CLINICAL INVESTIGATION

Key features of the EXPANSE clinical program for apixaban in the prevention and treatment of thrombotic disorders

Clin. Invest. (2011) 1(5), 725–737

Apixaban is a new oral selective factor Xa inhibitor. Its efficacy and safety are being investigated in a large clinical development program across various indications in venous and arterial thrombotic disorders. A twice-daily regimen was chosen for all the studied indications of apixaban. All three Phase III studies in the prevention of venous thromboembolism after total hip or knee replacement (ADVANCE-1, -2 and -3) have been completed. On the basis of the data obtained so far, apixaban appears to be a promising new drug for the management of thrombotic diseases.

Keywords: anticoagulant • apixaban • arterial thrombosis • atrial fibrillation • bleeding • factor Xa • oral • orthopedic surgery • thrombosis • venous thromboembolism

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For decades, only three types of anticoagulants, namely unfractionated heparin, low-molecular-weight heparins (LMWH) and vitamin K antagonists (VKA), have been available for the management of thrombotic diseases. Although widely used, these drugs are not ideal and have a number of well-known limitations. Fear of adverse events, notably bleeding, limits their use, even in appropriate indications. As a strong predictor of mortality in both surgical and medical patients [1,2], bleeding, the main adverse event associated with these anticoagulant drugs, is indeed a key concern of physicians [3]. Moreover, the use of these drugs in practice is not very convenient. Heparins are administered intravenously or subcutaneously. Oral VKA therapy requires frequent monitoring owing to a narrow therapeutic window and a highly variable interindividual and intraindividual response to treatment [4].

A number of novel anticoagulant compounds are currently being investigated in the hope that they will advantageously replace those available at present [5]. To optimize convenience and simplify the management of patients with thrombotic disorders, the aim is to develop drugs which are oral, effective, safe and have a simple fixed-dose regimen with no requirement for routine laboratory monitoring. Three new oral drugs at an advanced stage of development, and which, in contrast to conventional anticoagulant drugs, specifically and directly inhibit one major coagulation factor, appear to meet these criteria. One, dabigatran etexilate (Pradaxa®, Boehringer Ingelheim) directly targets thrombin, the final enzyme of the coagulation cascade which converts fibrinogen into fibrin. The other two drugs (rivaroxaban, Xarelto®, Bayer Healthcare and Johnson & Johnson; and apixaban, Bristol-Myers Squibb and Pfizer) directly target coagulation factor Xa, located upstream in the coagulation cascade.

The efficacy and safety of apixaban are currently being investigated in the context of a clinical development program called EXPANSE. The EXPANSE program comprises a number of studies in more than 60,000 patients across various indications in venous and arterial thrombotic disorders (Supplementary Table 1). After a brief description of the main pharmacological characteristics of apixaban, this article describes the EXPANSE program, focusing particularly on its key features.

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Pharmacological characteristics

The main pharmacological characteristics of apixaban are shown in Table 1. Apixaban is a direct, selective, factor Xa inhibitor [6]. Factor X is a major coagulation factor located at the junction of the extrinsic and intrinsic pathways of the coagulation cascade. Once activated, this factor binds to activated factor V on the surface of activated platelets to form the prothrombinase complex, which converts prothrombin to thrombin. By blocking this step, factor Xa inhibitors, therefore, inhibit the conversion of fibrinogen to fibrin [7]. It has been hypothesized that selective inhibition of coagulation factors located upstream in the coagulation pathway might be safer with respect to bleeding risk: by not inhibiting thrombin activity directly, this would allow traces of thrombin to escape neutralization and thereby facilitate hemostasis [8]. Furthermore, as the amount of serine protease is amplified at each step of the coagulation cascade, anticoagulants that target coagulation factors located upstream in the cascade, such as factor Xa, might be more effective than those directly targeting thrombin [8]. In contrast to indirect factor Xa inhibitors, such as fondaparinux, apixaban binds both free factor Xa in plasma and bound factor Xa, either located within the prothrombinase complex [9] or associated with a clot [10].

In terms of its pharmacokinetic profile, compared with those of VKA, apixaban exhibits a rapid onset of action after oral administration, its anticoagulant effect similarly wears off more rapidly [7,9,11]. Food does not affect the absorption of apixaban over a wide range of doses [9,12].

Apixaban is metabolized and eliminated via several routes [13]. Importantly, only 25% of apixaban is eliminated in unchanged form by the kidneys, compared with 33% for rivaroxaban and 80% for dabigatran [9]. The prominent circulating metabolite of apixaban is inactive against factor Xa [11].

The possibility for drug interactions is low [14]. Unlike dabigatran etexilate, apixaban is not a significant inhibitor of P-glycoprotein. In addition, apixaban neither induces nor inhibits major cytochrome (CYP) P450 enzymes, which play a crucial role in the metabolism of many licensed drugs. However, such as rivaroxaban, it is susceptible to interaction with strong CYP3A4 and P-glycoprotein inhibitors and inducers: the coadministration of these drugs may result in plasma concentrations of apixaban or rivaroxaban that are higher or lower than expected [9,14].

Apixaban in the prevention of venous thromboembolism after major orthopedic surgery

One of the main challenge facing manufacturers developing anticoagulant agents is to identify doses that are effective, but not at the cost of an increased risk of bleeding. Major orthopedic surgery is the context generally used for determining the dosage regimen that will afford the best benefit:risk ratio in the prevention of venous thromboembolism (VTE) [15]. Total hip and knee replacements are standardized operations, associated with relatively high rates of VTE (considering both symptomatic and asymptomatic events), and permitting reasonably easy

Table 1. Main pharmacological characteristics of new oral anticoagulants.

	Apixaban	Rivaroxaban	Dabigatran etexilate
Target	Factor Xa	Factor Xa	Thrombin
Prodrug	No	No	Yes
Bioavailability (%)	50	90	6.5
Dosing	Twice daily	Once or twice daily depending on the setting	Once or twice daily depending on the setting
Time to peak (h)	3–4	2–4	0.5–2
Half-life (h)	~12	7–11	12–14 (14–17 in MOS patients)
Protein binding (%)	87	92–95	35
Renal excretion (%)	25	66[†]	80
Drug interactions	Potent modulators of both CYP3A4 and P-glycoprotein[‡§]	Potent modulators of both CYP3A4 and P-glycoprotein[‡§]	Potent inhibitors of P-glycoprotein[¶]

[†]Approximately 33% as unchanged drug, the remainder as inactive metabolites.
[‡]Inhibitors of both CYP3A4 and P-glycoprotein include azole antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir).
[§]Strong CYP3A4 and P-glycoprotein inducers include rifampin, phenytoin, carbamazepine, phenobarbital and St John's wort.
[¶]Includes amiodarone and quinidine
MOS: Major orthopedic surgery.
Adapted from [65].

detection and quantification of bleeding. Furthermore, bleeding is particularly feared in this context, not only because it may lead to re-operation, wound infection and transfusion, but also because it is associated with an increased risk of mortality [2,16–18]. The risk of bleeding is considered by some surgeons as a barrier to the use of appropriate thromboprophylaxis [3,19]. In order to increase the safety of anticoagulant drugs with respect to bleeding in this surgical context, various approaches, not mutually exclusive, may be tested: initiating the drug after the surgical procedure, delaying the first postoperative administration after surgery, reducing the first postoperative dose or using a dose regimen giving a low peak:trough ratio. For apixaban, the selected approach, consisted first in initiating the drug 12–24 h after surgery, and second, studying both once- and twice-daily dose regimens in order to determine whether the frequency of administration impacted the benefit:risk ratio.

In the APROPOS dose-ranging Phase II study in 1238 patients undergoing total knee replacement, apixaban, administered either once or twice daily, was initiated 12–24 h after surgery **(Supplementary Table 1)** [20]. The data were compared with those obtained with enoxaparin or a VKA, namely warfarin. The results showed that all doses of apixaban (5, 10 and 20 mg/day) were associated with lower rates of VTE/death than those observed with enoxaparin or warfarin. Moreover, for each total daily dose of apixaban, there was a trend towards a lower VTE/death rate with twice-daily administration compared with a once-daily dosage regimen. Bleeding was dose-related and, at apixaban doses of 5 or 10 mg/day, comparable to that seen with enoxaparin; there was no apparent difference, in terms of bleeding, between once- and twice-daily dosage regimens. Thus, apixaban at doses of 2.5 mg twice daily or 5 mg once daily showed a promising benefit–risk profile. Subsequently, a therapeutic utility index was calculated from the analysis of 4694 drug concentration data points from 855 patients, who received one of six doses of apixaban in the context of the APROPOS study. The results suggested that the twice-daily 2.5 mg regimen provided a better balance between safety and efficacy than the once-daily 5 mg regimen [21,22]. Consequently, twice-daily 2.5 mg apixaban regimen initiated 12–24 h after surgery was selected for the Phase III clinical ADVANCE program in the prevention of VTE in total hip and knee replacement **(Table 2)**. It is noteworthy that, although the half-lives of apixaban, rivaroxaban and dabigatran are comparable **(Table 1)**, apixaban is the only drug being evaluated in all its potential indications using a twice-daily dose regimen.

The ADVANCE clinical program consisted of three large studies designed to demonstrate that apixaban was at least as effective as subcutaneous enoxaparin in subjects undergoing total knee (ADVANCE-1 and ADVANCE-2) or hip (ADVANCE-3) replacement surgery [23–25]. Enoxaparin was chosen as the comparator, this compound being the standard of care for VTE prevention in this setting when the studies were designed. The enoxaparin regimen was 40 mg once daily in two studies (ADVANCE-2 and ADVANCE-3) and 30 mg every 12 h in one study (ADVANCE-1). The 40 mg once-daily regimen is the European-approved regimen for total knee replacement and the globally approved regimen for total hip replacement; the 30 mg twice-daily regimen is the approved regimen in North America for total knee replacement. In accordance with the approved labeling for enoxaparin, enoxaparin 40 mg was started 12 ± 3 h before surgery, whereas enoxaparin 30 mg was started 12–24 h after surgery. The duration of therapy was as recommended in current guidelines, that is, 35 ± 3 days for total hip replacement and 12 ± 2 days for total knee replacement [26]. Follow-up lasted 60 days after the final dose of study medication. The primary efficacy end point in all three trials was all VTE/all-cause death, which was a composite of adjudicated symptomatic and asymptomatic deep-vein thrombosis (DVT), non-fatal pulmonary embolism (PE) and all-cause death. In ADVANCE-2 and ADVANCE-3, the main secondary outcome measure was major VTE, a composite of adjudicated symptomatic or asymptomatic proximal DVT, non-fatal PE and VTE-related death; in ADVANCE-1, it was a composite of major VTE and all-cause death. The primary safety end point was bleeding, which was assessed according to discrete categories of severity (major; clinically relevant non-major; minor and the composite of major and clinically relevant non-major bleeding). The definition of major bleeding included bleeding at the surgical site. Bleeding was assessed from the first dose of the double-blind study drug. Thus, in the two studies in which enoxaparin 40 mg was started preoperatively, records of bleeding included events that occurred before the first dose of apixaban, given 12–24 h after surgery; this was done to compare the two drugs over the same study period.

ADVANCE-1 was a non-inferiority trial comparing apixaban 2.5 mg twice daily with enoxaparin 30 mg twice daily in 3195 patients undergoing total knee replacement [23]. The rate of all VTE/all-cause death was 9.0% with apixaban and 8.8% with enoxaparin, giving an absolute difference of 0.1% (95% CI: -2.22–2.44) and a relative risk (RR) of 1.02 (95% CI: 0.78–1.32). Apixaban did not meet one of the two criteria for non-inferiority ($p = 0.06$), for which it was prespecified that the upper limit of the 95% CI for RR should not exceed 1.25. This result might be explained by the unexpectedly low rate of events in the enoxaparin group (8.8%), well below the rate of 16% envisaged on the basis of previous data obtained in the APROPOS study [20]. The rate of major VTE and death from any cause was 2.0% with apixaban and 1.6% with

Table 2. Main design characteristics and results of the clinical trials on apixaban, rivaroxaban and dabigatran etexilate in the prevention of venous thromboembolism after major orthopedic surgery.

Study	ADVANCE-1 [23]	ADVANCE-2 [24]	ADVANCE-3 [25]	RE-NOVATE [66]	RE-NOVATE II [67]	RE-MODEL [68]	RE-MOBILIZE [69]	RECORD-1 [70]	RECORD-2 [71]	RECORD-3 [72]	RECORD-4 [73]
Study drug	Apixaban (2.5 mg b.i.d.)	Apixaban (2.5 mg b.i.d.)	Apixaban (2.5 mg b.i.d.)	Dabigatran (150 or 220 mg o.d.)	Dabigatran (220 mg o.d.)	Dabigatran (150 or 220 mg o.d.)	Dabigatran (150 or 220 mg o.d.)	Rivaroxaban (10 mg o.d.)	Rivaroxaban (10 mg o.d.)	Rivaroxaban (10 mg o.d.)	Rivaroxaban (10 mg o.d.)
Setting	TKR	TKR	THR	THR	THR	TKR	TKR	THR	THR	TKR	TKR
Timing of first dose	12–24 h after surgery	12–24 h after surgery	12–24 h after surgery	1–4 h after surgery	1–4 h after surgery	1–4 h after surgery	6–12 h after surgery	6–8 h after surgery	6–8 h after surgery	6–8 h after surgery	6–8 h after surgery
Active comparator	Enoxaparin 30 mg b.i.d. initiated 12–24 h after surgery	Enoxaparin 40 mg o.d. initiated 12 h before surgery	Enoxaparin 40 mg o.d. initiated 12 h before surgery	Enoxaparin 40 mg o.d. initiated 12 h before surgery	Enoxaparin 40 mg o.d. initiated 12 h before surgery	Enoxaparin 40 mg o.d. initiated 12 h before surgery	Enoxaparin 30 mg b.i.d. initiated 12–24 h after surgery	Enoxaparin 40 mg o.d. initiated 12 h before surgery	Enoxaparin 40 mg o.d. initiated 12 h before surgery	Enoxaparin 40 mg o.d. initiated 12 h before surgery	Enoxaparin 30 mg b.i.d. initiated 12–24 h after surgery
Treatment duration (days)	10–14	10–14	32–38	28–35	28–35	6–10	12–15	31–39	10–14 vs enoxaparin, then up to 31–39 vs placebo	10–14	10–14
Study design	Non-inferiority, then superiority	Non-inferiority, then superiority	Non-inferiority, then superiority	Non-inferiority	Non-inferiority	Non-inferiority	Non-inferiority	Non-inferiority, then superiority	Not specified	Non-inferiority, then superiority	Non-inferiority, then superiority
Follow-up (days)	60	60	60	90	90	90	90	30–35	30–35	30–35	30–35
No. of patients (n)	3195	3057	5407	3494	2055	2101	2615	4541	2509	2531	3148
VTE/all-cause death, RR (95% CI)	1.02 (0.78–1.32)	0.62 (0.51–0.74)	0.36 (0.22–0.54)	0.90† (0.63–1.29)	0.88† (0.63–1.22)	0.97† (0.82–1.13)	1.23† (1.03–1.47)	0.30 (0.18– 0.51)	0.21 (0.13–0.35)	0.51 (0.39–0.65)	0.72 (0.52–0.99)
Major/ clinically relevant non-major bleeding, RR (95% CI)	0.67 (0.47–0.97)	0.74 (0.52–1.05)	0.96 (0.76–1.21)	1.23† (0.88–1.73)	1.27† (0.79–2.04)	1.11† (0.76–1.63)	0.86† (0.52–1.41)	1.18 (0.90–1.80)	1.21 (0.77–1.89)	1.19 (0.76–1.87)	1.34 (0.86–2.07)

†Using dabigatran etexilate 220 mg.

RR: Relative risk; THR: Total hip replacement; TKR: Total knee replacement; VTE: Venous thromboembolism.

enoxaparin (RR: 1.25; 95% CI: 0.70–2.23). The rate of major plus clinically relevant non-major bleeding was significantly lower in the apixaban group (2.9%) than in the enoxaparin group (4.3%; p = 0.03).

ADVANCE-2 compared apixaban 2.5 mg twice daily with enoxaparin 40 mg once daily in 3057 patients undergoing total knee replacement [24]. The rate of all VTE/all-cause death was significantly lower (RR reduction of 38%) with apixaban than with enoxaparin (15.1 vs 24.4%; RR: 0.62; 95% CI: 0.51 to 0.74; p < 0.0001 for superiority). Apixaban was also superior to enoxaparin in terms of major VTE with a RR reduction of 50% (1.1 vs 2.2%; RR: 0.50; 95% CI: 0.26–0.97, p = 0.0186 for superiority). The rates of major plus clinically relevant non-major bleeding were 3.5 and 4.8% for apixaban and enoxaparin, respectively (p = 0.09).

Similarly, in 5407 patients undergoing total hip replacement (ADVANCE-3), apixaban was more effective, in terms of all VTE/all-cause death, than enoxaparin 40 mg once daily (1.4 vs 3.9%; RR: 0.36; 95% CI: 0.22–0.54; p < 0.001 for both non-inferiority and superiority) [25]. Major VTE occurred in 0.5% of apixaban patients versus 1.1% of enoxaparin patients (RR: 0.40; 95% CI: 0.15–0.80, one-sided p < 0.001 for non-inferiority and two-sided p = 0.01 for superiority). Thus, the corresponding RR reduction for all VTE/all-cause death and major VTE with apixaban were 64 and 60%, respectively. The rates of major plus clinically relevant non-major bleeding events were comparable between the two groups (4.8 and 5.0% for apixaban and enoxaparin, respectively).

Overall, compared with enoxaparin 30 mg twice daily, apixaban 2.5 mg twice daily did not meet one of the two prespecified criteria for non-inferiority, in terms of VTE prevention, but was associated with a lower risk of bleeding. Compared with enoxaparin 40 mg once daily, apixaban 2.5 mg twice daily was more effective (in terms of both total and major VTE) without increasing the risk of bleeding. The frequencies of symptomatic VTE events and death were low and comparable between apixaban and enoxaparin, even when the 60-day follow-up period was taken into account (≤1.5%). There were no fatal bleeding events on apixaban in any of the ADVANCE studies, compared with one fatal bleeding event in the enoxaparin group during the treatment period in ADVANCE-1.

The timing of administration of the first dose of apixaban was 12–24 h after surgical closure (mean timing: ~19 h after surgery, i.e., typically the day after surgery), compared with 6–8 h after surgery for rivaroxaban and 1–4 or 6–12 h, depending on the trial, for dabigatran etexilate (Table 2). Delayed initiation of anticoagulant treatment after surgery may represent a substantial advantage in terms of bleeding risk, because it allows surgery-related bleeding to stop before starting the anticoagulant therapy. Furthermore, the dose regimen of apixaban allows thromboprophylaxis to be initiated conveniently the morning after the operation, regardless of whether surgery took place in the morning or the evening, which matches clinical practice. The risk of nausea and vomiting during the postoperative period is then less likely to interfere with the absorption of an oral drug [27]. This delayed initiation of apixaban may allow the anesthesiologist to continue anesthesia during the most painful period after surgery: in the ADVANCE trials, it was recommended to remove epidural or intrathecal catheters at least 5 h prior to the first dose of apixaban, that is, the catheter could remain in place for a maximum of 19 h after surgery. In patients undergoing neuraxial anesthesia, the experts of the European Society of Anaesthesiology recently recommended an interval of 26–30 h between the last dose of apixaban and puncture/catheter manipulation or removal, proposing administration of the next dose of apixaban 4–6 h after catheter withdrawal [28].

Apixaban in the prevention of venous thromboembolism in acutely ill medical patients

On the basis of several randomized trials and meta-analyses [29–33], it has been clearly demonstrated that thrombotic events are frequent and severe in medically ill patients and that LMWH or fondaparinux for up to 14 days are effective and safe in reducing the incidence of VTE (including fatal PE) by approximately 60%, without significantly increasing major bleeding. Consequently, the guidelines established in 2008 by the experts of the American College of Chest Physicians (ACCP) recommend (at a Grade 1A level) thromboprophylaxis with LMWH, low-dose unfractionated heparin or fondaparinux for acutely ill medical patients who are admitted to hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors [26]. More recently, the EXCLAIM trial showed that a 28 ± 4 day enoxaparin treatment was more effective than a 10 ± 4 day enoxaparin treatment, but at the cost of an increased risk of major bleeding events [34].

The benefit of both short-term (up to 14 days) and long-term (up to 30 days) treatment with oral apixaban in this setting is being investigated in the ongoing double-blind, double-dummy ADOPT trial (NCT00457002) [101]. The types of patient recruited in ADOPT are comparable to those enrolled in previous trials in the same setting, specifically patients (n = 6524) hospitalized with congestive heart failure, acute respiratory failure, infection (without septic shock), acute rheumatic disorder or inflammatory bowel disease [22]. Patients receive either apixaban (2.5 mg twice daily) for 30 days or enoxaparin (40 mg once daily) for 6–14 days. The primary outcome measure is a composite of VTE and VTE-related death at

day 30; secondary outcome measures include a composite of all-cause death, major bleeding and clinically relevant non-major bleeding. VTE events are diagnosed by ultrasonography, as in previous trials [30,34]. The recently completed MAGELLAN trial investigating rivaroxaban has a comparable study design (NCT00571649) [102].

Apixaban in the treatment of venous thromboembolism

In patients with established VTE, the main goal of treatment is to prevent fatal PE and recurrent VTE events. In view of the limitations of currently available anticoagulant drugs, the therapeutic strategy typically comprises a two-anticoagulant regimen consisting of an initial treatment with a rapidly acting parenteral anticoagulant (i.e., unfractionated heparin, LMWH or fondaparinux), followed by long-term treatment with an oral VKA [35]. This approach is cumbersome due to the initial need for injections and the frequent laboratory monitoring and dose adjustments required during the entire treatment period. Considering also that most patients with VTE are admitted to hospital for only 1 or 2 days or are treated entirely at home, there is a need for a simple, oral treatment that can be given as a fixed dose without laboratory monitoring. The rapid onset of action of apixaban offers the possibility of eliminating the need for such a two-anticoagulant regimen for the treatment of VTE.

In the BOTTICELLI-DVT double-blind, open-label, dose-ranging clinical trial, 520 patients with symptomatic DVT were randomized to receive apixaban (5 or 10 mg twice daily or 20 mg once daily) or conventional treatment with LMWH or fondaparinux, followed by open-label treatment with a VKA, with dose adjustment to maintain the international normalized ratio (INR) between 2.0 and 3.0 [36]. After 3 months of treatment, the primary efficacy outcome (a composite of symptomatic recurrent VTE and asymptomatic deterioration of bilateral compression ultrasound or perfusion lung scan) occurred in 4.2% of enoxaparin patients (95% CI: 1.4–9.6). With respect to apixaban, the rates were 6.0% with 5 mg twice daily, 5.6% with 10 mg twice daily and 2.6% with 20 mg once daily. The rates of major and clinically relevant non-major bleeding were 8.6% with 5 mg twice daily, 4.5% with 10 mg twice daily and 8.9% with 20 mg once daily in patients randomized to apixaban compared with 7.9% in patients randomized to enoxaparin. On the basis of this trial, the apixaban clinical development team chose to investigate the benefit of apixaban 10 mg twice daily for the initial treatment of VTE, and 2.5 or 5 mg twice daily for the long-term treatment of VTE.

The AMPLIFY trial is an ongoing 6-month double-blind non-inferiority Phase III trial comparing apixaban with enoxaparin/VKA in the treatment of patients with confirmed symptomatic DVT (2/3 of patients) or PE (a third of patients) requiring treatment for 6 months at least (NCT00643201) [103]. As in similar trials on rivaroxaban in this context (NCT00439777 [37, 104]), a higher dose is administered during the first weeks of treatment (i.e., 10 mg twice daily for 7 days), than during the subsequent treatment period (5 mg twice daily for 6 months).

AMPLIFY-EXT is an ongoing 12-month double-blind superiority trial comparing two doses of apixaban (2.5 and 5 mg twice daily) with placebo in the extended treatment of patients with DVT or PE who have completed 6–12 months of standard anticoagulant therapy (NCT00633893) [105]. By contrast, in the ongoing RE-SONATE dabigatran trial and recently published EINSTEIN Extension rivaroxaban trial [37] in the same setting, only one dose of anticoagulant was tested versus placebo (i.e., dabigatran 150 mg twice daily and rivaroxaban 20 mg once daily). Interestingly, because bleeding safety will be a major issue for the use of such a long-term therapeutic strategy in the future, the evaluation of two doses of apixaban will provide important clinical information for the physician.

Overall, AMPLIFY and AMPLIFY-EXT will establish whether a twice-daily regimen of oral apixaban might be an alternative to both LMWH and VKA in the short- and long-term treatment of patients with established VTE.

Apixaban in the prevention of thromboembolic events in patients with atrial fibrillation

Prevention of thromboembolism is a major component of the management of patients with atrial fibrillation (AF), the morbidity and mortality associated with this disease being related mainly to thromboembolic stroke [38]. Current antithrombotic strategies for patients with AF include anticoagulant drugs, notably VKA, and antiplatelet agents, notably aspirin either alone or associated with clopidogrel [39]. At present, oral VKA alone are recommended for patients with AF at moderate to high risk of stroke [38,39]. However, in practice 40–50% of patients of this type do not receive a VKA [40]. Besides concern about the risk of bleeding, other reasons for this include poor compliance with dosing or monitoring requirements; difficulty in maintaining the INR within the therapeutic range; need for other drugs that may interfere with VKA therapy; and lack of adherence to the restrictions on alcohol, diet or nonprescription medications imposed by the use of VKA. Aspirin, currently proposed as an alternative treatment, is not an ideal substitute for these patients, the drug being less effective than oral VKA [39]. Aspirin plus clopidogrel is considered in patients refusing to take VKA therapy or in patients presenting a clear contraindication to VKA therapy (e.g., inability to cope or continue with anticoagulation monitoring), provided that they exhibit a low bleeding risk [39].

The apixaban clinical development team designed two large Phase III trials (called ARISTOTLE and AVERROES) in this setting, with the goal of showing that apixaban may be beneficial for the entire population of patients with AF and at least one risk factor for thromboembolism (as classified using the $CHADS_2$ score), regardless of their 'suitability' for VKA therapy [40–42]. Thus, in ARISTOTLE, the comparator is VKA, the current standard of care, whereas in AVERROES, the comparator was aspirin. The same dosage regimen of apixaban (i.e., 5 mg twice daily) was chosen for both trials. Interestingly, the dose of apixaban could be adjusted at the time of randomization in patients with certain characteristics leading to a risk of high drug exposure (i.e., 2.5 mg twice daily for patients with at least two of the three following criteria: age ≥80 years, body weight ≤60 kg or serum creatinine concentration ≥1.5 mg/dl). This may offer the possibility to tailor the dosage regimen according to the patient's risk of bleeding, as in the case of dabigatran etexilate [43].

ARISTOTLE is an ongoing non-inferiority trial in 18,206 patients with AF and one risk factor for stroke, comparing apixaban versus warfarin with respect to the combined outcome of stroke (ischemic or hemorrhagic) and systemic embolism [41]. In contrast to the RE-LY trial comparing the benefit of dabigatran etexilate with that of open-label warfarin in the same setting [43], ARISTOTLE is double-blind (with the use of encrypted POC INR monitoring devices). This difference may impact the comparison of data between these two trials. In the previous SPORTIF trials investigating ximelagatran, an oral direct thrombin inhibitor, versus warfarin, ximelagatran demonstrated a trend toward better efficacy in the open-label trial and a trend toward lesser efficacy in the double-blind trial: whilst the primary end point rate for ximelagatran was similar in both trials, event rates on warfarin were different, with a trend toward being higher than with ximelagatran in SPORTIF III and lower in SPORTIF V [44–46]. Moreover, ARISTOTLE includes AF patients at moderate to high risk of thromboembolism (i.e., those with a $CHADS_2$ risk score of 1 or more). By contrast, the recently completed ROCKET-AF trial, investigating rivaroxaban 20 mg once daily versus VKA, recruited only patients with a $CHADS_2$ score of 2 or more [47]. The ARISTOTLE trial also aims to achieve a good representation of warfarin-naive patients (~40%), a population of patients more susceptible to complications until a stable warfarin dose has been established and more prone to warfarin discontinuation [48]. Thus, the ACTIVE-W trial comparing VKA versus aspirin plus clopidogrel in AF patients, demonstrated that data obtained in patients already successfully anticoagulated prior to participation could not be directly extrapolated to VKA-naive patients, the benefit of VKA therapy being limited to those already receiving this type of treatment at study entry [48].

AVERROES specifically evaluated patients who had failed or were unsuitable for VKA treatment. Therefore, this trial studied apixaban versus aspirin (81–324 mg/day) in a double-blind, superiority design [40]. So far, no other new oral anticoagulants have been compared with aspirin in this setting. This trial, performed in 5599 patients with AF and at least one risk factor for stroke, was stopped prematurely by the Data Monitoring Committee, based on the evidence of apixaban's superior efficacy and acceptable safety profile [42]. The annual rate of stroke or systemic embolism (primary outcome) was 1.6% per year in the apixaban group and 3.7% per year in the aspirin group (HR with apixaban: 0.45; 95% CI: 0.32–0.62; $p < 0.001$). The rate of major bleeding was 1.4% per year for apixaban and 1.2% per year for aspirin (HR with apixaban: 1.13; 95% CI: 0.74–1.75; $p = 0.57$); the respective rates of intracranial bleeding were 0.4% and 0.4% per year (HR with apixaban: 0.85; 95% CI: 0.38–1.90, $p = 0.69$). The risk of a first hospitalization for cardiovascular causes was also reduced with apixaban (12.6 per year versus 15.9% per year; $p < 0.001$). Thus, in patients with AF for whom VKA therapy was unsuitable, apixaban significantly reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage.

Apixaban in patients with acute coronary syndromes

Parenteral anticoagulants (unfractionated heparin, LMWH and fondaparinux) are effective for the short-term prevention of myocardial infarction and death in patients with acute coronary syndromes (ACS). However, patients may suffer adverse thrombotic events during the weeks and months following an episode of ACS. One potential strategy to prevent the risk of recurrent ischemic events is to continue anticoagulation in the long term [49]. However, bleeding safety is especially critical in this setting because patients are generally treated with dual antiplatelet therapy (e.g., aspirin and clopidogrel). Although oral VKA have been shown to prevent recurrent ischemic events after ACS, these drugs are rarely used owing to their narrow therapeutic window, necessitating frequent monitoring, and the risk of bleeding. In a meta-analysis of ten studies in this context, patients given warfarin and aspirin after an ACS experienced lower rates of myocardial infarction and ischemic stroke than those given aspirin alone, but at the cost of increased bleeding [50]. Thus, in the guidelines of the American College of Cardiology and American Heart Association for the management of

patients with ACS, VKA therapy is predominantly reserved for patients who are intolerant of aspirin or clopidogrel or who have an alternative indication for anticoagulation therapy (e.g., AF) [51–53]. It has been hypothesized that apixaban on top of standard therapy with aspirin or aspirin and clopidogrel may be valuable in patients with ACS.

APPRAISE-1 was a Phase II, double-blind, placebo-controlled, dose-ranging study in 1715 patients with recent ST-elevation or non-ST-elevation ACS, randomized to 6 months of treatment with placebo or one of four doses of apixaban (2.5 mg twice daily, 10 mg once daily, 10 mg twice daily or 20 mg once daily) (Supplementary Table 1) [54]. Nearly all patients received aspirin; 76% received clopidogrel. The primary end point was safety. On the recommendation of the Data Monitoring Committee, the two higher-dose apixaban arms were discontinued owing to an excess of bleeding events. Compared with placebo, apixaban 2.5 mg twice daily (HR: 1.78; 95% CI: 0.91–3.48; p = 0.09) and 10 mg once daily (HR: 2.45; 95% CI: 1.31–4.61; p = 0.005) resulted in a dose-dependent increase in major or clinically relevant non-major bleeding. However, these dosage regimens resulted in lower rates of ischemic events compared with placebo (HR: 0.73 [95% CI: 0.44–1.19; p = 0.21] and 0.61 [95% CI: 0.35–1.04; p = 0.07] with apixaban 2.5 mg twice daily and 10 mg once daily, respectively). The increase in bleeding was more pronounced and the reduction in ischemic events was less evident in patients taking aspirin plus clopidogrel than in those taking aspirin alone. On the basis of the APPRAISE-1 trial results, the Phase III APPRAISE-2 trial was designed, investigating apixaban at a total daily dose of 10 mg with dose adjustment according to the patient's individual risk of bleeding.

APPRAISE-2 was a randomized double-blind superiority trial in patients with recent ACS, comparing apixaban 5 mg twice daily versus placebo on top of antiplatelet therapy. As in the AF trials, the dose-regimen of apixaban was tailored to renal function: in patients with a creatinine clearance <40 ml/min at randomization, apixaban was given at the dose of 2.5 mg twice daily (NCT00831441) [106]. However, this trial was prematurely discontinued after it became clear that the increase in bleeding risk in patients randomized to apixaban would not be offset by reductions in ischemic events.

Box 1. Characteristics of an ideal anticoagulant drug.

- Oral administration
- Rapid onset of action/rapid offset of action
- Wide therapeutic window
- No food or drug interactions
- No monitoring required (but ability to monitor if necessary)
- Well-defined pharmacokinetics in the presence of renal or hepatic diseases
- Easily reversible
- Cost effective

Adapted from [65].

Future perspective

After almost 60 years of oral anticoagulation with VKA, the results obtained so far with new oral anticoagulants suggest that the days of VKA as the only choice for the oral management of thromboembolic diseases are numbered, as new oral drugs are approaching more and more closely the definition of the 'ideal anticoagulant' (Box 1). Among these new drugs, clinicians will have the difficult challenge of deciding which oral agent is the 'best'. This may be problematic, notably in the absence of head-to-head trials in the various settings in which these drugs may be proposed. Furthermore, the best anticoagulant drug may depend on the clinical indication and the patient's individual risk of bleeding or thrombosis.

A major issue in the development of new anticoagulant drugs is the choice of the dosage regimen. It is indeed likely that this point is the most important parameter determining the benefit:risk ratio of anticoagulant drugs rather than their specificity for either factor Xa or IIa. In the APROPOS Phase II study in VTE prevention, apixaban 2.5 mg twice daily appeared to provide enhanced efficacy without increasing bleeding risk [20]. Furthermore, pharmacokinetic modeling suggested that the peak:trough ratio for apixaban blood levels would be lower with twice daily than with once-daily administration (Figure 1) [21]. Based on the hypothesis that peak drug concentrations may be an important contributor to bleeding risk, the choice of a twice-daily dosage regimen appeared to be advantageous, in terms of bleeding safety. Interestingly, for ACS patients, who have a high risk of bleeding, the rivaroxaban clinical development team also specifically chose a twice-daily dosage regimen for the Phase III study, instead of a once-daily dosage regimen as in other settings, because pharmacokinetic and pharmacodynamic data suggested lower peaks and higher troughs with twice-daily compared with once-daily administration [55]. However, it is noteworthy that the APROPOS study did not show that the twice-daily dosage regimen was safer, in terms of bleeding risk, than once-daily administration [20]. Furthermore, in a Phase II trial on edoxaban, another new oral anticoagulant drug, in patients with AF, the once-daily dosage regimen was shown to confer greater safety, in terms of bleeding risk, than twice-daily administration [56]. We have no

explanation for these conflicting findings. It is, nevertheless, noteworthy that all these data were obtained in a relatively limited number of patients (~100 in APROPOS and 200 in the edoxaban study, for each study group), resulting in some degree of uncertainty. Thus, the true impact of once- versus twice-daily dosing on bleeding risk remains to be defined in larger studies. Finally, in a surgical context, the promising safety data of apixaban with respect to bleeding may be related to the delayed initiation of drug administration after the operation (Table 2).

Owing to the moderate role of renal function in the elimination of apixaban (25%), it may be expected that use of the drug in patients with moderate renal impairment or in elderly patients (who exhibit age-related impaired renal function) should not be a major issue. Furthermore, a model-based approach, using clinical data on apixaban in the prevention of VTE after major orthopedic surgery, suggested that dose adjustment should not be needed in patients with moderate renal impairment [21]. Nevertheless, since this category of patients was not well represented in Phase III clinical trials, further trials and registries are needed to examine the effect of apixaban in these special patient subgroups. Of note, in the Phase III trials in patients with AF, involving the long-term administration of apixaban, a lower dose of the drug was studied in this group of patient.

To date, there is no specific antidote for apixaban, or for any of the other oral anticoagulants in development. However, as the half-life of apixaban is approximately 12 h, its anticoagulant effect wears off rapidly once the treatment is discontinued: it may be expected that only 25% of the drug administered will still be active approximately 24 h later, this interval corresponding to two half-lives [57]. Recombinant factor VIIa (NovoSeven®) and activated prothrombin complex concentrate (FEIBA®) have been proposed to reverse the effects of direct factor Xa inhibitors, but as yet there are insufficient data to recommend their clinical use for this purpose. A specific universal antidote for factor Xa inhibitors is in development [58].

Safety with respect to the liver is of special interest with the new oral anticoagulants, due to observations of hepatotoxicity with the oral direct thrombin inhibitor ximelagatran [59]. So far, the data obtained with apixaban on this potential issue are reassuring. In the AVERROES study, administration of apixaban 5 mg twice daily for a mean follow-up period of 1.1 years was well tolerated in terms of liver function [42]. Furthermore, gastric intolerance does not seem to be a concern with apixaban. By contrast, among AF patients on long-term dabigatran etexilate, the incidence of dyspepsia was 11–12% (vs 6% with warfarin) [43].

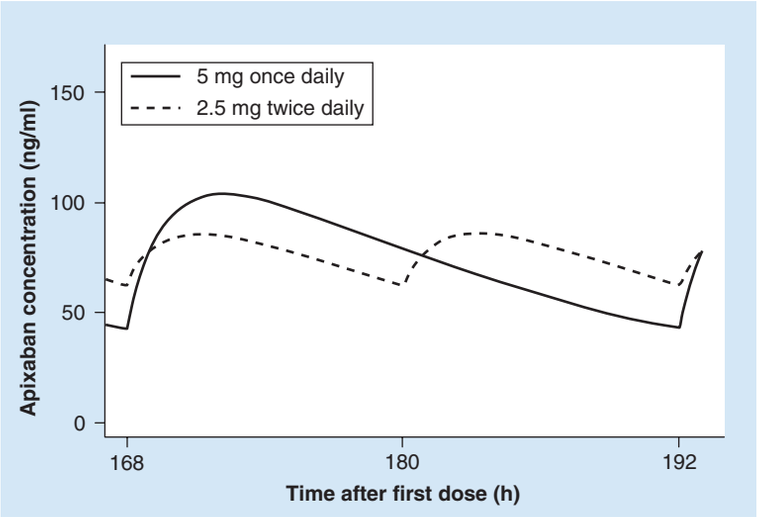

Figure 1. Predicted median steady-state apixaban plasma concentration versus time after first administration of apixaban.
Adapted from [21].

Similarly, in the RE-COVER trial, comparing 6-month dabigatran etexilate with VKA in patients with acute VTE, more patients discontinued dabigatran etexilate treatment due to adverse events (especially dyspepsia) than VKA treatment (9 vs 6.8%; p = 0.05) [60].

In clinical trials, apixaban was administered without laboratory monitoring. The drug indeed exhibits a linear, predictable therapeutic effect with fixed doses [9]. Furthermore, the pharmacokinetic profile of apixaban is not affected by food, and the potential for drug interactions is low [7,9,14]. Routine monitoring of apixaban should, therefore, not be necessary in practice, but this issue is still a matter of debate [61,62]. In any case, measurement of apixaban activity/concentration in the plasma may be useful as an aid to making informed clinical decisions in certain circumstances, such as populations at risk of high exposure, or evaluation of overdosing or patient compliance. Although apixaban prolongs clotting times, such as prothrombin time and activated partial thromboplastin time, these prolongations are small and subject to a high degree of variability; these tests, therefore, cannot be recommended as a means of assessing the pharmacodynamic effects of apixaban [63]. However, a commercial chromogenic assay for factor Xa inhibitors using apixaban as the laboratory reference standard and showing a direct and linear relationship between apixaban plasma concentrations and anti-factor Xa activity, might be suitable for satisfactorily monitoring the drug, if necessary [63].

Other important points that are likely to influence the use of apixaban in practice, as well as that of other new oral anticoagulant drugs, include long-term adherence, compliance and cost. With regard to

the first point, a systematic review showed that patient adherence to oral medication did not significantly differ between once- and twice-daily dosage regimens [64]. However, registry studies and health economic studies will be necessary to allay concerns about all these issues.

Other surgical and medical indications corresponding to an unmet need, warranting investigation of the potential benefits of apixaban, include the prevention of thromboembolic events in patients with cancer, or in those with mechanical valves. In ACS patients, as other more potent antiplatelet agents become available, additional studies may be needed to investigate how these antiplatelet agents and apixaban should be combined to achieve enhanced efficacy without increasing bleeding. Interestingly, if the coming years confirm the benefit of apixaban in patients with AF, its rapid onset and offset of action may avoid the need for an anticoagulant 'bridge' for pre- and post-invasive procedures in patients, as presently required for patients on VKA.

In conclusion, the impact of apixaban and other new oral anticoagulants on the management of thromboembolic diseases in practice will depend on the balance between efficacy and safety, improved convenience for patient and physician, and any potential cost–effectiveness benefits resulting from use of the drug. The coming years will indicate whether and how physicians and patients have adopted these new oral anticoagulants. Nevertheless, there is no doubt that the world of anticoagulant therapy is changing in the best interests of both physicians and patients.

Executive summary

- Apixaban is an oral, direct, selective factor Xa inhibitor.

Pharmacological characteristics

- Apixaban is metabolized and eliminated via several routes with renal excretion of the unchanged drug representing only 25% of the total.
- Apixaban is susceptible to interaction with strong CYP3A4 and P-glycoprotein inhibitors and inducers.
- Apixaban is being investigated in all its potential indications using a twice-daily dose regimen.

Apixaban in the prevention of venous thromboembolism after major orthopedic surgery

- The timing of administration of the first dose of apixaban in clinical trials was 12–24 h after surgical closure.
- Compared with enoxaparin 30 mg twice daily, apixaban 2.5 mg twice daily did not meet the prespecified criteria for noninferiority, in terms of venous thromboembolism (VTE) prevention, but was associated with a reduced risk of clinically relevant bleeding.
- Compared with once-daily enoxaparin 40 mg, twice-daily apixaban 2.5 mg was more effective, in terms of VTE prevention, without increasing the risk of bleeding.

Apixaban in the prevention of venous thromboembolism in acutely ill medical patients

- The benefit of both short-term (up to 14 days) and long-term (up to 30 days) oral apixaban in acutely medically ill patients is being investigated in the ongoing ADOPT Phase III trial.

Apixaban in the treatment of venous thromboembolism

- The ongoing AMPLIFY and AMPLIFY-EXT Phase III trials will determine whether a twice-daily regimen of oral apixaban might be an alternative to both low-molecular-weight heparins and vitamin K antagonists (VKA) in the short- and long-term treatment of patients with established VTE.

Apixaban in the prevention of thromboembolic events in patients with atrial fibrillation

- The ARISTOTLE and AVERROES Phase III trials were designed to evaluate whether apixaban may be beneficial for the entire population of patients with atrial fibrillation (AF) and at least one risk factor for thromboembolism, regardless of their 'suitability' for VKA therapy.
- ARISTOTLE is an ongoing non-inferiority double-blind trial in 18,206 patients with AF and at least one risk factor for stroke, comparing apixaban versus warfarin.
- The AVERROES trial showed that in patients with AF for whom VKA therapy was unsuitable, apixaban significantly reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage.

Apixaban in acute coronary syndromes

- APPRAISE-2, a randomized double-blind superiority trial in patients with recent acute coronary syndrome, was prematurely discontinued because it appeared that the increase in bleeding risk in patients randomized to apixaban would not be offset by reductions in ischemic events.

Future perspective

- In view of the only moderate role of renal function in the elimination of apixaban, it may be expected that the use of this drug in elderly patients or patients with moderate renal impairment would not require dose adjustment.
- Routine monitoring of apixaban should not be necessary in clinical practice.
- A commercial chromogenic anti-factor Xa assay may be suitable for satisfactorily monitoring the drug, if necessary.

Supplementary data

Supplementary data accompanies this paper and can be found at www.future-science.com/doi/suppl/10.4155/CLI.11.39

Financial & competing interests disclosure

The apixaban studies discussed in this review were sponsored by Bristol-Myers Squibb and Pfizer Inc. Nadia Rosencher reports serving on steering committees and advisory boards for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer Inc. and Sanofi-Aventis, and having received honoraria for this. Paul Zufferey reports serving on advisory boards for Boehringer Ingelheim and Sanofi-Aventis, and having received honoraria for this. Silvy Laporte reports serving on steering committees, data monitoring committees, and advisory boards for Bayer, Boehringer Ingelheim, GlaxoSmithKline and Sanofi-Aventis, and having received honoraria for this. Patrick Mismetti reports serving on steering committees and advisory boards for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer Inc. and Sanofi-Aventis, and having received honoraria for this. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing support was provided by Yves Cadroy at MediBridge S.A. and was funded by Pfizer.

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