CLINICAL INVESTIGATION

Clinical evidence of the role of edoxaban in anticoagulation

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Elena Fortuny & Jose Zamorano*

Cardiovascular Institute, Hospital Universitario San Carlos, Profesor Martin Lagos s/n, 28040, Madrid, Spain
*Author for correspondence:
Tel.: +34 913303394
Fax: +34 913303290
E-mail: zamorano@secardiologia.es

Atrial fibrillation (AF) and venous thromboembolism are important causes of increased morbidity and mortality. For several decades, heparin and oral vitamin K antagonists have been used to anticoagulate patients. The disadvantages of these drugs have led to the development of new agents that are safe, effective and easy to use. Edoxaban is a novel, oral, once daily, direct and reversible factor Xa inhibitor. It acts by dose-dependent anticoagulation effect and the safety and tolerability of this agent has been largely demonstrated. Preliminary results of Phase II trials have shown edoxaban to be potentially advantageous to traditional anticoagulants in terms of bleeding in AF and in terms of embolisms after orthopaedic surgery. Ongoing Phase III clinical trials for thromboembolic event prophylaxis and treatment and for prevention of strokes in patients with AF will provide more data. This review analyzes the clinical evidence of the role of edoxaban in anticoagulation.

Keywords: atrial fibrillation • edoxaban • factor Xa inhibitor • once daily • oral anticoagulation • venous thromboembolism

Venous thromboembolism (VTE) is a serious complication with especially high incidence after major orthopedic surgery, representing an important cause of increased morbidity and mortality [1]. Current guidelines recommend routine postoperative anticoagulation for VTE prophylaxis [2,3].

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia. The use of anticoagulation treatment significantly decreases the risk of ischemic stroke, which is increased from two to seven times in this group of patients [4,5]. Although the benefits derived from anticoagulation are proven, the most recent guidelines on the management of AF in Europe and the USA differ slightly on their recommendations [6,7]. Different scores are applied for risk estimation in AF patients between both guidelines and this fact has relevant implications in the management of these patients.

For several decades, parenteral agents such as unfractionated heparin or low-molecular-weight heparin (LMWH) and oral vitamin K antagonists (VKAs) have been the standard of care for anticoagulate patients (Table 1).

Less than half of patients who could benefit from anticoagulation actually receive these therapies because of the many disadvantages summarized in Table 1. The knowledge of these limitations has led to the development of new anticoagulant agents that are safe, effective and easy to use (Table 2) [8–10].

Novel oral anticoagulants

■ Thrombin inhibitors

Dabigatran, a direct thrombin inhibitor (DTI), has been shown to be as effective or superior (in higher doses) to warfarin in the prevention of stroke and

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Table 1. Summary of traditional anticoagulant drugs.

Drug	Administration	Mechanism of action	Limitations
Unfractionated heparin	Parenteral, continuous infusion	Heparin activates the enzyme inhibitor AT III. The activated AT inactivates thrombin and other proteases involved in blood clotting, most notably factor Xa	Frequent laboratory monitoring, variability in dose response among patients, heparin-induced thrombocytopenia and thrombosis, only in-hospital treatment
LMWHs	Parenteral, once or twice daily	Same as unfractionated heparin	Inconvenient for long-term use, mainly because of local AEs, heparin-induced thrombocytopenia, heparin-induced thrombocytopenia and thrombosis
Oral vitamin K antagonists (warfarin, acenocumarol, phenprocoumon)	Oral, once daily	The four vitamin K-dependent coagulation factors II, VII, IX and X all require γ-carboxylation for their procoagulant activity. Warfarin produces partially carboxylated and decarboxylated proteins with reduced coagulant activity	Slow onset and offset of action, narrow therapeutic window, frequent laboratory monitoring, higher risk of bleeding in elderly patients, variability in dose response among patients, multiple drug–drug and drug–food interactions, off-target AEs and poor patient adherence
Fondaparinux sodium	Parenteral, once daily	Factor Xa inhibitor	Poor patient adherence in long duration treatments, local AEs, bleeding complications in patients with renal function impairment

AE: Adverse effect; AT: Antithrombin; LMWH: Low-molecular-weight heparin.

embolisms, with lower risk of hemorrhagic stroke when compared with warfarin [11]. Dabigatran was approved in the most recent guidelines with a class I indication for management of AF [6,7].

The increased risk of myocardial infarctions observed with the use of DTIs [12–14] could be secondary to the insufficient activation of protein C with these drugs, causing a hypercoagulable state after their termination. Isolated studies have shown that low concentrations of DTIs enhance thrombin generation by suppressing the negative feedback reaction by activated protein C [15]. Currently, the possibility of a hypercoagulable state with DTIs has not been sustained after reviewing the results of new studies.

■ Factor Xa inhibitors

Factor Xa inhibitors have no increased hypercoagulability after termination of treatment [15]. They selectively inhibit factor Xa at the site of amplification of the coagulation cascade (Figure 1) [16]. The inhibition of one molecule of factor Xa can prevent the formation of 1000 thrombin molecules [17]. *In vitro* studies have shown a wide therapeutic window [9,11].

Rivaroxaban was approved in 2008 for deep vein thrombosis (DVT) prevention in Europe and Canada [18,19], receiving approval in the USA in 2011. Results of the ROCKET-AF [20] trial showed noninferiority when compared with warfarin and the EINSTEIN-DVT trial demonstrated noninferiority of rivaroxaban when compared with warfarin and enoxaparin, with no significant differences in bleeding rates [21].

Apixaban was approved for VTE prevention after orthopedic surgery in Europe following the results of ADVANCE, ADOPT and AMPLIFY trials. Results of the ARISTOTLE clinical trial showed noninferiority

Table 2. Novel oral and parenteral anticoagulant drugs.

New oral anticoagulant drugs	New parenteral anticoagulant drugs
DTIs, dabigatran (approved for clinical use for DVT prevention in Europe and Canada and for non-valvular patients with atrial fibrillation in Europe, Canada and the USA), ximelagatran (withdrawn from markets)	DTIs, bivalirudin, argatroban, TFPI, tifacogin
Factor Xa inhibitors, rivaroxaban (approved for clinical use in the USA, Europe and Canada for VTE prevention after knee and hip surgery), apixaban (approved for VTE prevention after knee and hip surgery in Europe), edoxaban, betrixaban, darexaban (discontinued), LY517717 (discontinued), TAK442 (discontinued)	Factor Xa inhibitors, idra(biota)parinux, otamixaban, DX-9065 (discontinued)
Factor IXa partial inhibitor, TTP889	Factor Va and VIIIa inhibitors, APC (drotrecogin α), sTM (ART-123)

DTI: Direct thrombin inhibitor; DVT: Deep vein thrombosis; TFPI: Tissue factor pathway inhibitor; VTE: Venous thromboembolism.

of apixaban when compared with warfarin in patients with non-valvular AF, with a reduction ($p < 0.05$) in bleeding rates [22].

Edoxaban is one of the new oral anticoagulants currently in development.

Edoxaban

Pharmacokinetic & pharmacodynamic properties

Edoxaban (the free base of DU-176b or edoxaban tosylate) [9] is a small molecule that directly inhibits factor Xa with a 10,000-fold higher affinity to factor Xa than to thrombin or factor IXa [23]. This molecule demonstrated in preclinical studies a reversible and competitive inhibition of factor Xa (Figure 1).

Plasma drug levels are strongly correlated to anti-factor Xa activity, protrombin time (PT) and international normalized ratio (INR), showing a weak association with aPTT [24]. However, currently available PT and INR tests do not accurately predict the anticoagulant activity of edoxaban. Factor Xa inhibitors do not influence bleeding time, in contrast to antiplatelet agents [24]. The development of new or modified anticoagulant assays is necessary to measure the effect of these novel drugs.

Edoxaban activity is linearly correlated with plasma levels of the drug, showing a consistent pharmacokinetic (PK) profile. Edoxaban shows low intersubject variability [25]. Time to peak plasma concentration is 1–2 h [25], and the mean elimination half-time of the drug is in the range of 5.8–10.7 h for single doses (10–150 mg daily) or 8.75–10.4 h for multiple doses (90–120 mg daily) [25,26]. In healthy volunteers, treatment with edoxaban led to sustained inhibition of coagulation for up to 24 h [27].

Edoxaban is excreted by one third via the kidneys, with most of its clearance occuring during the first 8 h [25]. Edoxaban dose is reduced by 50% in the ongoing Phase III clinical trial, ENGAGE AF in patients with a creatinine clearance of 30–50 ml/min [28]. Pharmacologic properties of edoxaban are summarized in Table 3.

Safety

The safety margin of edoxaban was studied in comparison with the thrombin inhibitor melagatran in a rat model with intracerebral hemorrhage [29], showing predictable and reversible anticoagulant effects in animal models. Edoxaban can be administered in fixed doses without periodical coagulation monitoring [24].

No relevant adverse effects (AEs) were reported with doses up to 150 mg orally daily in Phase I trials [24,25]. Liver function test abnormalities were not increased in comparison with warfarin or dalteparin [30,31].

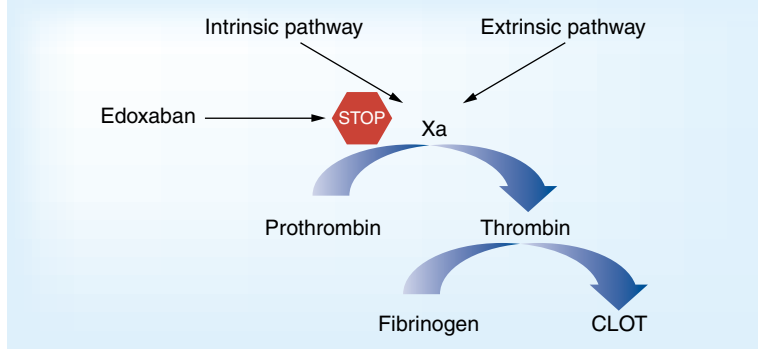

Figure 1. Coagulation cascade and site of action of edoxaban. Edoxaban inhibits factor Xa at the site of junction of the extrinsic and intrinsic pathways.

In the ongoing Phase III studies, reduction of edoxaban dosage by 50% is required in patients with creatinine clearance 30–50 ml/min, body weight <60 kg or concomitant administration of P-gp inhibitors, such as verapamil, quinidine and droneradone [28].

Given the efficacy of these drugs, there might be concern regarding a possible increased risk of bleeding with the new factor Xa inhibitors. In a Phase II trial in patients with AF, while twice-daily (b.i.d.) dosing had an increased risk of bleeding (probably because of higher trough plasma concentrations of edoxaban), single-daily dosing up to 60 mg/day had a comparable safety profile to warfarin [32].

Administration of a single dose of edoxaban in combination with a single dose of enoxaparin is safe and well tolerated. It is recommended that edoxaban should be initiated 12 h after discontinuation of enoxaparin 1 mg/kg b.i.d. [33]. A universal antidote for factor Xa inhibitors is currently being developed.

Clinical trials

Phase I studies

The first Phase I study demonstrated in 85 healthy young volunteers that edoxaban is safe and well tolerated in oral doses up to 150 mg daily, with linear PK and without a dose-dependent increase in AEs rate [25].

In a second study, thrombus formation and thrombin generation were studied 1.5, 5 and 12 h after administration of edoxaban. Maximum clot size and thrombin formation reduction occurred 1.5 h after administration of the drug [31].

In this study, the suitability of coagulation parameters was also investigated, showing the strongest correlation of drug levels with anti-factor Xa activity, followed by the parameters PT and INR [31]. A recent Phase I study involving 40 healthy elderly patients (aged between 65–75 years old) showed no effect of age on the pharmacological properties of edoxaban [34].

Table 3. Pharmacologic properties of oral factor Xa edoxaban.

Parameter	Edoxaban	Ref.
Time to C_{max} (h)	1–2	[25]
F_{abs} %	50 (animal model), absolute bioavailability of 62%	[41,42]
F_{rel} %	Not reported	
Protein binding %	40–59	[25]
Terminal elimination half time	5.8–10.7 h for single doses (10–150 mg daily), 8.75–10.4 h for multiple doses (90–120 mg daily)	[25]
Renal excretion %	35–39. Also metabolic and biliary clearance	[25]
Systemic accumulation	Ratio 1.10–1.13 10 days after last administration	[25]
Drug–food interaction	None	[25,43]
Drug–drug interactions	Substrate for P-gp, an intestinal transporter. The use strong P-gp inhibitors (verapamil, quinidine and droneradone) makes necessary an edoxaban dosage reduction by 50%	[28]
CYP metabolism	CYP3A4 (minimal)	[44]
Effect of age, body weight or gender	Not reported	

C_{max}: Maximum concentration; F_{abs}: Absolute bioavailability; F_{rel}: Relative bioavailability.

Phase II studies

Edoxaban in prevention of VTE

A Phase IIb trial involving 523 Japanese patients undergoing total knee replacement compared edoxaban (doses of 5, 15, 30 and 60 mg) with a placebo. Patients were treated for 11–14 days after surgery and were assessed for VTE at the end of the treatment period. Edoxaban showed a reduction in the incidence of VTE in the first 11–14 days after surgery when compared with the placebo. The reduction of VTE was greatest in the 60-mg daily group, with no differences in bleeding events across the five groups [35].

In another Phase II trial the reduction of VTE with edoxaban was demonstrated in a group of 903 patients undergoing elective total hip replacement in North America, Northern and Eastern Europe. Compared to subcutaneous dalteparin, oral once-daily (q.d.) edoxaban (assigned to treatment with doses of 15, 30, 60 and 90 mg/day) had a significant dose-dependent reduction in VTE after 7 to 10 days of postsurgical anticoagulant treatment. Incidence of bleeding events with edoxaban was similar to that observed in the dalteparin group [31].

Edoxaban in AF

A Phase II trial compared edoxaban and warfarin in 1146 patients diagnosed with AF and with a risk of stroke defined as a $CHADS_2$ score ≥2 [33]. Patients were randomized to receive warfarin (INR 2–3) or one of four edoxaban dosing regimens (30 mg q.d., 30 mg b.i.d., 60 mg q.d. or 60 mg b.i.d.). Edoxaban 30 and 60 mg q.d. regimens had a similar or better safety profile compared to warfarin without hepatotoxicity after a follow-up of 12 weeks. The increased bleeding with the b.i.d. regimens of edoxaban was associated with higher trough plasma concentrations. The incidence of stroke or transient ischemic attacks was very low in all treatment arms and numerically highest in the warfarin group. The rates of myocardial infarction and cardiovascular death were very low in all the groups [32].

In another Phase II trial that compared edoxaban 30 or 60 mg once daily with warfarin in Asian patients with nonvalvular AF there was a similar incidence of bleeding events for edoxaban as compared with warfarin [36].

A third open-label Phase II study involving 56 Japanese patients diagnosed with nonvalvular AF randomized to receive q.d. or b.i.d. dosing of edoxaban confirmed the linear pharmacodynamics of the drug [37].

Phase III trial programs

Many novel oral anticoagulant drugs, including DTIs and factor Xa inhibitors are currently in late-stage clinical development or already approved for clinical use (Table 4). Only Phase III trials refering to edoxaban (ongoing studies or complete programs) will be discussed in the article.

Treatment & prevention of DVT

Hokusai VTE (NCT00986154) is a randomized, double-blind, double-dummy study comparing edoxaban 60 mg once daily with warfarin after an initial period

Table 4. Summary of Phase III trials of factor Xa inhibitors and oral direct thrombin inhibitors.

Study drug	Prevention of strokes in AF	Treatment and prevention of VTE	Prevention of VTE (orthopedic surgery)
Edoxaban	ENGAGE AF-TIMI 48	HOKUSAI VTE	STARS E-3, STARS J-4, STARS J-5
Rivaroxaban	ROCKET-AF, J-ROCKET-AF	EINSTEIN-DVT, EINSTEIN-PE, EINSTEIN-Extension, MAGELLAN	RECORD 1, RECORD 2, RECORD 3, RECORD 4
Apixaban	AVERROES, ARISTOTLE	AMPLIFY, AMPLIFY-Extension, ADOPT	ADVANCE-1, ADVANCE-2
Dabigatran	RE-LY, RELY-ABLE	RE-COVER, RE-COVER II, RE-MEDY, RE-SONATE	RE-NOVATE, RE-NOVATE II, RE-MODEL, RE-MOBILIZE

AF: Atrial fibrillation; VTE: Venous thromboembolism.

with a heparin based (unfractionated and LMWH) treatment in both arms for 5–12 days [101]. Hokusai VTE started in October 2009 and is scheduled to be completed in 2012. With 7500 patients, it is currently the largest Phase III trial for the treatment and prevention of recurrent VTE in patients with acute DVT and/or symptomatic pulmonary embolism. Treatment of patients extends for up to 12 months after randomization.

STARS E-3 (NCT01181102) is a Phase III double-blind, double-dummy study that randomized 716 Japanese patients to receive edoxaban 30 mg orally q.d. or enoxaparin 20 mg subcutaneously b.i.d. Patients were treated for 11–14 days after unilateral total knee arthroplasty and followed for 25–35 days. Preliminary results showed that edoxaban was more effective than enoxaparin in the prevention of DVT (relative risk reduction 46.8%; $p < 0.001$). No pulmonary embolisms were documented and there was no significant difference in bleeding rates between the two groups [38].

Similar VTE incidence and bleeding rates were found in the STARS-J4 trial (NCT01181141), with nonstatistically significant differences. The trial enrolled 92 Japanese patients after hip fracture surgery. Patients were randomized to receive edoxaban 30 mg q.d. or enoxaparin 20 mg b.i.d. [39].

The STARS J-V (NCT01181167) is a Phase III, randomized, double-blind, double-dummy enoxaparin-controlled study of edoxaban. The study enrolled 610 Japanese patients after unilateral total hip arthroplasty. Patients were randomized to receive edoxaban 30 mg orally q.d. or enoxaparin 20 mg subcutaneously b.i.d. The incidence of the primary outcome (VTE events) was studied with clinical follow-up and by obtaining a venography at the end of the treatment period (11–14 days). Edoxaban was superior when compared with enoxaparin (incidence of VTE after hip arthroplasty of 2.4 vs 6.9%; $p = 0.0157$). The incidence of the major and clinically relevant non-major bleeding showed no differences between the two treatment groups [40]. These studies led to approval in Japan for VTE prevention in orthopedic surgery.

Prevention of stroke in AF

ENGAGE AF-TIMI study 48 (NCT00781391) is a Phase III, randomized, double-blind, double-dummy, multinational, noninferiority design clinical trial [28]. It compares two exposure strategies of edoxaban (60 mg orally q.d. and 30 mg q.d.) to warfarin (titrated to an INR 2.0–3.0) for the prevention of stroke and systemic embolism. Inclusion criteria include electrical documentation of AF ≤12 months and a $CHADS_2$ score ≥2. Primary outcomes include the composite of stroke and systemic embolisms. Secondary outcomes include the composite stroke plus systemic embolisms plus cardiovascular death or all-cause death. If patients have an anticipated increased drug exposure (renal function impairment, body weight ≤60 kg or concomitant administration of strong P-gp inhibitors) they receive a 50% dose reduction.

The study completed enrollment of 21,107 subjects between November 2008 and 2010, representing the largest trial in stroke prevention in AF so far, and the median follow-up is expected to be 24 months (Figure 2) [28].

Discussion

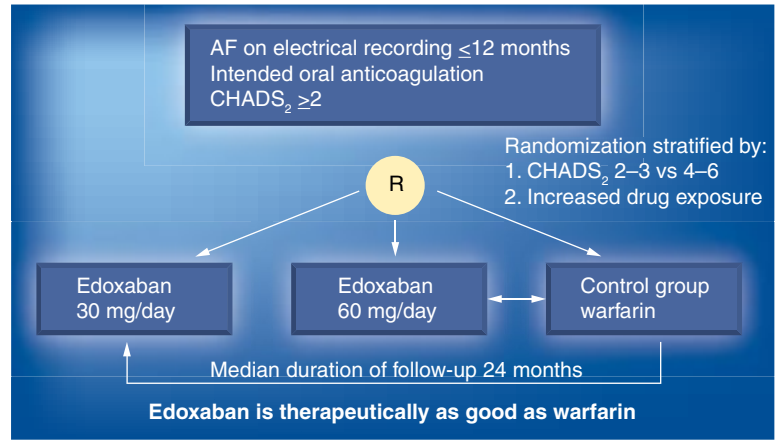

Figure 2. Protocol schema for ENGAGE AF-TIMI 48.
Reproduced with permission from [28].

Although very effective, traditional anticoagulant drugs (heparin, VKAs) have many disadvantages. Currently, less than half of patients who could benefit from anticoagulation receive these therapies [9,10]. The development of new anticoagulant drugs that are safe, effective and easy to use is mandatory.

Edoxaban, a novel oral q.d. factor Xa inhibitor, is emerging as an attractive agent in preventing and treating thromboembolic events. Edoxaban inhibits factor Xa, which plays a key role in the coagulation cascade, with few functions outside this pathway. This results in an effective inhibition of thrombus formation with potentially minimal AEs.

This agent has linear and predictable PK and pharmacodynamics. Edoxaban can be administered in fixed doses without periodical coagulation monitoring [24].

The anticoagulant effect is dose dependent, with few drug–drug interactions [28] and without relevant drug–food interactions. Only in patients with renal function impairment, body weight <60 kg or concomitant use of strong P-gp inhibitors, should dosage of edoxaban be reduced.

A potential advantage of edoxaban over other factor Xa inhibitors (apixaban, rivaroxaban) is its comparatively minor protein binding [25]. It could make the removal of the substance during dialysis treatment easier. Safety and tolerability of edoxaban have been largely demonstrated in many clinical studies, without documented hepatotoxicity in blood tests. Regarding bleeding complications, a direct antagonist is still being developed.

In Phase II trials, q.d. regimens of edoxaban have been shown to be advantageous to VKAs or heparins in the prevention of thromboembolisms. In a Phase II trial with AF patients there was a better bleeding profile seen when edoxaban was given q.d. compared with b.i.d. treatment regimens [32]. The resulting selection of q.d. dosing regimens for the Phase III trials represent a contrast to other novel agents with a b.i.d. regimen, such as dabigatran or apixaban.

Further studies are necessary to evaluate the efficacy and safety of edoxaban when compared with other factor Xa inhibitors or DTIs.

Conclusion

In the last decade a range of novel anticoagulant drugs have emerged to become new treatment options for patients diagnosed with AF or VTE. The advantages summarized make edoxaban an attractive alternative to warfarin, heparin or even to other new oral anticoagulant drugs.

Safety and tolerability have been largely demonstrated. Results obtained from Phase II studies are promising and ongoing Phase III clinical trials will help to further determine the potential of edoxaban.

Future perspective

Executive summary

Background

- The limitations of traditional anticoagulants has led to the development of new anticoagulant agents that are safe, effective and easy to use.

Novel oral anticoagulants

- Edoxaban is a novel, orally delivered, small molecule that acts as a reversible and direct factor Xa inhibitor.

Pharmacokinetic & pharmacodynamic properties

- Edoxaban plays a key role at the primary site of amplification of the coagulation cascade.
- Its activity is linearly correlated with plasma levels of the drug that are predictable depending on the dose of edoxaban administrated.
- Edoxaban is administered once daily with no need for routine monitoring.
- The drug is cleared via multiple pathways, with one third cleared by the kidney. Dosage should be reduced in patients with renal function impairment.
- Relevant drug–food interactions have not been reported. Edoxaban presents few drug–drug interactions (especially with strong P-gp inhibitors), although further investigation is required.

Clinical trials

- Preliminary results of Phase II trials have shown edoxaban to be advantageous to traditional anticoagulants, especially in terms of bleeding in the prevention of stroke and embolisms.
- Edoxaban completed Phase III trials for venous thromboembolism prevention in orthopedic surgery and is licensed for this indication in Japan.
- HOKUSAI-VTE is a Phase III study that compares edoxaban with warfarin in the treatment and prevention of recurrent venous thromboembolism and represents the largest trial in this indication so far.
- ENGAGE AF-TIMI 48 is a Phase III clinical trial that studies the efficacy, safety and optimal dosage of edoxaban in 21,105 patients diagnosed with atrial fibrillation, making it the largest stroke prevention trial in this indication so far.

Work is still needed to develop the optimal laboratory test to measure the anticoagulant activity of edoxaban and other oral direct factor Xa inhibitors, as well as to create a universal antidote for reversal of factor Xa inhibition, even though the half-lives of the new oral anticoagulants are short, which could be sufficient in many cases.

The results of the ongoing Phase III clinical trials will provide more data about edoxaban's safety and efficacy and will help to establish the optimum dosing.

In a few years oral factor Xa inhibitors could become a standard of care for the prevention of stroke in AF, as well as treatment and prevention of VTE, enabling many more patients to receive anticoagulation.

The selection of an oral anticoagulant drug will largely be dependent on the pharmacologic properties of each anticoagulant and the patient's particularities.

Financial & competing interests disclosure

The authors have no 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. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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