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Review Article

The mechanism of action of rivaroxaban – an oral, direct Factor Xa inhibitor – compared with other anticoagulants

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ABSTRACT

Although results of some phase III clinical trials of new oral anticoagulants are now known, it is important to understand the mechanisms of their actions. These new agents exert their anticoagulant effect via direct inhibition of a single Factor within the coagulation cascade (such as Factor Xa or thrombin). Rivaroxaban – the first oral, direct Factor Xa inhibitor – is a small-molecule oxazolidinone derivative that binds directly and reversibly to Factor Xa via the S1 and S4 pockets. Rivaroxaban competitively inhibits Factor Xa and is more than 10,000-fold more selective for Factor Xa than other related serine proteases, and it does not require cofactors (such as antithrombin) to exert its anticoagulant effect. Unlike indirect Factor Xa inhibitors, rivaroxaban inhibits both free and clot-bound Factor Xa, as well as prothrombinase activity, thereby prolonging clotting times. Dabigatran etexilate is a direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin. Although the mechanism of action differs between the direct Factor Xa and direct thrombin inhibitors, phase III studies of these new agents confirmed that both Factor Xa and thrombin are viable anticoagulation targets.

Contents

Abbreviations: ACS, acute coronary syndrome; aPTT, activated partial thromboplastin time; AT, antithrombin; AUC, area under the curve; bid, twice daily; C_{max}, maximum plasma concentration; CrCl, creatinine clearance; CYP, cytochrome P450; IC_{50}, inhibitory concentration 50; INR, international normalized ratio; LMWHs, low molecular weight heparins; od, once daily; PD, pharmacodynamic(s); PK, pharmacokinetic(s); PT, prothrombin time; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TG, thrombin generation; THR, total hip replacement; TKR, total knee replacement; UFH, unfractionated heparin; VKAs, vitamin K antagonists; VTE, venous thromboembolism.

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Introduction

Thromboembolic disorders are major causes of morbidity and mortality. Arterial thrombosis is the most common cause of myocardial infarction and ischaemic stroke, whereas deep vein thrombosis can lead to pulmonary embolism [1]. In the USA, pulmonary embolism causes almost 300,000 deaths per annum [2]. It is estimated that 12% of the annual deaths occurring in France, Germany, Italy, Spain, Sweden and the UK are due to venous thromboembolism (VTE), varying from 10% in the UK to 14% in Italy [3].

Great advances have been made in understanding the molecular and cellular basis of thrombus formation in the past few decades, with anticoagulants remaining the cornerstone for the prevention and treatment of thromboembolic disorders [4–6]. Conventional anticoagulant therapies, such as unfractionated heparin (UFH), low molecular weight heparins (LMWHs) and vitamin K antagonists (VKAs), act on multiple factors within the coagulation cascade. The heparins exert their anticoagulant effect by binding to antithrombin (AT) via a pentasaccharide sequence and increasing the ability of AT to inhibit Factor Xa and thrombin and other factors [7]. The anticoagulant effect of the VKAs is achieved by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide, leading to the hepatic production of partially carboxylated and decarboxylated coagulation factors (VII, IX, X and II) with reduced coagulant activity [8]. Although effective, these traditional agents are associated with several drawbacks, including parenteral route of administration or routine coagulation monitoring and dose adjustments. Recent efforts in finding new approaches to anticoagulation have focused on targeting a single enzyme within the coagulation pathway, such as thrombin and Factor Xa, and inhibition of either of these coagulation enzymes attenuates fibrin formation.

Factor Xa has emerged as a promising target for effective anticoagulation because it is positioned at the convergence point of the intrinsic and extrinsic coagulation pathways. Several new oral agents that specifically target Factor Xa have been developed, and rivaroxaban is one of the agents in late-stage clinical development. This article will give an overview of the oral, direct Factor Xa inhibitor rivaroxaban, comparing it with the indirect Factor Xa inhibitor (fondaparinux), other direct Factor Xa inhibitors (apixaban and edoxaban), and the direct thrombin inhibitor dabigatran etexilate. The potential advantages of direct Factor Xa inhibition will also be discussed.

The coagulation pathway

Tissue factor (TF) is the sole initiator of thrombin generation (TG) and fibrin formation [9]. Under normal conditions, the endothelium acts as a barrier separating TF from Factor VIIa in flowing blood. However, TF is also present in circulating blood, and this blood-borne TF plays an important role in the initiation of coagulation when vessel injury is limited to endothelial activation [9]. TF binds to circulation Factor VIIa to form the TF–Factor VIIa complex, which activates Factor IX and Factor X (Fig. 1). Tissue factor pathway inhibitor (TFPI) is an important physiological inhibitor of Factor Xa at the initial phase of blood coagulation. It binds to Factor Xa and blocks the TF–Factor VIIa–Factor Xa complex [10]. Recent evidence suggests that TFPI also plays a role in the protein S pathway; TG is increased when TFPI is inhibited [11]. It should be noted that TFPI is present in a low concentration (~2.5 nmol/l) in blood [10]. The anticoagulant role of TFPI in combination with that of Factor Xa inhibition requires further attention. Factor Xa converts small amounts of prothrombin to thrombin. Thrombin then amplifies coagulation by activating Factor V and Factor VIII (on the surface of activated platelets), platelets and platelet-bound Factor XI. The coagulation cascade is amplified by further generation of Factor Xa by the Factor IXa–Factor VIIIa–Ca^{2+}–phospholipid complex. Factor Xa binds to negatively charged phopholipid surfaces (e.g. activated platelets), together with Factor Va to form the prothrombinase complex – the central prothrombin activator, which converts prothrombin to thrombin [12]. Thrombin plays a central role in the clotting process. In addition to converting soluble fibrinogen to fibrin and activating platelets, thrombin also amplifies its own generation by feedback activation of Factor VIII and Factor V, as well as activating Factor XIII, which further stabilizes the clot. The coagulation pathway is regulated by natural anticoagulants, such as the TF pathway inhibitor, AT and the protein C and protein S system [13].

Indirect Factor Xa inhibitor

Fondaparinux

Fondaparinux is a synthetic analogue of the AT-binding pentasaccharide found in UFH or in the LMWHs. Its molecular weight (1728 g/mol) is approximately three times lower than that of LMWHs. It exerts its anticoagulant effects by binding to AT and evoking a conformational change at the reactive site of AT, which enhances its reactivity with Factor Xa [14]. Because it is too short to bridge AT to thrombin, fondaparinux does not increase the rate of thrombin inhibition by AT [15]. Fondaparinux produces a predictable anticoagulant response that precludes the need for routine coagulation monitoring and does not cause heparin-induced thrombocytopenia [15]. Unlike the direct Factor Xa inhibitors or direct thrombin inhibitors, fondaparinux does not prolong prothrombin time (PT) and has a very weak effect on the activated partial thromboplastin time (aPTT) [16]. However, as with the LMWHs, fondaparinux must be administered subcutaneously (Table 1).

Direct Factor Xa inhibitors

Rivaroxaban

Rivaroxaban is an oral, direct Factor Xa inhibitor. The onset of inhibition of Factor Xa activity with rivaroxaban is rapid and the inhibition is reversible. The values for k_{on} and k_{off} are 1.7×10^7 M^{-1} s^{-1} and 5×10^{-3} s^{-1}, respectively [17]. It is a small molecule (Mr 435.9 g/mol) and it binds directly to the active site of Factor Xa via the S1 and S4 pockets (Fig. 2) [18].

The X-ray crystal structure of rivaroxaban in complex with human Factor Xa clarified the binding mode and the requirements for high

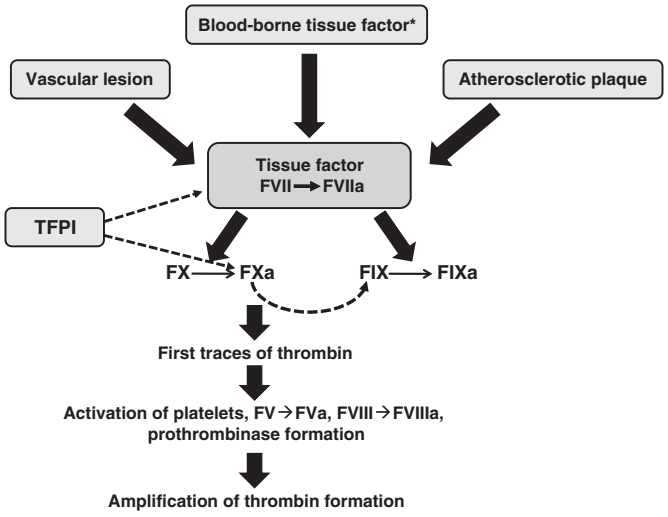

Fig. 1. Schematic representation of the coagulation cascade. Tissue factor pathway inhibitor (TFPI) binds to FXa, then the complex TFPI–FXa binds to tissue factor–FVIIa forming an inactive quaternary complex. *Activated monocytes/macrophages. FV, Factor V; FVa, activated Factor V; FVII, Factor VII; FVIIa, activated Factor VII; FVIII, Factor VIII; FVIIIa, activated Factor VIII; FIX, Factor IX; FIXa, activated Factor IX; FX, Factor X; FXa, activated Factor X.

Table 1
Comparison of the pharmacological characteristics of rivaroxaban and fondaparinux.

	Rivaroxaban	Fondaparinux
Target	Factor Xa (direct)	Factor Xa (indirect)
Molecular weight	435.9	1728
Cofactor required	No	Antithrombin
Route of administration	Oral	Subcutaneous
Bioavailability	80–100%	~100%
Terminal half-life	7–11 hours	14–20 hours
Renal excretion	One-third unchanged	Unchanged
Inhibition of Factor Xa	Free and clot-associated Factor Xa	Free and clot-associated Factor Xa
Inhibition of prothrombinase activity	Yes (IC_{50} 2.1 nM)	No effect
Clotting times	Prolongation of PT, aPTT, HepTest and dilute Russell's viper venom time	Prolongation of HepTest

aPTT, activated partial thromboplastin time; IC_{50}, inhibitory concentration 50; PT, prothrombin time.

affinity observed within the oxazolidinone series. Supported by these two bonds, the (*S*)-oxazolidinone ring provides the L-shape needed for Factor Xa binding, directing the morpholinone residue into the S4 pocket and the chlorothiophene moiety into the S1 pocket. The key interaction of rivaroxaban with Factor Xa in the S1 pocket involves the chlorothiophene moiety – the chlorine substituent interacts with the aromatic ring of Tyr228 located at the bottom of the S1 pocket. This chlorine–Tyr228 interaction obviates the need for strongly basic groups to achieve high affinity for Factor Xa, thus enabling non-basic rivaroxaban to achieve both high potency and sufficient oral bioavailability [18]. Because rivaroxaban is non-basic and more lipophilic than inhibitors with highly basic residues, it has a greater ability to pass through the lipophilic epithelia of the gastrointestinal tract. In addition, this chlorine–Tyr228 interaction contributes to the high potency in a number of ways. The primary reason is that the formation of this chlorine–Tyr228 interaction displaces a water molecule in the binding pocket. This contributes enthalpically and entropically to ligand binding, giving a high affinity [18,19].

Preclinical studies

In vitro kinetic analysis in the absence of AT indicated that rivaroxaban is a selective, reversible, direct Factor Xa inhibitor that does not require cofactors for its anticoagulant effect [20]. Rivaroxaban inhibits Factor Xa activity with a low K_i value (0.4 nM) [20,21]. In humans, the mean minimum plasma concentration (C_{trough}) of rivaroxaban was 9.1 ng/ml after a 10 mg dose [22], giving a free plasma concentration range of 0.45–0.73 ng/ml (taking into account the plasma protein binding), which is approximately threefold higher than the K_i (0.174 ng/ml). In a phase I study, it was shown that the TF-induced TG was slightly inhibited even after 24 hours of rivaroxaban administration [23], demonstrating that free plasma levels at around Ki value are sufficient to inhibit TG. Rivaroxaban also inhibits clot-bound Factor Xa (inhibitory concentration 50 [IC_{50}] 75 nM) [24] and prothrombinase activity (IC_{50} 2.1 nM) [20]. Rivaroxaban is more than 10,000-fold more selective for Factor Xa than for other related serine proteases – it does not inhibit related serine proteases at concentrations up to 20 μM [20].

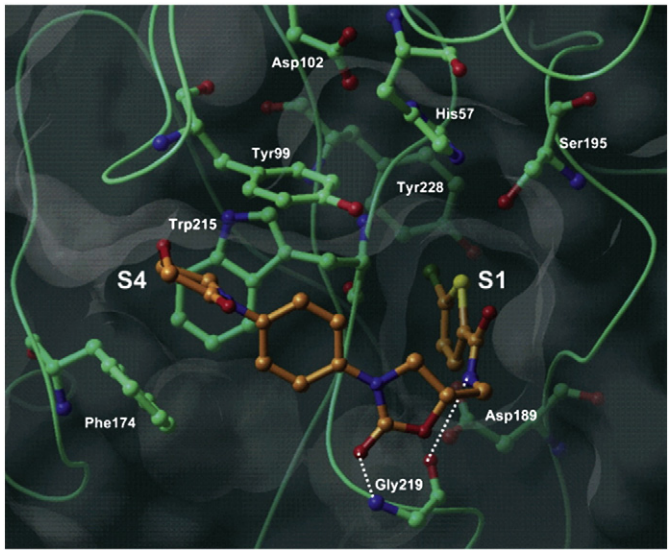

Fig. 2. X-ray crystal structure of rivaroxaban (orange carbons) in complex with human Factor Xa [18]. Essential amino acids and binding pockets are indicated; the two hydrogen bonds between rivaroxaban and Gly219 are shown as dotted lines.

In human plasma, rivaroxaban concentration-dependently inhibited TG [25,26] and, thus, the amplification processes of coagulation, through inhibition of Factor Xa. TG was almost completely inhibited at therapeutically relevant concentrations (80–100 nM) of rivaroxaban. *In vitro* studies demonstrated that rivaroxaban prolonged the initiation phase of TG, inhibited the physiologically relevant prothrombinase complex-bound Factor Xa on the surface of activated platelets and reduced the thrombin burst produced in the propagation phase [26,27]. In addition, a recent study on whole blood clot structure showed that rivaroxaban, by decreasing TG, increased clot permeability and degradability, which may also contribute to its antithrombotic effect [28].

When given prophylactically, rivaroxaban had consistent antithrombotic effects in venous [20,29,30] and arterial thrombosis models in mice, rats and rabbits [20,30,31]. In a rabbit treatment model, rivaroxaban reduced the growth of venous thrombi when given after thrombus formation – it reduced the growth of pre-formed thrombi to a similar extend as the LMWH nadroparin and the indirect Factor Xa inhibitor fondaparinux [29]. Bleeding times were not significantly increased at antithrombotic doses in these models [20]. Furthermore, rivaroxaban dose-dependently prevented thromboembolic death induced by TF in a mouse model, whereas fondaparinux was less effective compared with rivaroxaban [32].

Clinical pharmacology

Rivaroxaban is rapidly absorbed, with maximum concentrations appearing 2–4 hours after oral administration [33,34]. It has a high (80–100%) oral bioavailability after a 10 mg dose – the dose that was selected for the phase III studies for the prevention of VTE after elective total hip or total knee replacement (THR/TKR) surgery [35]. No relevant accumulation was observed at any dose after multiple dosing in healthy subjects beyond steady state [34]. The elimination of rivaroxaban from plasma occurs with a mean terminal half-life of 7–11 hours [35]. Low intra-individual variability and moderate interindividual variability have been observed [36].

Rivaroxaban has been shown to have predictable pharmacodynamics (PD) in healthy subjects [36] and in patients undergoing major orthopaedic surgery [37]. In a randomized, placebo-controlled, single-dose escalation study (1.25–80 mg) in healthy males, its PD effects (inhibition of Factor Xa activity, prolongation of PT, aPTT and HepTest) were dose dependent. Maximum inhibition of Factor Xa activity was achieved 1–4 hours after administration, with PT prolongation following a similar profile. Rivaroxaban has no effect

on ecarin-induced thrombin activity or AT activity in healthy subjects, demonstrating that rivaroxaban selectively inhibits Factor Xa activity [33].

In a randomized, placebo-controlled, multiple-dosing study in healthy males, rivaroxaban was administered on days 0 and 3–7. Dosing regimens were 5 mg once, twice or three-times daily, and 10 mg, 20 mg or 30 mg bid. Factor Xa activity was dose-dependently inhibited and maintained for approximately 12 hours after dosing [34]. After twice-daily dosing, median PT, aPTT and HepTest were dose-dependently prolonged and reached maximum prolongations 1–4 hours after the administration of rivaroxaban. Maximum inhibition of Factor Xa activity and prolongation of PT on day 7 were similar to those measured after the first dose on day 0. Trough values for PT and aPTT after the administration of rivaroxaban 10 mg, 20 mg and 30 mg twice daily (bid) on day 7 were still elevated after 12 hours compared with baseline [34].

Because unchanged rivaroxaban (approximately one-third) is excreted renally, decreased renal function led to increases in rivaroxaban plasma concentrations: the area under the curve (AUC) for plasma concentration increased by 44% with mild impairment (creatinine clearance [CrCl] 50–79 ml/min); 52% with moderate impairment (CrCl 30–49 ml/min) and 64% with severe impairment (CrCl <30 ml/min), compared with healthy subjects [35,38]. In healthy elderly subjects, the PD effects of rivaroxaban showed a similar pattern, with maximum inhibition of Factor Xa activity increasing from 68% after a 30 mg dose to 75% after 40 mg and no further increase with a 50 mg dose [39].

Numerous phase I interaction studies demonstrated that rivaroxaban had a low propensity for clinically relevant food–drug and drug–drug interactions. Food prolonged the time to maximum concentration, but maximum plasma concentration (C_{max}) and AUC were increased, with reduced interindividual variability at higher doses of rivaroxaban. However, the terminal half-life remained unchanged [40]. The co-administration of rivaroxaban with acetylsalicylic acid, naproxen or clopidogrel had no significant influence on the inhibition of Factor Xa activity and the prolongation of PT, aPTT and HepTest, compared with rivaroxaban alone. In addition, rivaroxaban did not affect the inhibition of platelet aggregation associated with these agents [41–43]. No interactions were observed when rivaroxaban was co-administered with digoxin or atorvastatin [44,45].

Rivaroxaban was shown to have no effect on the corrected QT interval [46]. *In vitro* studies showed that rivaroxaban did not induce or inhibit cytochrome P450 (CYP) enzymes [47]. It had low affinity for CYP3A4 and moderate susceptibility for drug–drug interactions only with strong CYP3A4 inhibitors. However, rivaroxaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of CYP3A4 and P-glycoprotein – azole-antimycotics (e.g. ketoconazole) or HIV protease inhibitors (e.g. ritonavir) – because they may increase rivaroxaban plasma concentrations to a clinically relevant degree. The co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its PD effects. The concomitant use with other strong CYP3A4 inducers (e.g. phenytoin or St John's wort) may also lead to reduced rivaroxaban plasma concentrations, thus strong CYP3A4 inducers should be co-administered with caution [35] .

Clinical trials

The efficacy and safety of rivaroxaban (10 mg once daily [od]) for the prevention of VTE were investigated in four large-scale, phase III studies in patients undergoing THR or TKR surgery [48–51]. In all these studies, rivaroxaban was more effective than the LMWH enoxaparin in the prevention of VTE without a significant increase in bleeding events. A pooled analysis of these four studies showed that rivaroxaban significantly reduced the incidence of symptomatic VTE and death compared with enoxaparin regimens, without a significant increase in major bleeding events [52].

There have been some debates regarding the different definitions of major bleeding events used in phase III trials for the prevention of VTE. The exclusion of surgical-site bleeding from the major bleeding definition in the RECORD studies has caused some concerns. However, when surgical-site bleeding events were included in the analysis of major bleeding rates, the rivaroxaban regimens showed a rate that was comparable with that of the enoxaparin regimens [53].

Trials are being conducted for several other indications including the treatment of VTE, stroke prevention in patients with atrial fibrillation and secondary prevention after acute coronary syndrome (ACS). The results of the ATLAS ACS TIMI 46 phase II dose-escalation study in patients stabilized after an ACS indicate that the use of an oral Factor Xa inhibitor (in combination with antiplatelet therapy) increases bleeding in a dose-dependent manner and may reduce the risk of important clinical events (death, myocardial infarction or stroke) [54]. Based on the outcomes of this study, lower doses of rivaroxaban (2.5 mg and 5 mg bid) have been selected for further assessment in a large, phase III study (ATLAS ACS TIMI 51) of high-risk ACS patients.

Apixaban

Apixaban is a small-molecule, direct Factor Xa inhibitor that selectively and reversibly inhibits both free Factor Xa and prothrombinase activity [55,56]. Apixaban rapidly reacts with Factor Xa (K_{on} $2\times10^7\ M^{-1}\ s^{-1}$), and binds with high affinity (K_i 0.3 nM at 37 °C) [57]. It has high oral bioavailability in chimpanzees and dogs [58] and has a half-life of 8–15 hours [59]. Phase III studies for the prevention of VTE in patients undergoing TKR surgery showed that apixaban did not meet non-inferiority to enoxaparin 30 mg bid (ADVANCE-1) [60] but was more effective than enoxaparin 40 mg od in the prevention of VTE (ADVANCE-2) [61]. Investigations are ongoing in a number of other indications including the treatment of VTE, stroke prevention in patients with atrial fibrillation and secondary prevention after ACS. A phase II, dose-ranging study of apixaban showed a dose-related increase in bleeding and a trend towards a reduction in ischaemic events with the addition of apixaban to antiplatelet therapy in patients with recent ACS [62].

Edoxaban

Edoxaban (DU-176b) is an oral, direct and specific Factor Xa inhibitor (K_i 0.56 nM) with a >10,000-fold selectivity for Factor Xa compared with thrombin [63]. Peak plasma levels of edoxaban were observed at 1.5 hours after a single oral dose, corresponding to the maximum inhibition of Factor Xa activity; in an *ex vivo* experimental model, the antithrombotic effects were sustained for up to 5 hours [64,65]. In general, plasma edoxaban concentrations are linearly correlated with coagulation parameters [66].

Phase II studies for the prevention of VTE in patients undergoing TKR and THR showed promising results [67,68]. Edoxaban has also been assessed in a phase II study for the prevention of stroke in patients with atrial fibrillation; it was shown that edoxaban (30 and 60 mg od) had a safety profile similar to warfarin [69]. A phase III study is currently ongoing comparing edoxaban with warfarin in patients with atrial fibrillation.

Several other oral, direct Factor Xa inhibitors, such as betrixaban [70] and YM150 [71], have been investigated in phase II studies in patients undergoing THR or TKR surgery, and results from these studies provided proof of principle for their safety and tolerability.

Vitamin K or protamine is used as an antidote in patients treated with warfarin or heparin, respectively. Specific antidotes are not currently available to reverse the anticoagulant effects of the new oral anticoagulants, although encouraging preclinical results have been obtained with Factor VIIa and activated prothrombin complex concentrate for the potential management of severe bleeding with direct

Factor Xa or thrombin inhibitors [72,73], but the clinical utility of these agents is yet to be established. It has been reported recently that plasma-derived or recombinant Factor Xa, modified to lack catalytic and membrane-binding activities, could neutralize the anticoagulant activities of Factor Xa inhibitors and LMWH, demonstrating the potential of Factor Xa to act as a universal antidote for the reversal of anticoagulation of all current direct and indirect Factor Xa inhibitors, in patients with bleeding-related medical emergencies or those requiring the immediate cessation of anticoagulation prior to surgery [74].

Direct thrombin inhibitor

Dabigatran etexilate

Dabigatran is an oral, reversible, direct thrombin inhibitor [75]. The active site of thrombin is composed of the specificity (S1), proximal (S2) and distal pockets. The S1 pocket contains Asp189 at the bottom, which provides specificity for a basic arginine residue at the P1-position of substrates. Dabigatran effectively inhibits thrombin by an ionic interaction between its basic functional group and Asp189 in the S1 pocket [76].

The prodrug dabigatran etexilate has an oral bioavailability of approximately 6% [77]. It is converted by esterases into its active metabolite dabigatran once absorbed from the gastrointestinal tract [78]. Stangier et al. found that peak plasma concentrations of dabigatran were reached within 2 hours of administration, with an estimated half-life of 14–17 hours with multiple dosing (50–400 mg three-times daily) [77]. Dabigatran exhibited linear pharmacokinetic (PK) characteristics, with dose-proportional increases observed in C_{max} and AUC [77,79]. In healthy men, dabigatran dose-dependently increased thrombin time, ecarin clotting time, international normalized ratio (INR) and aPTT [77]. There was a close correlation between prolongation of blood coagulation assays and dabigatran plasma concentrations. Routine coagulation monitoring is not required due to its predictable PK and PD. Dabigatran is predominantly excreted via the kidneys, is not metabolized by the CYP system and has no *in vitro* effects on human CYP enzymes. Drug–drug interactions were not observed with concomitant administration of atorvastatin, diclofenac or digoxin [80]. Co-administration of dabigatran with pantoprazole and other proton-pump inhibitors had no effect on bleeding or efficacy. However, the P-glycoprotein inhibitor quinidine is contraindicated, and the daily dose of dabigatran etexilate should be reduced from 220 mg to 150 mg in patients receiving amiodarone concomitantly [81].

Dabigatran etexilate was investigated in three phase III trials for the prevention of VTE in patients undergoing hip or knee replacement surgery. The results showed that it was non-inferior to enoxaparin 40 mg od [82,83], but failed to meet non-inferiority to enoxaparin 30 mg bid [84]. Trials are being conducted for other indications including the treatment of VTE and secondary prevention after ACS. The results of the RE-LY trial in patients with atrial fibrillation showed that dabigatran etexilate 110 mg bid was non-inferior, whereas 150 mg bid was superior to warfarin for the prevention of stroke and systemic embolism, with a significantly lower rate of major bleeding in the 110 mg dose group. The incidence of gastrointestinal adverse events was higher in both the dabigatran etexilate dose groups, which contributed to significantly higher rates of treatment discontinuation [85]. In the recently completed RECOVER trial, dabigatran was shown to be as effective as warfarin for the treatment of acute VTE with a similar safety profile [86].

Potential advantages of direct Factor Xa inhibition

Factor Xa is the first factor activated after the activation of TF, and one molecule of Factor Xa catalyzes the formation of approximately 1000 thrombin molecules. In addition, the formation of the prothrombinase complex, which is vastly more efficient than free Factor Xa (approximately 300,000-fold) at cleaving prothrombin to form thrombin, is ultimately limited by the concentration of Factor Xa [10]. Thus, inhibition of TG will ultimately prevent thrombin-induced positive feedback via the activation of Factors Va and VIIIa (key components of the prothrombinase complex and the tenase complex, respectively).

A major difference between the direct and indirect Factor Xa inhibitors is that AT-dependent, indirect Factor Xa inhibitors (such as UFH, LMWH and fondaparinux) are unable to inhibit Factor Xa within the prothrombinase complex [87,88]. A recent study using computational model systems suggested that rivaroxaban would be more effective in the suppression of an ongoing coagulation process than the AT-dependent, indirect Factor Xa inhibitor fondaparinux, reflecting its higher reactivity towards the prothrombinase complex [89]. Direct Factor Xa inhibitors are able to inhibit free, prothrombinase-bound and clot-associated Factor Xa [20,24,90]. Clot-associated Factor Xa has been shown to be enzymatically active *in vitro* and able to activate prothrombin to thrombin [91,92]. Factor Xa has also been shown to be an important contributor of clot-associated procoagulant activity *in vitro* [93]. Thus, direct inhibition of clot-associated Factor Xa could be an effective and localized approach to the prevention of thrombus growth. In addition, it has been demonstrated recently that rivaroxaban concentration-dependently inhibited the procoagulant activity of activated monocytes and macrophages, whereas the indirect Factor Xa inhibitor fondaparinux was without this effect [94]. This property is thought to be attributed to the ability of rivaroxaban to inhibit Factor Xa bound to monocytes. By contrast, the secretion of inflammatory chemokines by activated monocytes and macrophages was inhibited by both rivaroxaban and fondaparinux, suggesting that this effect may be due to the decrease in TG in plasma, which affects the protease-activated receptor-1 signalling system [94].

Inhibition of Factor Xa prevents TG, resulting in sustained attenuation of thrombus-associated procoagulant activity, but at the same time it may allow the functions of existing thrombin to continue. However, direct thrombin inhibition is also believed to be a logical choice of anticoagulant target due to its multiple roles in the regulation of coagulation [95]. Indeed, recent clinical studies have provided further evidence that both Factor Xa and thrombin are viable targets for anticoagulant therapy. Although the mechanisms of action are different, both direct Factor Xa inhibition and direct thrombin inhibition could provide effective and safe anticoagulation [95,96]. However, no data is available at present for a direct comparison of these two classes, and their efficacy might be different when used in different indications.

Discussion and conclusions

Clot formation is a fast process, taking less than 5 minutes from activation to thrombus formation [97]. Therefore, for a direct anticoagulant to function effectively, it should exert a rapid effect. Moreover, directly targeting a critical point in the coagulation cascade could result in more predictable anticoagulation, via a reliable and well-understood pathway [96].

Factor Xa, positioned early in the coagulation cascade, is the first factor to be activated after TF activation. The oral, direct Factor Xa inhibitor rivaroxaban has demonstrated a good efficacy/risk profile. Its mode of action may explain the efficacy and safety profiles reported in the four phase III studies that constituted the RECORD programme.

There has been poor compliance to guideline recommendations for thromboprophylaxis, particularly in patients undergoing THR or TKR surgery [98], partly due to the limitations of conventional anticoagulants (such as parenteral administration or the need for frequent coagulation monitoring). The convenient, oral, fixed-dose mode of administration without the need for routine coagulation monitoring could potentially improve guideline adherence and thus overall clinical outcomes. Similarly, clinical studies with dabigatran etexilate

have provided further evidence that thrombin is also a viable anticoagulant target, with advantages over conventional therapy.

Both rivaroxaban and dabigatran etexilate have been approved in some countries for VTE prophylaxis in patients undergoing THR or TKR surgery, with fixed dose regimens (i.e. 10 mg od for rivaroxaban; 220 mg or 150 mg od for dabigatran) in the majority of patients without the need for routine coagulation monitoring. However, while the new agents can be used in the majority of patients without routine coagulation monitoring, recent consensus suggests that measuring the concentrations of the drug or its activity might be useful in certain patients, such as those with impaired renal and/or hepatic function, advanced age, suspected overdose and extreme body weights, or in those that require urgent surgery (to ensure that their anticoagulant effect or plasma concentrations are below a clinically significant level) [99,100]. Accumulating evidence suggests that the commonly used global clotting assays are not appropriate for measuring the new oral anticoagulants [101,102]. For rivaroxaban, if the PT assay is used, the results need to be expressed as rivaroxaban plasma concentrations (ng/ml) using rivaroxaban calibrators [103], and the INR should not be used. However, the PT assay is not specific for Factor Xa, and lacks sensitivity at low rivaroxaban concentrations. By contrast, Factor Xa activity assays are specific and may be useful for measuring rivaroxaban plasma concentrations [103–105]. The utility of these assays is currently under evaluation.

In summary, targeting a single Factor within the coagulation cascade (such as Factor Xa or thrombin) could provide effective and safe anticoagulation. The development of these new oral agents represents a major advance in anticoagulant therapy. The results of further studies of the long-term use of new oral anticoagulants are eagerly awaited. Patients may soon be able to experience convenient, oral anticoagulation without the need for frequent coagulation monitoring for both short- and long-term anticoagulation therapy.

Conflict of interest statement

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