis and treatment of patients with type II heparin-induced thrombocytopenia with simultaneous thrombosis (HIT II).[4]

Dabigatran etexilate

Dabigatran directly inhibits both free and clot-bound thrombin. It is administered orally, once or twice daily in fixed doses, as a pro-drug. It is rapidly absorbed and soon after ingestion is converted to its active form.[4] Dabigatran reaches peak plasma concentration within 1.5-2 hours. The half-life of dabigatran is approximately 14-17 hours and is not dose-dependent.[4] However, following administration of multiple 50 mg doses, a half-life of approximately 7-8 hours is observed. Conversion to the active metabolite takes place in the liver by specific esterases.[4] Cytochrome P450 is not involved in dabigatran metabolism and consequently the risk of multiple drug interactions is diminished. It is not well known if there are any significant interactions with other drugs or food. Dabigatran has an 80% renal excretion; therefore, accumulation may occur in patients with severe kidney dysfunction.[4]

Dabigatran binds with free and thrombus-bound thrombin at the site exocite 1. It inhibits the transformation of fibrinogen to insoluble fibrin and the feedback activation of factors FVIII, FXI, FV by thrombin and thrombin-related platelet activation.[4,5] Dabigatran also improves endogenous fibrinolysis by both inhibiting thrombin activatable fibrinolysis inhibitor (TAFI) and increasing t-PA and subsequently plasmin levels.[11]

Therapeutic dabigatran administration - clinical trials

Dabigatran has been orally administered for the prevention of VTE in patients after hip and knee replacement, for the treatment of patients with DVT and for the prevention of cerebrovascular and peripheral embolic events in patients with atrial fibrillation.[12-19]

The safety and efficacy of oral dabigatran administration was first evaluated in two phase II dose-escalating studies.[12,13] Approximately, 2300 patients who underwent elective hip or knee replacement were enrolled.[12,13] In a dose-escalating study estimating the safety of dabigatran, 314 patients who had undergone total hip arthroplasty were included. Dabigatran was administered in doses ranging from 12.5 to 300 mg twice daily, or 150 and 300 mg once daily. The use of the drug was safe in doses ranging from 12.5 to 300 mg. Although the study was not designed to test the efficacy of the drug, a satisfactory effect in preventing VTE was observed (BISTRO I Study).[12] The efficacy and safety of several dabigatran doses ranging from 50-150 mg twice daily, or 225 and 300 mg once daily, were compared to the subcutaneous administration of 40 mg enoxaparin once daily in patients after knee arthroplasty.[13] The primary endpoint was the incidence of VTE, detected either by venography or in symptomatic patients.[13] Patients treated with dabigatran in the higher doses had significantly fewer thrombotic events (p ranging from 0.04 to 0.0001 for several doses) relative to those treated with enoxaparin.[13] Major bleeding episodes were significantly lower, compared to enoxaparin, in patients treated with the lower (50 mg) dabigatran doses ($p=0.047$), but elevated in patients treated with the higher doses (300 mg) (BISTRO II Study).[13]

The safety and efficacy of dabigatran compared with enoxaparin were also evaluated in phase III studies enrolling patients after hip and knee arthroplasty.[14,15] In two studies, RE-MODEL and RE-MOBILIZE, 2100 and 2615 patients, respectively, were enrolled after knee arthroplasty.[14,15] The duration of prophylaxis was 6-10 days and 12-15 days, respectively.[14,15] Dabigatran was administered in doses of 150 or 220 mg once daily in both studies.[14,15] The first dose was administered 1-12 hours after surgery.[14,15] Enoxaparin was administered in subcutaneous doses of 40 or 30 mg, respectively.[14,15] The first dose was administered in the evening prior to the surgery or 12-24 hours after the surgery.[14,15] The endpoints of these two studies were total VTE-related mortality, all-cause related mortality rate and venographic or symptomatic DVT or PE occurrence.[14,15] Haemorrhagic events were categorised as major, non-major, clinically relevant haemorrhage and minor bleeding.[14,15] In the RE-MODEL study dabigatran administration in both doses, 220 mg and 150 mg, was at least as effective as enoxaparin administration ($p=0.0003$ and 0.017, respectively) in preventing VTE incidence and VTE-related deaths.[14] In terms of safety, fatal bleeding effects were not observed.[14] There was no significant difference in total bleeding events between either of the two doses of dabigatran and enoxaparin.[14] Nor were there any significantly increased adverse effects leading to treatment discontinuation, or liver enzyme elevation.[14]

In the RE-MOBILIZE study, oral dabigatran administration, in doses of 150-220 mg daily, was found to be inferior in preventing VTE versus enoxaparin 30 mg two times daily, but bleeding rates were similar. No drug-related liver enzyme elevation was observed.[15] In another double-blind study enrolling approximately 3500 patients after hip arthroplasty, dabigatran was administered for 28-35 days in doses of 150 and 220 mg orally once daily, starting 1-4 hours after surgery in 2300 patients (RE-NOVATE study).[16] Enoxaparin 40 mg was administered subcutaneously, starting on the evening prior to the surgery, in 1162 patients.[16] Study endpoints were venographic or symptomatic VTE and death from all causes. The duration of treatment was 33 days. Dabigatran in both doses was equally as effective as enoxaparin in preventing venographic and symptomatic VTE ($p<0.0001$).[16] The frequency of major bleeding episodes was similar in both groups of patients treated with dabigatran (any dose) and enoxaparin.[16] Elevated liver enzyme and coronary deaths did not differ significantly between the two groups of patients.[16]

Dabigatran was also tested as a long-term treatment after a DVT episode.[17] In the RE-COVER study, a double-blind randomised trial, 2539 patients were enrolled.[17] After initial treatment with parenteral anticoagulants, patients were randomised to receive either warfarin (1266 patients) or dabigatran 150 mg twice daily (1273 patients).[17] The warfarin dose was adjusted to achieve a target INR of 2.0 to 3.0.[17] The endpoints of the study were the six-month incidence of recurrent VTE and related deaths.[17] Patients were followed for the occurrence of bleeding episodes, acute coronary syndromes, liver dysfunction and other adverse events.[17] The duration of treatment was six months.[17] Dabigatran proved equally effective ($p<0.001$) and safe as warfarin.[17] Major bleeding episodes were similar in both groups of patients.[17] Patients on dabigatran discontinued treatment more often than patients on warfarin ($p=0.05$).[17] The adverse event leading more patients in the dabigatran group to discontinuation of therapy was dyspepsia ($p<0.001$).[17] An unexplained finding is the increased but not significant incidence of acute coronary syndromes in the group of patients on dabigatran therapy.[17] Moreover, approximately 500 patients in the warfarin group and an equal number in the dabigatran group gave informed consent to participate in an extended secondary prophylaxis study, the RE-MEDY trial.[17]

Dabigatran's efficacy in preventing stroke and systemic embolism in high-risk patients with electrocardiographically confirmed, long-standing, non-valvular atrial fibrillation was also tested.[18] In the RELY study, a double-blind, phase III, randomised, controlled trial, two fixed doses of dabigatran, 110 or 150 mg twice daily, were compared to warfarin in adjusted doses.[18] In this study 18,113 patients who had at least one risk factor for stroke were enrolled.[18] The majority of the patients were elderly, male and pretreated with VKAs.[18] The mean $CHADS_2$ score of the enrolled patients was 2.1.[18] Approximately half of the patients had a previous history of one or more strokes or transient ischaemic attacks.[18] The majority of patients were on concomitant therapy with aspirin, ARB or ACE inhibitors, beta-blockers, amiodarone, statins and proton pump inhibitors.[18] Patients with creatinine clearance <30 ml/min and severe hepatic disease were excluded.[18] In contrast, patients with mild or moderate severity renal dysfunction with creatinine clearance >30 ml/min, were included. The primary efficacy outcome was stroke or peripher-

al embolism prevention, and the primary safety outcome was major haemorrhage, myocardial infarction and vascular deaths of any cause, including deaths related to bleeding.[18] The median follow-up period was two years.[18] Dabigatran doses, 110 and 150 mg twice daily, were proven to be non-inferior to warfarin ($p<0.001$).[18] The higher dabigatran dose was superior to warfarin in preventing stroke ($p<0.001$).[18] Similarly, dabigatran 150 mg was superior to 110 mg in preventing stroke or systemic embolism ($p=0.005$).[18] The incidence of haemorrhagic transformation of infarcts was significantly lower in both dabigatran groups, relative to the patients on warfarin ($p<0.001$).[18] Any-cause related mortality was lower in the group of dabigatran patients ($p=0.051$).[18] An unexplained finding was the slightly increased incidence of myocardial infarction in the group of patients treated with dabigatran in both doses ($p=0.07$ and 0.048 respectively).[18] The risk of bleeding was lower in patients treated with dabigatran 110 mg ($p=0.003$) and similar to that observed with warfarin, in the patients treated with dabigatran 150 mg ($p=0.31$).[18] Severe life-threatening bleeding was higher in patients treated with warfarin ($p<0.05$).[18] Interestingly, gastrointestinal bleeding episodes were more common in patients treated with dabigatran 150 mg than in the warfarin group.[18] More patients on either dose of dabigatran discontinued treatment (21% versus 17% on warfarin), probably because of dyspepsia ($p<0.001$).[18] Elevation (more than 3-fold) of hepatic enzymes and hepatobiliary disorders were not significantly more frequent at either dose of dabigatran.[18]

In another study including 500 patients with atrial fibrillation, the concomitant administration of dabigatran and aspirin relative to warfarin alone was tested. Several dabigatran doses (50-300 mg), in combination with aspirin (80-325 mg) for 12 weeks, were tested. The results showed that, although high-dose dabigatran was more effective than warfarin alone in preventing stroke, the risk of serious haemorrhagic adverse events was higher ($p<0.02$) in patients on therapy with dabigatran 300 mg (PETRO Study).[19]

In the near future the results will be available of studies concerning:

1. Secondary prophylaxis from recurrent VTE in 2000 patients after the initial six-month treatment. This study will compare dabigatran 150 mg twice daily with warfarin.
2. Secondary prophylaxis from recurrent VTE and or PE in patients treated with dabigatran 150 mg twice daily or placebo.
3. Efficacy of dabigatran 150 mg twice daily, for six months, versus placebo, in 2200 patients on dual antiplatelet therapy (aspirin+clopidogrel), after myocardial infarction.

Drugs with anti-Xa action

Fondaparinux is a widely used drug of this group. It is administered subcutaneously and has been proven effective for the prevention and treatment of VTE and acute coronary syndromes.[4] Orally available derivatives with anti-Xa properties are rivaroxaban, apixaban, betrixaban and edoxaban.[4]

Rivaroxaban

Rivaroxaban is an oxazolidinone derivative and acts as a direct, moderately potent, inhibitor of FXa.[4] It exhibits high oral bioavailability and rapid-onset action.[4] Maximum plasma concentrations are reached within 1.5-2 hours after ingestion. Plasma half-life is 5-9 hours in young individuals and 12-13 hours in subjects aged >75 years.[4] Activity begins soon after administration and is closely correlated with plasma concentration.[4] Rivaroxaban is eliminated by both liver and kidneys.[4] It is mainly metabolised by the liver (70%) in the cytochromes CYP3A4 and CYP2J2.[4] In phase I studies it has been demonstrated that gender and body weight do not affect the pharmacokinetic and pharmacodynamic properties of the drug.[4] Therefore, it may be administered in constant doses irrespective of body weight or sex.[4] Further studies have shown that rivaroxaban has a low-propensity for interactions with commonly used drugs, such as aspirin, clopidogrel, digoxin, and naproxen.[4] Moreover, there are no reported interactions between food and the drug.[4] The most common non-haematological adverse effect of this agent is dyspepsia.[4] Rivaroxaban acts as an FXa inhibitor, whereby it inhibits the transformation of prothrombin to thrombin and finally inhibits clot formation.[5] No specific antidote for the reversal of the anticoagulant effects of rivaroxaban is available. Protamine sulphate is not effective, but there are reports suggesting that recombinant factor VIIa (Novo Seven®), activated prothrombin complex concentrates, and FEIBA® may reverse the anticoagulant effect of this agent.[4] Attractive properties of rivaroxaban relative to LMWHs and VKAs are oral administration, rapid onset of action, predictable anticoagulant effect, lack of drug and dietary interactions and no need for monitoring the anticoagulant effect.[20-28]

Clinical studies supporting the use of rivaroxaban

The safety and efficacy of rivaroxaban in treating DVT and preventing PE and DVT in patients after hip and knee arthroplasty have been investigated.[20-28] Rivaroxaban was administered for the treatment of acute symptomatic DVT in two studies that enrolled approximately 1150 patients.[20,21] Several doses of rivaroxaban, ranging from 10-30 mg two times daily, or 40 mg once daily, were administered in patients with DVT and compared to enoxaparin and/or warfarin. The duration of both studies was three months. These studies proved that rivaroxaban is equally as safe and effective as conventional therapy for the treatment of proximal DVT and may be further tested in phase III studies.[20,21]

Similarly, rivaroxaban, administered in doses ranging from 5 to 30 mg twice daily or 40 mg once daily starting at 6-8 hours after surgery, was compared to enoxaparin, 30 or 40 mg once daily subcutaneously, in two phase II studies enrolling patients after hip (618 patients) and knee (613 patients) replacement.[22,23] Treatment lasted for 5-10 days after surgery and then a venogram was recorded. All administered doses of rivaroxaban were equally as effective as enoxaparin in preventing DVT, PE or death. Although high rivaroxaban doses resulted in a reduced incidence of thrombotic events, they caused increased bleeding episodes relative to enoxaparin.[22,23]

In addition, rivaroxaban administration in a constant dose, 10 mg once daily orally, was investigated in four studies, (RECORD Program).[24-27] In these studies a total of 12,729 patients underwent randomisation.[24-27] Efficacy and safety were compared with the subcutaneous administration of 40 mg enoxaparin.[24-27] In the RECORD-1 and RECORD-2 studies, 7550 patients who had undergone hip replacement were scheduled to received either 10 mg rivaroxaban or 40 mg enoxaparin.[24,25] The duration of treatment was 40 days in both studies.[24,25] Rivaroxaban was more effective than enoxaparin in preventing DVT, PE and death ($p<0.001$ and <0.0001, respectively in both studies).[24,25] Major thromboembolic episodes occurred less commonly in patients treated with rivaroxaban ($p<0.001$).[24] Major bleeding episodes were similar in patients treated with rivaroxaban or enoxaparin in both studies ($p=0.18$ and $p=0.25$, respectively).[24,25]

Rivaroxaban was compared to enoxaparin in two studies (RECORD-3 and RECORD-4) enrolling 5679 patients after elective knee replacement.[26,27] The duration of the study was 15-17 days. Rivaroxaban 10 mg orally was more effective than enoxaparin 40 mg subcutaneously in preventing DVT, PE and death ($p<0.001$), without a significant increase in major bleeding episodes ($p=0.77$).[26] Even when enoxaparin 30 mg twice daily was administered, rivaroxaban was as effective in preventing DVT, PE and death ($p=0.018$), without a significant increase in major bleeding ($p=0.109$).[27]

The safety and efficacy of rivaroxaban were also investigated in patients with acute coronary syndromes. In the ATLAS ACS-TIMI 46 (a dose-finding phase II study), 3491 patients who had suffered an acute coronary event – myocardial infarction with or without S-T elevation, or unstable angina – were included.[28] All patients were on standard therapy with aspirin and clopidogrel. Rivaroxaban in a total dose ranging from 5-20 mg, administered in one or two divided doses, or placebo was added. A trend towards reduction in myocardial infarctions, revascularisations and deaths was demonstrated. With respect to the safety, increased bleeding was observed in patients treated with higher rivaroxaban doses.[28] The safety and efficacy of two doses (2.5 or 5 mg twice daily) of rivaroxaban are currently being investigated in a phase II trial that includes 16,000 patients with acute coronary syndromes (ATLAS ACS-TIMI 51).

Rivaroxaban is currently being investigated in patients with atrial fibrillation, for preventing stroke, death and systemic embolism. In a phase III, double-blind, multicenter study (ROCKET-AF) 14,000 patients with atrial fibrillation and elevated $CHADS_2$ score have been randomised to receive either rivaroxaban 20 mg once daily or warfarin in adjusted doses. Patients will be under evaluation for a median period of two years and results will soon be available.

Also, the efficacy of rivaroxaban versus enoxaparin in preventing VTE will be investigated in medically ill patients (MAGELAN study).

Apixaban

This is a small, highly potent molecule that reversibly inhibits FXa. It has a half-life of 12 hours, excellent bioavailability and is eliminated from both kidneys and bile.[29] It has been tested in preventing VTE in 3,000 patients after elective unilateral knee arthroplasty. It has been proven equally as effective as enoxaparin 40 mg once daily ($p<0.0001$), but the risk of major or clinically relevant bleeding episodes was significantly lower ($p=0.09$).[30] Apixaban is also currently being evaluated in treating patients with DVT.

Its safety and efficacy will be compared to enoxaparin and warfarin.[31] In addition, the safety and efficacy of apixaban will be investigated in two studies including more than 15,000 patients with atrial fibrillation, where it will be compared with warfarin or with aspirin in patients ineligible to receive VKAs.[32,33]

Betrixaban

This molecule reversibly inhibits FXa, has a half-life of 19 hours and is eliminated from the bile.[34,35] In a phase II study, betrixaban was administered in two doses, 15 and 40 mg, to patients who had undergone knee replacement.[35] It was shown to be equally as effective as enoxaparin. Serious bleeding events were not observed.[35] Betrixaban is also currently being investigated in the prevention of stroke and peripheral embolism in patients with atrial fibrillation and in the treatment of DVT.

Edoxaban

This is a molecule with very short half-life time (5 hours). Studies demonstrating efficacy in preventing VTE and stroke are under way.[36] Two studies involving the treatment of DVT and acute coronary syndromes are also designed.

Concerns about the use of new anticoagulants

The new orally administered anticoagulants have proven at least equally as effective as LMWHs or VKAs in preventing and treating VTE, stroke and ACS. They are administered orally, in fixed doses once or twice daily. Monitoring of the anticoagulant effect was not necessary in these trials.[12-36] Although these drugs exhibit a favourable profile, similar to that of an ideal anticoagulant, there are concerns about their widespread use.

Haemorrhagic adverse events

Haemorrhage is the most frequent complication of any antithrombotic therapy. Although new oral anticoagulants seem to cause a similar incidence of haemorrhagic adverse events, or in some cases fewer, compared to conventional anticoagulant drugs, there is a need to define precisely the severity of bleeding complications.[37,38] Disparity in the definitions used for bleeding episodes makes it difficult to compare safety between drugs and also between different studies.[37,38] Bleeding events are usually classified as major, significant, minor, or clinically relevant, but this characterisation does not necessarily reflect the severity of haemorrhage.[37,38] One option for obtaining accurate information about the propensity of these new anticoagulants to cause haemorrhagic complications is to evaluate the rate of haemorrhagic adverse events. Otherwise, it is more reliable to follow the pre-specified EMEA criteria for the identification of major bleeding in medical and surgical patients.[37,38] Criteria for identifying major bleeding in surgical patients are more complicated. In the studies referring to rivaroxaban administration in patients who underwent orthopaedic surgery, bleeding episodes in a surgical wound were classified in a separate category and thus it was difficult to compare safety with other drugs or studies classifying haemorrhagic complications according to the commonly used criteria.[37,38] Moreover, the lack of a reliable test indicating the intensity of the anticoagulant effect of these drugs is an additional confounding factor in determining the rate and severity of haemorrhagic events.[37,38]

Reversal of the anticoagulant effect

When patients treated with conventional anticoagulants exhibit haemorrhagic complications, there is a well defined and evidence-based strategy for the reversion of their anticoagulant activity.[1-3] Protamine sulphate is suitable for the reversion of haemorrhage following UFH administration.[1,2] It may also be used for partial reversion of the anticoagulant activity of LMWHs.[1,2] Plasma (FFP) or recombinant factor VII may also be administered to patients who present with severe haemorrhage following LMWH administration.[1,2] Vitamin K is a specific antidote and effectively reverses the anticoagulant effect of VKAs.[3] In cases of severe bleeding or urgent surgery, FFP, recombinant factor VII and prothrombin complex concentrates should be infused in combination with vitamin K to reverse the anticoagulant effect of VKAs.[9,10] In addition, the widespread use of tests (INR, aPTT or anti-Xa activity) to assess the intensity of the anticoagulant effect of these drugs may facilitate the treatment of haemorrhagic complications.[4]

New drugs lack a specific antidote and it is not clearly defined which agents can cause rapid reversal of their anticoagulant effect in case of overdosing, active bleeding or emergency interventions. Moreover, treatment of haemorrhagic complications caused by the novel agents is more complicated, due to the fact

that there is no simple and effective way to monitor their activity. Infusion of plasma and coagulation factors is probably not sufficient to reverse their anticoagulant effect, because these novel agents do not cause the depletion of coagulation factors, as VKAs do, but rather inhibit their action.[4] It is possible that the administration of activated prothrombin complex concentrates and recombinant FVIIa may reverse the action of the new drugs, but there is not sufficient evidence that this can terminate active bleeding. Although it has been suggested that recombinant FVIIa may reverse the anticoagulant effect of these agents, there is a low but existing potential risk of thrombosis that may complicate its use.[4]

Nevertheless, it has been proposed that agents with anti-fibrinolytic activity and desmopressin may be used for reversal of the anticoagulant effect of these novel agents.[4] Desmopressin is commonly used for the treatment of mild haemorrhages in patients with haemophilia A, type I von Willebrand disease and congenital platelet defects.[9] Although in some *in vitro* studies it has been shown to effectively reverse the anticoagulant effect of a direct thrombin inhibitor, hirudin, it may also exert adverse effects, such as hyponatraemia, headaches and palpitations, that are undesirable in patients suffering from cardiovascular disease.[9]

Although anti-fibrinolytic agents (tranexamic acid, aprotinin and ε-aminocaproic acid) have a different mode of action, they inhibit endogenous fibrinolysis. They have been used in patients undergoing orthopaedic, cardiac and urological surgery who exhibit mild haemorrhages.[9] It is uncertain whether anti-fibrinolytic agents and desmopressin can be used for the reversal of the anticoagulant effect of oral direct thrombin inhibitors and anti-Xa drugs, in patients with active bleeding.[4,9]

Although the need for rapid and specific reversal of the anticoagulant action of these novel agents may be infrequent, the lack of a specific antidote may be a disadvantage in some categories of patient, especially those needing urgent surgical or interventional procedures.[4] Furthermore, it remains unknown if oral direct thrombin inhibitors and anti-Xa drugs may be removed from circulation by mechanical means such as haemodialysis or plasmapheresis.[9]

Pharmakokinetics

Absorption

Dabigatran is orally administered as a pro-drug (dabigatran etexilate) and is rapidly absorbed and converted to its active component.[39] Absorption is better in an acidic milieu. The drug capsules contain an acidifying component and facilitate absorption.[39] Thus, the drug may be administered irrespective of food ingestion. Antacids and ranitidine do not seem to affect dabigatran absorption. However, proton pump inhibitors may affect the mean serum concentration of the drug.[39]

Rivaroxaban is absorbed better when food is ingested simultaneously. Therefore, it is recommended that it should be taken with meals or at least within two hours after meals for better absorption.[40]

Elimination issues

Dabigatran is mainly excreted by the kidneys.[39] Patients with severe renal disease (creatinine clearance <30ml/min) or patients on dialysis were not enrolled in the studies.[39] However, data for the treatment of patients with moderate renal insufficiency (creatinine clearance 30-50 ml/min) are available from the RELY study. In this study, 3500 patients with moderate severity kidney disease were enrolled and effectively treated without an increased bleeding risk.[17]

Rivaroxaban is eliminated by both the liver and the kidneys and there is no need for dose modification in patients with mild to moderate renal impairment. In patients with severe renal impairment (creatinine clearance <15 ml/min), or on haemodialysis, the use of the drug is not recommended.[40] Additionally, rivaroxaban is not recommended in patients with liver disease-related coagulopathy.[40] Although rivaroxaban has been described as having a longer half-life in the elderly, there is no sufficient indication that there is a need for dose modification.[40]

Laboratory monitoring of the anticoagulant activity

The novel agents were introduced into therapeutics with the aim of eliminating the need for routine monitoring of their anticoagulant effect.[1-3] In the published series referring to their prophylactic or therapeutic administration, monitoring of the anticoagulant effect was not carried out.[12-36] However, in some clinical conditions there is a need for monitoring.[4] These include assessment of compliance with therapy; assessment of efficacy or over-treatment in patients with severe renal or liver insufficiency; evaluation of the anticoagulant effect in cases of drug interactions; monitoring of patients with treatment failure and recurrent thrombotic episodes, in circumstances

where there is severe bleeding into critical organs, such as the central nervous system; and when investigation of the coagulation adequacy in treated patients who are going to have emergency surgery or other interventional procedures is warranted.[4]

Few data indicating the impact of the novel agents on the commonly used coagulation assays are available.[41] Dabigatran prolongs aPTT in an insensitive manner relatively to plasma concentrations.[39,41] Moreover, aPTT determination may vary according to the type of the coagulometer and the sensitivity of the reagents used, and it is not suitable for precise evaluation of the anticoagulant effect, especially in high plasma concentrations.[39,41] Similarly, dabigatran has little impact on INR at clinically relevant plasma concentrations and is not suitable for the evaluation of patients on therapeutic doses.[41] Thrombin time (TT) assesses the activity of thrombin. It is sensitive to the anticoagulant effect of dabigatran and expresses a linear dose-related response in patients on therapeutic concentrations. It may serve as a useful index of the anticoagulant effect of the drug.[39] Activated clotting time (ACT) has been used to determine the anticoagulant effect of UFH in patients undergoing percutaneous interventions and open heart surgery.[41] Elevated dabigatran concentrations may prolong ACT, but this test needs further evaluation.[41] Hemoclot® assay is a diluted thrombin time assay that is suitable for the measurement of the activity of thrombin inhibitors. A specific modification of this assay specifically for the determination of dabigatran plasma levels will soon be commercially available.[41] The ecarin clotting time (ECT) is an assay indicating thrombin generation. ECT probably provides a sensitive method for assessing the anticoagulant activity of direct thrombin inhibitors and is currently used only for research purposes. Until the development of commercially available kits, this test cannot be recommended for use in everyday clinical practice.[41]

In this context, thrombin time and ECT are the most sensitive currently available tests for monitoring the anticoagulant effect of dabigatran. They show a linear relationship with even high dabigatran concentrations. Thrombin time is currently commercially available and may be used in emergency situations.[39,41]

Rivaroxaban induces a concentration-related INR prolongation. However, results show significant variation related to the type of thromboplastin used. The effect of rivaroxaban on aPTT prolongation is weak and is observed only at low concentrations.[40,41] Thromboelastography is a not widely used test that needs special equipment. Results are not specific and a only a small number of laboratories and personnel are familiar with the proper interpretation.[40,41] Anti-Xa activity determination is currently used for the interpretation of LMWHs efficacy.[41] It may sufficiently indicate rivaroxaban activity and is clearly dependent on plasma concentrations.[41] However, this test is time consuming and needs experienced personnel; it is not widely available in the majority of laboratories and its utility in estimating the activity of rivaroxaban needs further evaluation.[41] The diluted Russell's viper venom test (dRVVT) is currently used for the detection of lupus anticoagulant. It expresses a linear relation with administered doses of rivaroxaban and it can be used for the evaluation of the anticoagulant effect of this drug.[40,41] The thrombin generation test (TGT) is influenced by rivaroxaban. Thrombin generation is completely inhibited in the presence of high concentrations of the drug. This test is not widely available.[40,41] Coagulation tests, such the as Hep-test and prothrombinase-induced clotting time (PiCT), are rarely used; they require experienced personnel and are not suitable for routine anticoagulant monitoring.[41]

Consequently, on the basis of relatively limited experience, the most reliable test for evaluating rivaroxaban activity is the anti-FXa assay.[41]

Although it is believed that coagulation monitoring will not be necessary in the majority of patients treated with the novel anticoagulants, it is clinically relevant for a simple, inexpensive and well standardised test to be available for the assessment of coagulation status in several categories of patients.[4] The number of these patients will probably increase within the coming years, as these drugs will be widely used by several categories of patients (this occurred with the use of LMWHs). Therefore, the effort to establish a reliable test for patients who need monitoring (patients with kidney and liver disease, elderly, children and critically ill) should be continued.[4]

Interactions with other drugs and diet

One of the main concerns with the use of VKAs was interactions with other drugs and food.[3] Availability of the INR, which is a widely used, relatively inexpensive and reliable monitoring test, allowed the concomitant use of VKAs and interacting drugs safely. This was achieved by increasing the frequency of monitoring and subsequently making the necessary dose adjustments. However, in an effort to ameliorate

the interactions of VKAs, new products with a mode of action similar to that of VKAs, but without interference with other drugs metabolised in cytochrome P450, such as tecarfarin, have been developed.[3]

Dabigatran is metabolised in the system of cytochrome CYP3A4; therefore there are not as many interactions as with VKAs.[39] However, drugs such as verapamil, clarithromycin, rifampin and quinidine may interfere with the metabolism of dabigatran because they inhibit the P-glycoprotein transporter system. This system decreases the absorption of several drugs from the gut and increases the elimination by the kidneys. Dabigatran and rivaroxaban are both a substrate for this protein and their plasma levels and anticoagulant effect are influenced by these drugs.[39] Similarly, rivaroxaban is partly metabolised in cytochrome CYP3A4. Drugs such as ketoconazole, ritonavir, clarithromycin, erythromycin and rifampin may interfere with the metabolism of rivaroxaban.[40] Moreover, it is not well known whether food interacts with the P-glycoprotein transporter system and subsequently alters the drug's plasma levels.[40]

Compliance and tolerability

VKAs are generally well tolerated and practically none of the treated patients discontinue therapy.[1-3] Both rivaroxaban and dabigatran are administered orally once or twice daily.[39,40] Dabigatran may be administered irrespectively of food ingestion, and rivaroxaban at least within two hours after meals for better absorption. Patients on short-term therapy show good compliance.[39] However, it is notable that patients on prolonged treatment with dabigatran exhibit significant gastrointestinal discomfort (abdominal pain, diarrhoea, vomiting and dyspepsia) more commonly than do patients treated with warfarin ($p<0.001$).[17,19] Similarly, it is noteworthy that gastrointestinal symptoms were the main reason for the discontinuation of treatment in patients receiving long-term therapy for atrial fibrillation ($p<0.001$) and DVT ($p<0.001$).[17,19]

Cost-effectiveness evaluation

The novel orally administered anticoagulant drugs have been proven effective and safe in preventing VTE and death in patients undergoing hip and knee arthroplasty and in treating patients with acute DVT and atrial fibrillation.[12-36] Currently, many other studies in progress may confirm that these drugs could be also used safely and effectively in other categories of patients at high risk for thrombosis, such as medical patients, patients undergoing general surgery and patients with acute coronary syndromes. Thromboembolic complications have a financial impact on both surgical and medical patients, because they not only increase morbidity and mortality but also lengthen the duration of hospital stay.[42,43] A large proportion of medical and surgical in-patients or individuals in an outpatient setting do not receive anti-thrombotic prophylaxis according to the consensus guidelines of the ACCP, mainly because subcutaneous administration of LMWHs is not convenient, or VKA administration requires monitoring of the anticoagulant effect.[42,43] The new drugs offer an effective alternative, because they are more convenient to use and they may increase adherence to the guidelines. However, their cost is high relative to the conventionally used antithrombotics.[44,45]

A cost-effectiveness analysis of prophylactic dabigatran administration relative to enoxaparin in patients undergoing elective knee and hip replacement was carried out in the United Kingdom.[44] Patients were treated for ten days following knee arthroplasty and for 28-35 days following hip replacement.[44.] The cost of dabigatran administration was significantly lower than that of enoxaparin administration for both groups of patients.[44] Cost was also estimated when other LMWHs were administered. Although the cost was lower when patients were treated with any of the other less costly LMWHs, apart from enoxaparin, the dabigatran cost-effectiveness ratio did not alter.[44] Moreover, even if patients injected enoxaparin by themselves, dabigatran administration was cost-effective. Dabigatran therapy was more costly only when the duration of treatment was prolonged (30 days), while enoxaparin was administered only for seven days.[44]

In another study, rivaroxaban administration was proven to be a more cost-effective strategy for thromboprophylaxis in patients who underwent knee and hip replacement than either dabigatran or enoxaparin administration.[45] The cost of 150 mg dabigatran administration, once daily for thromboprophylaxis in the elderly, or in patients with moderate renal function impairment, was evaluated relatively to enoxaparin 40 mg once daily. Dabigatran proved to be a more cost-effective strategy relative to enoxaparin.[45]

An economic evaluation of long-term dabigatran administration relative to warfarin is not currently available. However, even if the cost for regular or repeated INR monitoring is considered, it is unlikely that dabigatran will be more cost-effective than warfarin.

Conclusions and future trends

Orally administered direct thrombin inhibitors and anti-FXa drugs are safe and effective in preventing and treating VTE, peripheral embolism and stroke in patients with atrial fibrillation or following orthopaedic surgery. However, there are concerns about their wide use in everyday clinical practice, especially given that they may be administered to large number of patients with thrombotic diseases and replace the traditionally administered VKAs, LMWHs and UFH, which have established efficacy, a sufficient safety profile and relatively low cost.

The use of novel agents offers advantages relative to the conventional drugs. They have a short half-life, their anticoagulant effect begins soon after their oral administration and probably in acute thrombotic episodes there is no need for initial therapy with rapidly acting anticoagulants, such as UFH and LMWHs. Similarly, in patients on long-term treatment, "bridging therapy" with heparins should not be necessary for those who are going to have percutaneous or surgical interventions. This is expected to reduce hospital admissions and long-lasting hospital stay. The major advantages of these drugs are the predictable anticoagulant effect related to the administered dose, and the lack of a need for laboratory monitoring of their anticoagulant effect.

A serious concern about the use of warfarin was interactions with several drugs and diet products rich in vitamin K. Both categories of the novel anticoagulants have no known interactions with food. Little information about drug interactions is available; however, manufacturers already recommend that these drugs should not be co-administered, or must be administered with caution together with some antibiotics, verapamil and amiodarone, because these may affect their plasma levels and anticoagulant activity. Nevertheless, it is uncertain if these advantages are sufficient to lead VKAs and heparins to oblivion.

Although there are studies indicating that, in short-term use, novel anticoagulants may also confer economic advantages over LMWH administration, it is unlikely that they will totally replace warfarin when long-term administration is needed, because warfarin is significantly less expensive than both rivaroxaban and dabigatran, even if the cost of laboratory monitoring is taken into consideration.

Another concern about long-term administration is safety. Recently, ximelagatran, a drug with a similar mode of action to dabigatran and a favourable efficacy profile, has failed to be approved because of unexpected liver toxicity and related mortality. Nevertheless, patients with DVT and atrial fibrillation have been treated safely with these agents for at least two years and no serious non-haematological toxicity was observed.

These drugs may be administered without a need for regular monitoring of their anticoagulant effect. However, it is essential that a simple, inexpensive and widely approved test, like aPTT and INR, be available for clinical use, occasionally, in patients with severe haemorrhagic complications, recurrent thrombotic episodes or prior to percutaneous interventions and surgery.

In the already published series, the elderly and patients with moderate kidney disease have been enrolled and treated safely. However, it is not known if patients with end-stage renal or liver disease, children, pregnant and lactating women can be safely treated. Moreover, up to the present, there are no studies indicating that patients with prosthetic mechanical valves may receive effective lifelong treatment with these agents. Not is it known whether these agents may be considered for anti-thrombotic therapy when intensive anticoagulation treatment is indicated (patients with recurrent VTE, or thrombophilic states). It is not also well defined if increased doses are related with intensification of the anticoagulant effect without a significant increase in the risk of haemorrhagic complications.

Although recombinant FVIIa and FEIBA are considered effective in reversing the anticoagulant effect of these novel agents, the lack of a specific antidote is of concern, especially when patients with acute thrombotic events treated with these agents exhibit active bleeding.

Although VKAs are administered once daily, compliance is troublesome in several patients, especially the elderly. Some of these drugs should be administered twice daily for the treatment of thrombotic diseases; therefore, it is unlikely that compliance will be better with dabigatran than with warfarin. Moreover, VKAs exert an excellent tolerability profile. In contrast, long-term dabigatran administration is reported to have high rates of dyspepsia. Finally, significantly greater numbers of patients discontinue therapy in comparison to those treated with warfarin. This reflects another factor for poor compliance and adherence to therapy with the new drugs.

In conclusion, although the novel anticoagulant agents offer an attractive option for the treatment

and prevention of thrombotic diseases, it remains uncertain whether they will be widely used and replace the older anticoagulants. As they present a favourable safety and efficacy profile and are well tolerated in short-term administration, they will probably be established for VTE prevention in patients after orthopaedic surgery. Concerns about their long-term administration may be assuaged by the results of already ongoing studies, or others that remain to be designed and carried out.

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