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Efficacy and Toxicity of Factor Xa Inhibitors

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ABSTRACT - Venous thromboembolism (VTE) is a serious disease that is often neglected, and effective and safe antithrombotic treatments are a public health priority. New antithrombotics such as rivaroxaban, apixaban, betrixaban, edoxaban, darexaban, TAK-442, LY517717, eribaxaban, otamixaban are being developed to overcome current therapeutic limitations. The new oral anticoagulants and parenteral otamixaban are under evaluation in clinical trials for VTE treatment, for VTE prevention in orthopedic surgery, for stroke prevention in patients with atrial fibrillation and for cardiovascular event prevention in patients with acute coronary syndrome. These antithrombotic agents directly and selectively inhibit factor Xa, and do not require coagulation monitoring and dose adjustment. Several of these drugs have shown promising results and have the potential to either replace or act as alternatives to traditional anticoagulants (heparins, vitamin K antagonists).

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INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, causes significant morbidity and mortality. There are more than 600,000 symptomatic venous thromboembolic events and 300,000 deaths per year in the USA (1), and more than one million thromboembolic disorders including 500,000 venous thromboembolic events leading to death each year in the European Union (2). Major orthopaedic surgery of the lower limbs is associated with an increased risk of VTE, responsible for 50% of asymptomatic thromboembolic events and between 5 and 15% of clinical thromboembolic events (3). Atrial fibrillation is the most common arrhythmia and a major risk factor for ischemic stroke. It affects approximately 2% of the general population and 10% of people over 75 years of age, and entails major health expenditure (4,5).

The annual cost of health care for VTE is approximately from \$7,594 to \$16,644 per patient in the USA, depending on whether there is primary or secondary diagnosis of deep vein thrombosis and pulmonary embolism (6) Despite the costs of thromboprophylaxis, the prevention of venous thromboembolic events following major orthopaedic surgery is considered more cost-saving than its absence (7). Thus, VTE is a

major public health problem whose prevention and treatment (8-10) needs to be both effective and safe with respect to bleeding, particularly in high-risk patients.

Conventional antithrombotic therapy comprises unfractionated heparin (UFH), the low molecular weight heparins (LMWHs), the synthetic pentasaccharide fondaparinux and the vitamin K antagonists (VKAs). All these agents have a potential bleeding risk, and their limitations of use are well known (Table 1) (10-12). To compensate for the drawbacks, new anticoagulants with characteristics similar to those of an "ideal" anticoagulant have been developed (Table 2) (13-16), namely rivaroxaban, apixaban, betrixaban, edoxaban, darexaban, TAK-442, LY517717, eribaxaban, otamixaban. Dabigatran (Pradaxa[®], Boehringer Ingelheim) a new orally direct thrombin inhibitor is also available. A wide variety of indirect comparisons studies of FXa inhibitors *versus* dabigatran have been performed, and have found different results.

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For stroke prevention in atrial fibrillation several studies suggested that dabigatran 150 mg is superior to rivaroxaban for some efficacy endpoints (17-19) and is the most cost-effective therapy (20). In the same indication, another study with subgroup analysis has found no statistically significant differences in efficacy between apixaban and dabigatran or rivaroxaban (21). Furthermore, several authors emphasize that such indirect comparisons should be used only to generate hypotheses, which need to be tested in a clinical trial comparing the FXa inhibitors and dabigatran directly (18). Because it plays a central role in the coagulation cascade, activated factor X (FXa) appears an interesting target in the search for new agents.

New antithrombotic agents selectively and directly inhibit FXa by binding to the active site of factor Xa. Antithrombin-independent inhibitors have the potential to inhibit FXa when it is free

and clot-bound, as well as the activity of prothrombinase. This leads to interruption of the intrinsic and extrinsic coagulation cascade pathways and thus to inhibition of thrombin formation and thrombus development (Figure 1) (22,23). With the exception of parenteral otamixaban, these synthetic low molecular weight FXa inhibitors are orally active. The new drugs present a low variability in pharmacokinetic and pharmacodynamic profiles and more stable anticoagulant activity over time, which means that biological monitoring of haemostasis and dose adjustments are not required (13,22,23).

Direct FXa inhibitors are under evaluation in clinical trials for the treatment of VTE, the prevention of VTE in orthopaedic surgery, the prevention of systemic thromboembolism in atrial fibrillation and of cardiovascular events in acute coronary syndrome.

Table 1. Limitations of current anticoagulants.

VKAs	UFH	LMWH	Fondaparinux	Dabigatran
Slow onset of action	Parenteral administration	Parenteral administration	Parenteral administration	Oral administration bid
Unpredictable anticoagulant effect and patient response	Unpredictable anticoagulant effect due to unspecific binding	Contraindication in patients with severe renal insufficiency	Contraindication in patients with severe renal insufficiency	Contraindication in patients with severe renal insufficiency
Narrow therapeutic window	Potential for severe heparin-induced thrombocytopenia	Risk of heparin-induced thrombocytopenia		Multiple drug interactions
Multiple food and drug interactions	Coagulation monitoring (aPTT or anti-factor Xa activity)			Intestinal absorption pH dependant with low bioavailability (6%)
Regular coagulation monitoring (INR) and dose adjustment	Regular monitoring of platelet count			

Abbreviations: VKAs, vitamin K antagonists; UFH, unfractionated heparin; LMWH, low molecular weight heparin; INR, international normalized ratio; aPTT, activated partial thromboplastin time; bid, twice daily.

Table 2. Characteristics of an "ideal" anticoagulant.

Oral administration
Rapid and predictable action
Wide therapeutic window
No requirement for routine coagulation monitoring and dose adjustment
High efficacy-to-safety index
Minimal interactions with food and other drugs
Use in patients with severe renal insufficiency, hepatocellular insufficiency, in old age and with extreme body weight
Availability of an antidote

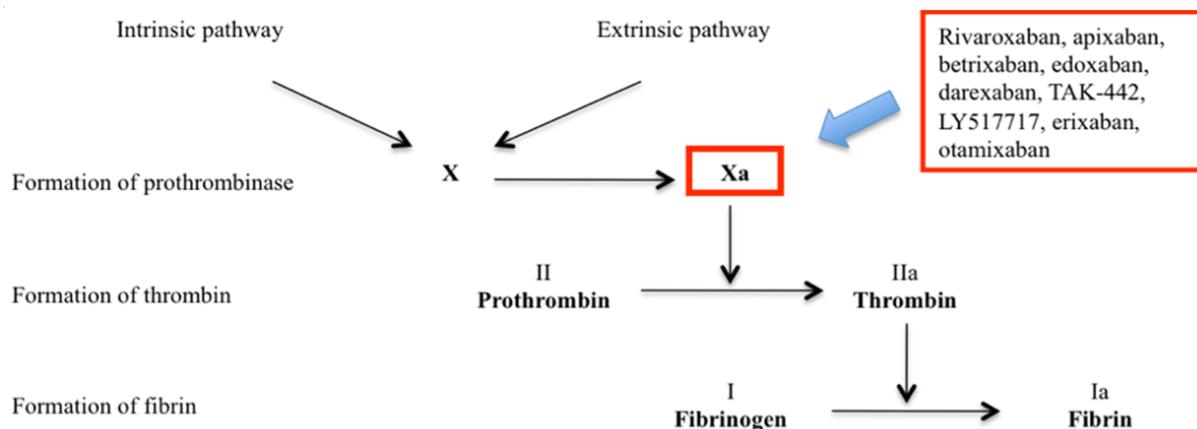


Figure 1. Schematic representation of the coagulation cascade and site of action of the novel anticoagulants.

Many of these drugs appear promising as new therapeutic options, even as alternatives to conventional antithrombotic therapy including heparins and VKAs.

The purpose of this review is to describe the direct FXa inhibitors and where they stand in relation to the antithrombotic therapies currently used in clinical practice. This paper focuses on new anticoagulants in clinical development, their efficacy and safety. We highlight two drugs that have recently obtained marketing authorisation.

Drugs which have Obtained Marketing Authorization

Rivaroxaban

Rivaroxaban (Xarelto[®], Bayer / Johnson & Johnson) is the oral direct factor Xa inhibitor that has been investigated the most thoroughly. Based on the results of four dose studies (ODIXa program) and four clinical studies (RECORD program), it has recently been approved at a dosage of 10 mg taken once daily for the prevention of venous thromboembolic events after scheduled orthopaedic surgery of the lower limbs (total hip or knee replacement) (24,25). These studies demonstrated the superior efficacy of rivaroxaban compared with enoxaparin in thromboprophylaxis for major orthopaedic surgery, and tolerance of rivaroxaban was not different or lower in terms of major bleeding, elevation of liver enzymes or incidence of cardiovascular events (25,26). Rivaroxaban is contraindicated in patients with severe hepatic insufficiency and it is not recommended in patients with severe renal insufficiency. There are a number of known drug interactions with potent inhibitors and inducers of cytochrome P450 3A4

due to a partial metabolism of rivaroxaban by this cytochrome (24).

Two dose studies, the ODIXa-DVT (27) and EINSTEIN-DVT studies (28), on the treatment of VTE suggest that the initial treatment of VTE requires more aggressive dosing, whereas a subsequent dose reduction maintains the initial efficacy while decreasing the risk of bleeding. Thus, the optimal dosage regimen used in phase III studies is 15 mg twice daily for 3 weeks followed by long-term treatment with 20 mg once daily (29).

The EINSTEIN program assessed the safety and efficacy of new anticoagulants in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and in long-term thromboprophylaxis. The EINSTEIN-DVT study (clinicaltrials.gov NCT00440193) found that rivaroxaban 15 mg twice daily for 21 days followed by 20 mg once daily was effective in the reduction of symptomatic recurrent venous thromboembolism after 6 months of treatment, in addition to the standard treatment regimen including parenterally administered enoxaparin for 5 days followed by a VKA with a target international normalized ratio (INR) of 2.5. Major and clinically relevant non-major bleeding rates were similar between the two treatment groups (Table 3) (24,30). Results from the recently published EINSTEIN-PE study (clinicaltrials.gov NCT00439777) were similar, with rivaroxaban non-inferiority to standard therapy, at the same regimen, but in the treatment of PE. Major or clinically relevant non-major bleeding composite rates were also similar between the two treatment groups, but major bleeding rates alone, which were defined as secondary outcome, were found significantly inferior for rivaroxaban (31).

Patients receiving initial antithrombotic therapy for DVT or PE were enrolled in the EINSTEIN-Extension study (clinicaltrials.gov NCT00439725), the results of which showed that rivaroxaban could be used for the long-term secondary prevention of VTE. Nevertheless, the risk of bleeding during long-term anticoagulant therapy should be evaluated carefully. Indeed, this study showed that after 6-12 months of treatment, rivaroxaban at a dose of 20 mg once daily significantly reduced the risk of recurrent VTE at the cost of a moderate increase in clinically relevant non-major bleeding (Table 3) (24,30,32).

Following a pivotal ROCKET AF study (clinicaltrials.gov NCT00403767) rivaroxaban has recently obtained marketing authorisation for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF) and with one or more risk factor(s), such as congestive heart failure, hypertension, age \geq 75 years, diabetes mellitus, previous stroke or transient ischaemic attack. According to guidelines, VKAs are the reference oral anticoagulant therapy for stroke prevention in AF in patients with high risk of stroke, while acetylsalicylic acid is prescribed as first-line therapy in patients with low risk of stroke (33,34). For this reason, rivaroxaban was compared to adjusted-dose warfarin (INR of prothrombin times ranging between 2.0 and 3.0) and only the non-inferiority of rivaroxaban was established in the ROCKET AF study (Table 4). Major bleeding rates were similar between the two treatment groups, with fewer intracranial haemorrhages (0.5% vs. 0.74% $p = 0.02$) and fatal bleeding (0.2% versus 0.5%, $p = 0.003$) in the rivaroxaban group (24,35). As a result, rivaroxaban can be prescribed as a first-line or second-line therapy (in cases of poorly-controlled INR under VKAs) in patients with moderate-to-high risk of stroke, in accordance with the marketing authorisation (36).

The efficacy and safety of rivaroxaban compared to enoxaparin were investigated for thrombosis prevention in hospitalized medically ill patients in the MAGELLAN program (clinicaltrials.gov NCT00571649). Although this study was completed in 2010, the results have not yet been published. Rivaroxaban was also assessed for the prevention of cardiovascular events in patients with acute coronary syndrome (ACS), with the ATLAS 2 TIMI 51 program following the ATLAS ACS TIMI 46 dose-finding phase II study (Table 5) (37).

Apixaban

Apixaban (Eliquis[®], Bristol-Myers Squibb / Pfizer) is the second advanced direct FXa inhibitor. The risk-benefit balance for apixaban was evaluated in two pivotal (non-inferiority) phase III studies on VTE prevention after major orthopaedic surgery in patients undergoing total knee replacement (ADVANCE-2) or total hip replacement (ADVANCE-3). Results from the ADVANCE program led to marketing authorisation in 2011. In both studies, apixaban at a dose of 2.5 mg twice daily showed superior efficacy compared to enoxaparin in reduction of thromboembolic events after major orthopaedic surgery without increased risk of bleeding. It appears to have the same type of drug interactions as rivaroxaban, namely with inhibitors and inducers of CYP3A4 and with P-glycoprotein. Apixaban is contraindicated in patients with hepatic impairment and should be used with caution in patients with severe renal impairment (38,39).

Apixaban is currently under evaluation for VTE prevention in patients hospitalized for an acute medical illness by the ADOPT phase III study (clinicaltrials.gov NCT00457002) and for VTE prevention in cancer patients by the ADVOCATE phase II study (clinicaltrials.gov NCT00320255).

Following the BOTTICELLI DVT dose-ranging study, a treatment regimen (10 mg apixaban twice daily for 7 days followed by 5 mg twice daily) was selected for investigation in phase III studies (40). The AMPLIFY study (clinicaltrials.gov NCT00643201), investigating apixaban for the treatment of VTE at a higher dose for the first 7 days, as with rivaroxaban, compared to conventional therapy (LMWH followed by VKA), is underway. In the AMPLIFY-EXTENSION study (clinicaltrials.gov NCT00633893), apixaban 2.5 mg or 5 mg twice daily is compared to placebo for the secondary prevention of VTE. Both dosages of apixaban were significantly superior to placebo on the primary efficacy endpoint, defined as the composite of symptomatic recurrent venous thromboembolism or death from any cause, without increasing the rate of major bleeding. Only 15% of patients in this study were older than 75 years of age, and less than 6% had a creatinine clearance below 50 ml/min. Therefore, for such patients, the authors conclude that more data are needed to clarify the benefit-to-risk profile of apixaban. (41)(Table 3).

The ARISTOTLE program found that apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients) was non-inferior and even superior to warfarin in the prevention of stroke and systemic embolism in patients with non-valvular AF and at least one risk factor for stroke (age > 75 years; previous stroke, transient ischaemic attack or systemic embolism; symptomatic heart failure or left ventricular ejection fraction < 40%; diabetes mellitus; hypertension). Lower rates of bleeding and mortality were reported (Table 4). Indeed, the new anticoagulant reduces the risk of stroke or systemic embolism by 21%, major bleeding by 31%, and death by 11% compared to warfarin. Apixaban would prevent a haemorrhagic stroke in 4 patients per 1000 and an ischaemic or unknown type of stroke in 2 patients per 1000 (42).

In the ongoing AVERROES study (clinicaltrials.gov NCT00496769), apixaban 5 mg twice a day (or 2.5 mg twice daily in selected patients) seems promising for the prevention of stroke and systemic embolism in AF and demonstrates superior efficacy compared to acetylsalicylic acid (81-324 mg once daily). Indeed, apixaban substantially reduces risk of stroke or systemic embolism with no significant increase in major bleeding rates (Table 4). It presents fewer serious side effects and lower rates of discontinuation of medication compared with aspirin. Treating 1000 patients with apixaban rather than with aspirin for one year would prevent 21 strokes or systemic emboli, 9 deaths and 33 hospitalizations for cardiovascular causes at the cost of 2 major haemorrhages (43).

The APPRAISE-2 phase III trial evaluating the clinical benefit of apixaban for the secondary prevention of ACS was terminated prematurely at the recommendation of an independent monitoring and follow-up committee, because a significant increase in bleeding without a significant reduction in recurrent ischaemic events was reported in the apixaban group taken in combination with aspirin alone or with aspirin and clopidogrel compared to placebo (Table 5) (44).

The promising results from the AMPLIFY, ARISTOTLE and AVERROES programs could lead to indications for apixaban being extended in the coming years.

Drugs currently in Clinical Development

Betrixaban

Betrixaban (PRT 054021, Portola Pharmaceuticals) at doses of 15 mg and 40 mg twice daily showed an effective antithrombotic

action and was well tolerated by patients during the EXPERT phase II study ongoing in the US and Canada for the prevention of VTE after orthopaedic surgery for total knee replacement (Table 6) (45). The efficacy and safety of this new anticoagulant have not yet been evaluated in phase III trials.

The results of the EXPLORE-Xa dose-ranging study (clinicaltrials.gov NCT00742859) investigating betrixaban for stroke prevention in patients with non-valvular AF are not yet available (Table 4).

Edoxaban

Edoxaban (DU-176b, Daiichi Sankyo), another oral direct factor Xa inhibitor, is currently under investigation for the prevention and treatment of VTE and for the prevention of systemic thromboembolism in AF.

The effectiveness of edoxaban as thromboprophylaxis for major orthopaedic surgery has been established in phase III studies (Table 6): for total knee replacement (STARS E-3, clinicaltrials.gov NCT01181102), total hip replacement (J-STARS 5, clinicaltrials.gov NCT01181167) and hip fracture surgery (J-STARS 4 clinicaltrials.gov NCT01181141). Edoxaban at a dose of 30 mg once daily was compared to enoxaparin 20 mg twice daily and showed a significant reduction in venous thromboembolic events with no difference in major bleeding rates between treatment groups (46).

The HOKUSAI-VTE study (clinicaltrials.gov NCT00986154) is designed to investigate the efficacy and safety of edoxaban for the initial treatment of VTE. There is no specific dose study, therefore it is not possible to speculate on a higher dosage during the first days of treatment followed by a subsequent dosage reduction, as for rivaroxaban and apixaban. In the phase III study, edoxaban 60 mg once daily is administered after initial parenteral anticoagulant therapy and this is compared to initial parenteral treatment followed by VKA (Table 3) (14).

The ENGAGE-AFTIMI-48 phase III study (clinicaltrials.gov NCT00781391) (47) is designed to compare edoxaban with warfarin for the prevention of thromboembolism in patients with AF. This study follows the dose-finding study (clinicaltrials.gov NCT00504556) (48), in which edoxaban 30 mg or 60 mg once daily showed a favorable side-effect profile in terms of efficacy and safety (Table 4).

Darexaban

A number of phase II and III studies (clinicaltrials.gov NCT00353678, NCT00913120, NCT00902928) investigate darexaban (YM150, Astellas Pharma) in VTE prevention after hip arthroplasty (49-51) and evaluate the superiority of the new anticoagulant over enoxaparin (PEARL-1, clinicaltrials.gov NCT00408239), warfarin (PEARL, clinicaltrials.gov NCT00595426) and placebo (clinicaltrials.gov NCT00917254) in thromboprophylaxis after knee arthroplasty (Table 6).

Darexaban is also evaluated for the treatment of DVT and PE (clinicaltrials.gov NCT00937820) (Table 3), for the prevention of VTE in hospitalized medically ill patients (clinicaltrials.gov NCT01028950), after a hip fracture (clinicaltrials.gov NCT00937911) and after major abdominal surgery (clinicaltrials.gov NCT00942435).

Two phase II studies were designed to investigate an antithrombotic effect of the new drug in stroke prevention in patients with AF (clinicaltrials.gov NCT00448214 and OPAL-2, clinicaltrials.gov NCT00938730) (Table 4). Results were only published as abstracts (52,53).

The RUBY-1 study (clinicaltrials.gov NCT00994292) evaluated darexaban in combination with dual antiplatelet therapy for the secondary prevention of ischemic vascular events after ACS. It found a two- to four-fold increase in major and clinically relevant non-major bleeding, with no significant increase in efficacy compared to placebo (Table 5). On the other hand, darexaban was well tolerated, with no signs of hepatotoxicity. A large phase III trial is required to demonstrate the potential of low-dose darexaban to prevent major cardiac events after ACS (54). However, considering these reserved results and intense competition for fruitful market of FXa inhibitors, Astellas has decided to discontinue development of darexaban for all indications.

TAK-442

Two dose-finding studies investigated the efficacy, safety and tolerability of TAK-442 (Takeda) in the prevention of VTE after total knee replacement and in the secondary prevention of ischemic vascular events in patients with ACS. In the first study (clinicaltrials.gov NCT00641732) recruitment was stopped early in the groups receiving TAK-442 at doses of 10 mg or 20 mg twice daily due to a high rate of DVT, EP or all-cause mortality compared to control group. The efficacy and safety profiles of other doses were

similar to enoxaparin (Table 6) (55). In the second study (clinicaltrials.gov NCT00677053), 8 dosage regimens of TAK-442 in combination with standard antiplatelet therapy were evaluated in terms of efficacy and safety versus placebo (Table 5). The results of this study are not yet available.

LY517717

In the phase II study (clinicaltrials.gov NCT00074828) LY517717 (Lilly), difumarate at doses of 100, 125 and 150 mg demonstrated non-inferior efficacy and similar bleeding rates compared to enoxaparin in the prevention of venous thromboembolic events after orthopaedic surgery of the lower limbs (hip or knee replacement) (Table 6) (56). No information on the future development of this drug is available.

Eribaxaban

Eribaxaban (PD 0348292, Pfizer) was assessed in a dose-ranging study (clinicaltrials.gov NCT00306254) for VTE prevention after total knee replacement. All doses were well tolerated. A dose-related increase in the incidence of bleeding events was not statistically significant (Table 6) (23). No information on future trials is available.

Otamixaban

Otamixaban (XRP0673, Sanofi-Aventis) is a novel intravenous short-acting direct FXa inhibitor that can be used in acute situations. Initially evaluated in non-urgent percutaneous coronary intervention (SEPIA-PCI clinicaltrials.gov NCT00133731), this drug showed promising results in terms of efficacy and safety (57).

In the SEPIA-ACS1 TIMI 42 phase II study, otamixaban was investigated in patients with non-ST-segment elevation acute coronary syndromes and requiring revascularisation versus conventional anticoagulant (UFH) and antiplatelet (glycoprotein IIb/IIIa inhibitor) therapies (58). Administering eptifibatid before and during percutaneous coronary intervention in patients with unstable angina was found to significantly reduce the risk of death and myocardial infarction (59,60).

The SEPIA-ACS1 TIMI 42 study recommended using intermediate doses of otamixaban in future studies as more appropriate: low doses were ineffective and high doses were shown to be dangerous. Treatment with otamixaban at doses of 0.105 and 0.140 mg/kg/h was associated with a 40% reduction in myocardial infarction, ischaemic events and all-

cause death without a significant increase in bleeding rates compared to UFH plus eptifibatid (Table 5) (61). A phase III study (clinicaltrials.gov NCT01076764) has begun recruitment.

Furthermore, the pharmacokinetic and pharmacodynamic profiles of otamixaban will be investigated in patients with mild, moderate or severe renal insufficiency (clinicaltrials.gov NCT01120314) and with mild or moderate hepatic insufficiency (clinicaltrials.gov NCT01126086).

DISCUSSION

Numerous direct and selective FXa inhibitors are currently in clinical development and emerging data suggest that new antithrombotic agents are safe and effective in preventing and treating VTE, stroke and systemic embolism in patients with AF or following orthopaedic surgery. Most of these drugs will probably replace VKAs, and sometimes even initial parenteral treatment with heparin.

The use of new anticoagulants offers advantages over conventional therapy: for example, orally administered FXa inhibitors can be taken at home; their rapid and predictable antithrombotic action does not require dose adjustment or routine coagulation monitoring; food does not modify blood concentration with these new agents and information about drug interactions is available. The most common side effects observed in clinical trials, other than haemorrhages, are anaemia, nausea, increase in transaminases and/or bilirubin. Concerning liver laboratory assessments, data from four studies conducted to compare the efficacy and safety of rivaroxaban (6131 subjects) with enoxaparin (6131 subjects) were included in a pooled analysis (62). 2.33% rivaroxaban subjects and 3.64% enoxaparin subjects experienced a peak of alanine transaminase superior of three times upper limit of normal (ULN) without elevation of total bilirubin superior of two times ULN. 0.16% of rivaroxaban and enoxaparin subjects experienced a peak of alanine transaminase superior of three times ULN with a peak of total bilirubin superior of two times ULN. Nevertheless, several potential limitations of these novel drugs should be considered in daily clinical practice:

- At present there is a lack of validated tests to monitor the antithrombotic action of these new drugs. Yet monitoring can be helpful in certain situations (e.g. urgently-needed

surgery, suspected overdose, recurrence under treatment, doubts about drug administration) and adding intermediary endpoint measurement concerning bleeding risk in future clinical trials would be interesting.

- At the moment there is no specific antidote available to antagonize the effects of these drugs, so the treatment of major bleeding will be difficult when it occurs, or in emergency interventions. However, the search for an antidote is underway, and a recombinant factor Xa (PRT06445) presenting high affinity for direct and indirect FXa inhibitors was recently proposed as a potential antidote for new anticoagulants (63,64).
- A number of new agents will become available over a relatively short time, without comparative studies. Pharmaceutical companies only provide the results of indirect comparisons of the new anticoagulants (rivaroxaban, apixaban, dabigatran).
- New antithrombotics are being investigated for some, but not all, indications. For example, no study about FXa inhibitors has involved patients with mechanical heart valves, although direct thrombin inhibitor dabigatran was investigated in this indication (65).
- The cost-effectiveness of new drugs compared with traditional anticoagulants has not yet been evaluated. VKAs are cheap and effective, although the cost and difficulty of routine coagulation monitoring should be taken into account.
- Potential long-term side effects are unknown, and this implies increased vigilance in clinical practice. It should be remembered that ximelagatran was withdrawn owing to serious hepatotoxicity. Moreover, although FXa inhibitors drug data mention a possible rise of amylase and lipase, pancreatic function has not been clearly studied.
- Clinical data are scarce for patients with renal insufficiency; for this reason, UFH and VKAs will probably remain the reference drugs for these patients.

CONCLUSION

The short- and long-term therapeutic management of VTE will be considerably changed in the near future by the arrival on the market of new anticoagulants with targeted action on factor Xa, most of them orally active. Direct factor Xa inhibitors present a favorable safety and efficacy profile and offer an attractive option for the

prevention and treatment of venous and arterial thromboembolism, in comparison to standard therapy with heparins and VKAs. At present, two drugs (Xarelto® and Eliquis®) have obtained marketing authorisation for the prevention of venous thromboembolic events after scheduled orthopaedic surgery of the lower limbs, and rivaroxaban is also indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. However, it is early to talk of replacing standard antithrombotic therapy, given the current lack of objectivity and evidence. Further studies will be required before clinicians can be confident of the real conditions of use of these drugs, and of their ability to monitor coagulation and to manage adverse events associated with this new therapeutic class.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

KEYWORDS

factor Xa inhibitors, new anticoagulants, rivaroxaban, apixaban, betrixaban, edoxaban, darexaban, TAK-442, LY517717, eribaxaban, otamixaban.

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Table 3. Clinical development of factor Xa inhibitors for the treatment and secondary prevention of venous thromboembolism.

Anticoagulant	Study / Design	Number of patients / period	Regimen	Control	Efficacy endpoint	Results: Efficacy	Safety endpoint	Results: Safety
Rivaroxaban	EINSTEIN- DVT: phase III, randomized, open-label, non-inferiority	3 449 / 3, 6, or 12 months	15mg bid for 3 weeks followed by 20mg od	Enoxaparin for 5 days followed by VKA (INR 2-3)	Symptomatic recurrent VTE	2.1% vs 3.0% (p<0.0001 for non-inferiority)	Major bleeding; clinically relevant non-major bleeding	0.8% vs 1.2% (p=0.21); 7.3% vs 7.0%
	EINSTEIN- Extension: phase III, randomized, double-blind, superiority	1 197 / 6 or 12 months	20mg od	Placebo	Symptomatic recurrent VTE	1.3% vs 7.1% (p<0.0001 for superiority)	Major bleeding; clinically relevant non-major bleeding	0.7% vs 0% (p=0.11); 5.4% vs 1.2%
	EINSTEIN-PE: phase III, randomized, open-label, non-inferiority	4 833 / 3, 6 or 12 months	15mg bid for 3 weeks followed by 20mg od	Enoxaparin for 5 days followed by VKA (INR 2-3)	Symptomatic recurrent VTE	2.1% vs 1.8% (p=0.003 for non-inferiority)	Major bleeding; clinically relevant non-major bleeding	1.1% vs 2.2% (p=0.003)
Apixaban	AMPLIFY: phase III, randomized, double-blind, non-inferiority	5 400 / 6 months	10mg bid for 7 days followed by 5mg bid	Enoxaparin followed by VKA (INR 2-3)	Venous thromboembolic recurrence or death	Underway	Bleeding	Underway
	AMPLIFY-EXT: phase III, randomized, double-blind, non-inferiority	316 / 12 months	5 or 2.5mg bid	Placebo	Venous thromboembolic recurrence or death	5mg: 4.2% vs 11.6% 2.5mg: 3.8% vs 11.6% (p<0.001)	Major bleeding	5mg: 0.1% 2.5mg: 0.2% placebo: 0.5%
Edoxaban (DU-176b)	HOKUSAI-VTE: phase III, randomized, double-blind, non-inferiority	8 250 / 12 months	60mg od + heparin	Heparin/VKA	Symptomatic recurrent VTE	Underway	Clinically relevant bleeding	Underway
Darexaban (YM150)	NCT00937820: phase III, non-randomized, open-label	87 / 52 weeks	-	-	Incidence of DVT and PE	Underway	Incidence of bleeding event	Underway

Abbreviations: bid, twice daily; DVT, deep vein thrombosis; INR, international normalized ratio; od, once daily; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Table 4. Clinical development of factor Xa inhibitors for the prevention of stroke and systemic embolism in atrial fibrillation.

Anticoagulant	Study / Design	Number of patients / Period	Regimen	Control	Efficacy endpoint	Results: Efficacy	Safety endpoint	Results: Safety
Rivaroxaban	ROCKET AF / phase III, randomized, double-blind, non-inferiority	14 264 / 32 months up to 4 years	20mg od (15mg od in patients with moderate renal insufficiency)	Warfarin (INR 2-3)	Composite of stroke and non-central nervous system systemic embolism	1.7%/year vs 2.2%/year (p<0.001 for non-inferiority)	Major and clinically relevant non-major bleeding events; major bleeding	14.9%/year vs 14.5%/year (p=0.44 for superiority); 3.6%/year vs 3.4%/year (p=0.58)
Apixaban	ARISTOTLE / phase III, randomized, double-blind	18 201 / 1.8 years on average	5mg bid (2.5mg bid in selected patients)	Warfarin (INR 2-3)	Stroke or systemic embolism; death from any cause	1.27%/year vs 1.60%/year (p<0.001 for non-inferiority, p=0.01 for superiority); 3.52%/year vs 3.94%/year (p=0.047)	Major bleeding	2.13%/year vs 3.09%/year (p<0.001)
	AVERROES / phase III, randomized, double-blind, superiority	5 599 / 1.1 years on average	5mg bid (2.5mg bid in selected patients)	Acetylsalicylic acide (81-324mg od)	Stroke or systemic embolism	1.6%/year vs 3.7%/year (p<0.001)	Major bleeding	1.4%/year vs 1.2%/year (p=0.57)
Betrixaban	EXPLORE-Xa / phase II, randomized, double-blind	508 / 3 months	40mg, 60mg or 80mg od	Open-label warfarin (INR 2-3)		Underway	Major and clinically relevant non-major bleeding events	Underway
Edoxaban	NCT00504556/ phase II, randomized, double-blind	1 146 / 3 months	30mg and 60mg od, 30mg and 60mg bid	Open-label warfarin (INR 2-3)		Underway	Major and clinically relevant non-major bleeding events	10.6%, 7.8%, 3.8%, 3.0% for 60mg bid, 30mg bid, 60mg od, 30mg od, respectively, vs 3.2%
	ENGAGE-AF TIMI-48 / phase III, randomized, double-blind, non-inferiority	20 500 / 24 months	30mg and 60mg od	Warfarin (INR 2-3)	Stroke and systemic embolism	Underway	Major bleeding	Underway
Darexaban (YM-150)	NCT00448214 / phase II, randomized, double-blind	448 / 16 weeks	30mg, 60mg, 120mg and 240mg od	Open-label warfarin (INR 2-3)	Stroke and systemic embolism	No thromboembolic strokes reported	Major and clinically relevant non-major bleeding events	2.2%, 2.2%, 3.2% and 16.7% for 30mg od, 60mg od, 120mg od, 240mg od vs 2.1%
	OPAL-2 / phase II, randomized, double-blind	1 280 / 16 months	6 doses	Warfarin (INR 2-3)	Stroke, systemic embolism, all deaths	Not detailed	Major and clinically relevant non-major bleeding events	Not detailed

Abbreviations: bid, twice daily; INR, international normalized ratio; od, once daily.

Table 5. Clinical development of factor Xa inhibitors for secondary prevention of vascular and ischaemic events in patients with acute coronary syndrome.

Anticoagulant	Study / Design	Number of patients / Period	Regimen	Control	Efficacy endpoint	Results : Efficacy	Safety endpoint	Results : Safety
Rivaroxaban	ATLAS ACS 2 TIMI 46 / phase II, randomized, double-blind	3 491 / 6 months	5mg, 10mg, 15mg, 20mg od or bid + aspirin or aspirin /thienopyridine	Placebo	Composite of death, MI, stroke, or severe recurrent ischaemia requiring revascularisation	8.7%, 5.3%, 5.2%, 5.3%, 4.4%, 6.5% for 5mg, 10mg, 20mg od, respectively, vs 7.0%; 5mg, 10mg, 20mg bid, respectively, vs 7.0%; 6.3% and 6.5% (15mg od and bid) vs 5.1%	Clinically significant bleeding according to the TIMI definition	7.4%, 10.8%, 16.0% for 5mg, 10mg, 20mg od, respectively, vs 3.3%; 4.8%, 11.0%, 14.6% for 5mg, 10mg, 20mg bid, respectively, vs 3.3%; 13.1% and 12.3% (15mg od and bid) vs 3.8%
Apixaban	APPRAISE-2 / phase III, randomized, double-blind, superiority	7 392 / terminated prematurely	5mg bid	Placebo	Composite of cardiovascular death, MI, or ischemic stroke	7.5% vs 7.9% (p=0.51)	Major bleeding according to the TIMI definition	1.3% vs 0.5% (p=0.001)
Darexaban (YM150)	RUBY-1 / phase II, randomized, double-blind	1 279 / 26 weeks	5mg bid, 10mg od, 15mg bid, 30mg od, 30mg bid or 60mg od + dual antiplatelet therapy	Placebo	Composite of all-cause mortality, non-fatal MI, non-fatal stroke, severe recurrent ischaemia	3.8%, 3.8%, 6.3%, 6.4%, 5.9%, 7.8% for 5mg bid, 10mg od, 15mg bid, 30mg od, 30mg bid, 60mg od, respectively, vs 4.4%	Major and clinically relevant non-major bleeding events	5.7%, 5.0%, 6.3%, 5.1%, 9.8%, 6.5% for 5mg bid, 10mg od, 15mg bid, 30mg od, 30mg bid, 60mg od, respectively, vs 2.8%
TAK-442	NCT00677053 / phase II, randomized, double-blind	2 753 / 24 weeks	40, 80 and 160mg od, 10, 20, 40, 80 and 120mg bid + antiplatelet therapy	Placebo + antiplatelet therapy	Composite of cardiovascular mortality, non-fatal MI, non-fatal stroke or myocardial ischaemia requiring hospitalization	Underway	Major bleeding events defined by the thrombolysis in MI scale	Underway
Otamixaban (XRP0673)	SEPIA-ACS/TIMI 42/ phase II, randomized, double-blind	3 241 / 7-30 days	0.08mg/kg bolus followed by infusions of 0.035, 0.070, 0.105, 0.140 or 0.175mg/kg/h	UFH + eptifibatide	Composite of all-cause death, MI, urgent revascularisation or bailout glycoprotein IIb/IIIa inhibitor use up to 7 days	7.2%, 4.6%, 3.8%, 3.6% et 4.3% for 0.035, 0.070, 0.105, 0.140 and 0.175mg/kg/h, respectively, vs 6.2%	TIMI major or minor bleeding not related to coronary-artery bypass grafting up to 7 days	1.6%, 1.6%, 3.1%, 3.4% and 5.4% for 0.035, 0.070, 0.105, 0.140 and 0.175mg/kg/h, respectively, vs 2.7%
	NCT01076764 / phase III, randomized, double-blind, superiority	30-180 days		UFH + eptifibatide	Composite of all-cause death and MI	Underway	TIMI major and minor bleeding	Underway

Abbreviations: bid, twice daily; MI, myocardial infarction; od, once daily; TIMI, thrombolysis in myocardial infarction; UFH, unfractionated heparin.

Table 6. Clinical development of factor Xa inhibitors for the prevention of venous thromboembolism in orthopaedic surgery.

Anticoagulant	Study / Design	Number of patients / Period	Regimen	Control	Efficacy endpoint	Results : Efficacy	Safety endpoint	Results : Safety
Betrixaban	EXPERT / phase II, randomized, open-label, TKR	215 / 10-14 days	15mg bid or 40mg bid	Enoxaparin 30mg	Incidence of VTE	20% (15mg), 15% (40mg) vs 10%	Major or clinically significant non-major bleeding events	major bleeding: 0% vs 2.3%; non-major bleeding: 0% (15mg) and 2.4% (40mg) vs 4.6%
Edoxaban	STARS E-3 / phase III, randomized, double-blind, TKR	716 / 2 weeks	30mg od	Enoxaparin 20mg bid	Incidence of VTE	Underway	Bleeding events	Underway
	STARS J-5 / phase III, randomized, double-blind, THR	610 / 2 weeks	30mg od	Enoxaparin 20mg bid	Incidence of VTE	Underway	Bleeding events	Underway
	STARS J-4 / phase III, randomized, open-label, hip fracture surgery	92 / 2 weeks	30mg od	Enoxaparin 20mg bid	Incidence of VTE	Underway	Bleeding events	Underway
Darexaban (YM150)	phase II, dose escalation, randomized, double-blind, THR	174 / 7-10 days	3, 10, 30 or 60mg od	Enoxaparin 40mg	Incidence of VTE	51.9%, 38.7%, 22.6% and 18.5% for 3, 10, 30 and 60mg od, respectively, vs 38.7%	Major or clinically relevant non-major bleeding events	No major and 3 clinically relevant non-major bleeding (2.9%, 5.7%, 0% and 0% in the 3, 10, 30 and 60mg, respectively) vs 0 event
	ONYX-2 / phase II, dose finding, randomized, double-blind, THR	1 017 / 5 weeks	5, 10, 30, 60 or 120mg od	Enoxaparin 40mg	Incidence of VTE up to 9 days after surgery	27.4%, 31.7%, 19.3%, 13.3% or 14.5% for 5, 10, 30, 60 and 120mg, respectively, vs 18.9%	Major bleeding up to 9 days after surgery	1 event (60mg) vs 1 event
	NCT00913120 / phase II and III, randomized, double-blind, THR	610 / 2 weeks	15 and 30mg bid	Enoxaparin and placebo	Incidence of VTE	2.9%, 5.2% for 15 and 30mg vs 17.1% placebo and 2.4% enoxaparin	Bleeding events	9.5%, 10.3% for 15 and 30mg vs 7.4% placebo and 11.7% enoxaparin
	ONYX-3 / phase II and III, randomized, double-blind, THR	1 992	4 doses	Enoxaparin 40mg	Incidence of VTE and death from all causes	Underway	Bleeding events	Underway
	PEARL-1 / phase II, dose escalation, randomized, open-label, TKR	367 / 2 weeks	2 doses	Enoxaparin	Incidence of VTE	Underway	Major or clinically relevant non-major bleeding events	Underway

	PEARL / phase II, randomized, double-blind, TKR	685 / 6 weeks	4 doses (od or bid)	Warfarin (INR 2-3)	Incidence of VTE	Underway	Major bleeding	Underway
	NCT00917254 / phase II and III, randomized, double-blind, TKR	369 / 2 weeks	2 doses (low and high)	Enoxaparin and placebo	Incidence of VTE	Underway	Bleeding events	Underway
TAK-442	NCT00641732 / phase II, dose finding, randomized, double-blind, TKR	1 038 / 10 days	40mg or 80mg od, 10mg, 20mg, 40mg or 80mg bid	Enoxaparin 30mg	Composite of DVT, non-fatal PE, all-cause mortality	39.0%, 38.4%, 23.5%, 21.4%, 26.8%, 14.3% for 10mg bid, 20mg bid, 40mg od, 40mg bid, 80mg od, 80mg bid, respectively, vs 22.0%	Major bleeding	Similar incidence
LY517717	NCT00074828 / phase II, randomized, double-blind, TKR and THR	511 / 6-10 days	25, 50, 75, 100, 125 and 150mg od	Enoxaparin 40mg	Incidence of VTE	42.3%, 40%, 54.6%, 18.8%, 18.8% and 15.6% for 25, 50, 75, 100, 125 and 150mg od, respectively, vs 21.2%	Major bleeding	0.9% (100mg) vs 0%
Eribaxaban (PD 0348292)	NCT00306254 / phase II, randomized, double-blind, TKR	1 225	0.1, 0.3, 0.5, 1.0, 2.5, 4.0 and 10.0mg od	Enoxaparin 30mg	Incidence of VTE	37.1%, 37.1%, 28.8%, 19.2%, 14.3%, 1.4% and 11.1% for 0.1, 0.3, 0.5, 1.0, 2.5, 4.0 and 10.0mg od, respectively, vs 18.1%	Total bleeding	No significant dose-related increase in the incidence of total bleeding

Abbreviations: bid, twice daily; DVT, deep vein thrombosis; INR, international normalized ratio; od, once daily; PE, pulmonary embolism; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.