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Review Article

Factor Xa inhibitors, Era to replace traditional anticoagulants

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ABSTRACT

The past 15 years have seen increased usage of factor Xa inhibitor anticoagulants such as rivaroxaban, apixaban, and edoxaban, along with dabigatran (competitive direct thrombin inhibitor), which have been used increasingly in various clinical settings, for the prevention and treatment of thrombosis. In many ways Factor Xa inhibitors have replaced the use of warfarin, which requires prudent monitoring . Factor Xa inhibitor short half-lives, compared to warfarin's, provide some assurance that the drug concentrations will decline rapidly when therapy is discontinued in patients with normal renal function. Good haemostatic efficacy was achieved in 83% patients on apixaban and 80% patients on rivaroxaban . Major bleeding events in nonvalvular atrial fibrillation patients on rivaroxaban were 3.6% per year and on apixaban were 2.13% per year in respective landmark trials conducted. Some drawbacks of Factor Xa inhibitors include uncertainty about dosing in some patient populations (eg, renal dysfunction, marked extremes of body weight), and their higher drug cost.

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1. Introduction

1. *Coagulation cascade:* is propagated in multiple steps.
2. *Initiation:* TF in damaged vessel which binds factor VIIa to activate factor IX and factor X. Activation of factor IX by TF-VII a complex serves as the bridge between classical extrinsic and intrinsic pathways. Factor Xa then binds to factor II to form thrombin (factor II a).
3. *Amplification:* Thrombin that is generated in the initiation phase further activates factor V and factor VIII, which serves as a cofactor in prothrombinase complex and accelerates the activation of Factor II by F Xa and of F a by F IXa, respectively.
4. *Propagation:* The accumulated enzyme complexes (tenase complex and prothrombinase complex) on platelet surface support robust amounts of thrombin generation and platelet activation.
5. *Stabilization:* Thrombin generation leads to activation of factor XIII (fibrin stabilizing factor) which covalently links fibrin polymers and provides strength and stability to fibrin incorporated in platelet plug. As thrombin acts as a procoagulant, it also acts as a negative feedback by activating plasminogen to plasmin and stimulating the production of antithrombin (AT).

Factor Xa is a crucial site of amplification in the coagulation process, generating approximately 1,000 thrombin molecules from a single Xa molecule. Prothrombin is physiologically activated by the prothrombinase complex (factor Xa, factor Va, phospholipids, and calcium). The conversion of fibrinogen to fibrin, the basic building block of all blood clots, is then catalysed by thrombin. Direct factor Xa inhibitors are potent and selective direct inhibitors of factor Xa without affecting platelet aggregation.[2]

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Table 1: Properties of ideal anticoagulant [4]

Oral administration	Convenient use both in and out of hospital and having Linear kinetics
Predictability	Safe and effective regulation of coagulation from the first dose and throughout therapy
Wide therapeutic window	Broad safety margin at a wide range of effective doses
Minimal food/drug interactions	No induction or inhibition of cytochrome P450 Ease of use with concomitant medication and diet
No monitoring	No need for laboratory monitoring saves healthcare costs through fewer hospital physician visits time and patients'

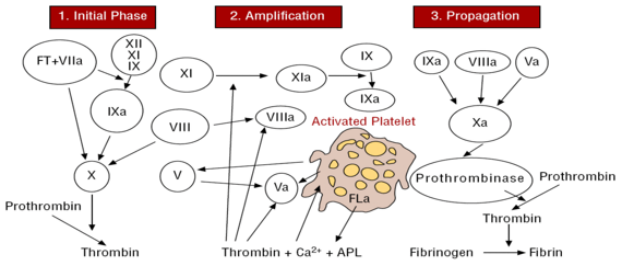

Fig. 1: The coagulation cascade [1]

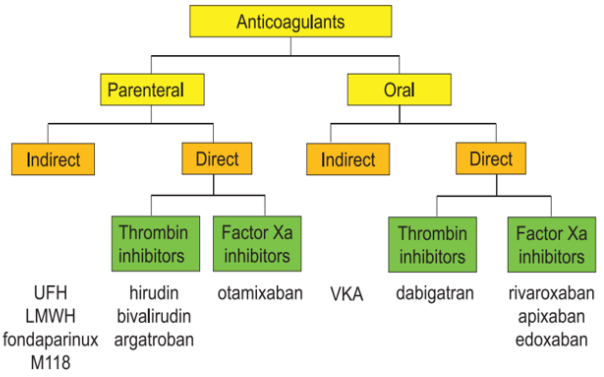

Fig. 2: Classification of anticoagulants

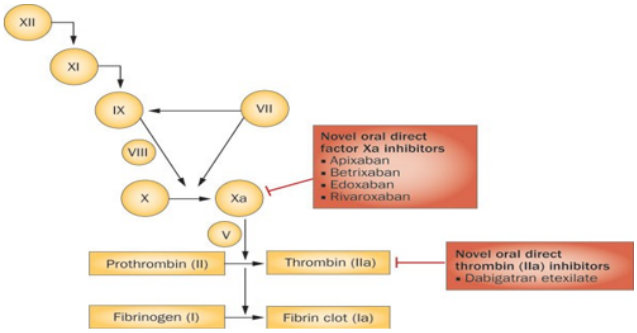

Fig. 3: Action of factor Xa inhibitors [3]

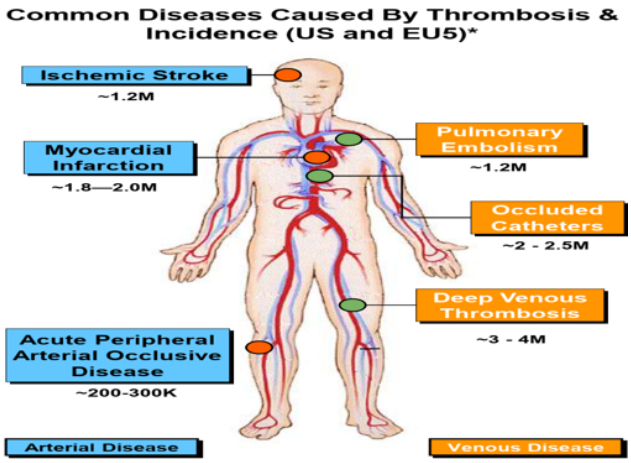

Fig. 4: Conditions leading to thrombosis

Anticoagulants achieve their effect by suppressing the synthesis or function of various clotting factors that are normally present in the blood. Direct factor Xa inhibitors are able to inhibit both free and prothrombinase-boundfactor Xa, and eventually even clot-associated factor Xa. This prevents all forms of factor Xa from activating prothrombin, thus contributing to counteracting the procoagulant activity of thrombi and the propagation of thrombosis. [5]

The oral direct factor Xa inhibitors are able to inhibit factor Xa directly without interacting with antithrombin. [6] Professor Ajay Kakkar from Thrombosis Research Institute, London has done major pioneering work on various Factor Xa inhibitors. Factor Xa inhibitors are a type of anticoagulant that work by selectively and reversibly blocking the activity of clotting factor Xa, preventing clot formation. Factor Xa inhibits both free and clot-bound Factor Xa, as well as prothrombinase activity, thereby prolonging clotting times. Factors Xa inhibitors completely inhibited thrombin generation, suggesting that they can access the active site of FXa within the prothrombinase complex more effectively than indirect FXa inhibitors.

1.1. Drug interactions

Concomitant use of the FX a inhibitors with aspirin or other antiplatelet agents, other antithrombotic agents, fibrinolytic therapy, and chronic use of nonsteroidal anti-inflammatory

Table 2: The FX a inhibitors have several approved indications for use as shown in Table 2

.	Prophylaxis for prevention of venous thromboembolism (VTE) inhigh-risk patients, e.g. post orthopaedic surgery
.	Treatment of deep vein thrombosis (DVT), pulmonary thromboembolism and prevention of recurrence
.	Stroke prevention in nonvalvular atrial fibrillation (NVAF)
.	Prophylaxis of cardiac thromboembolism in atrial fibrillation (AF), severe left ventricular (LV) dysfunction, mechanical heart valves, bioprosthetic heart valves (first 3 months),
.	Embolic peripheral arterial disease

Table 3: Pharmacokinetic properties and dosing for the direct oral factor Xa inhibitors

	Rivaroxaban	**Apixaban**	**Betrixaban**	**Edoxaban**
Bioavailability	> 80%	> 50%	~ 35%	> 80%
Onset of, hrs	2–4	~ 3	1–3	1–2
Half-life, hrs	5–13	9–14	~ 20	8–10
Metabolism action	1/3 renal; 2/3 liver (CYP 450)	Multiple pathways (25% renal)	Via bile (~ 5% renal)	Multiple (majority renal)
Drug interactions	Low–Mod	Low	Low	Low-Mod
Dosing	Oral once	Oral twice	Oral once	Oral once

drugs (NSAIDs) further increases the risk for bleeding.

1.2. Side effects

The most serious bleeding event associated with anticoagulation use is intracranial hemorrhage (ICH) . Other side effects include a stomach upset, dizziness, anaemia and raised hepatic enzymes.

Table 4: Cautions while usingXa inhibitors [7,8]

Congenital or acquired bleeding disorders
Uncontrolled severe arterial hypertension
Active ulcerative gastrointestinal disease
Recent gastrointestinal ulcerations
Vascular retinopathy
Recent intracranial or intracerebral hemorrhage
Shortly after brain, spinal or ophthalmological surgery

2. Factor Xa Antagonists and Dabigatran Antagonists

Andexanet has high affinity for the Factor Xa inhibitors and competes with native Factor Xa to bind the anticoagulants, which frees uninhibited FXa to assemble into the prothrombinase complex and generate thrombin.

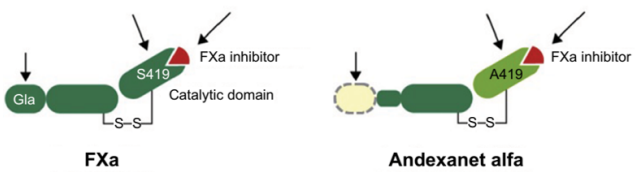

Fig. 5: Action of andexanet

It is marketed as Andexxa in May 2018 Andexanet alfa is a recombinant and inactivated form of factor Xa engineered to be a universal antidote of the factor Xa inhibitors: apixaban, rivaroxaban, and edoxaban.[9]

There are two dosing procedures for Andexanet alfa

2.1. Low dose

1. Initial IV bolus: 400 mg IV; target infusion rate of 30 mg/min
2. Follow-on IV infusion: 4 mg/min IV for up to 120 min

2.2. High dose

1. Initial IV bolus: 800 mg IV; target infusion rate of 30 mg/min
2. Follow-on IV infusion: 8 mg/min IV for up to 120 min[10]

A single IV dose of ciraparantag (100 to 300 mg) demonstrated full reversal of anticoagulation within 10 minutes and sustained for 24 hours. It has the potential to be a universal antidote, inhibiting nearly all anticoagulants except vitamin K antagonists and argatroban.

Ciraparantag is a small synthetic molecule that binds directly to direct factor Xa inhibitors, direct thrombin inhibitors, and unfractionated and low-molecular-weight heparin (LMWH)[11]

Idarucizumab- is a humanized monoclonal antibody fragment (Fab) indicated in patients when reversal of the anticoagulant effects of dabigatran is needed. The indications for use is rapid reversal of dabigatran is bleeding from critical sites (intracranial, intraspinal, pericardial, intraocular, pulmonary, retroperitoneal, or intramuscular with compartment syndrome) or persistent major bleeding despite local hemostatic measures (gastrointestinal, gynecologic, or urologic). The recommended dose of Idarucizumab-is 5 g, provided as two separate vials each containing 2.5 g/50 mL.[12]

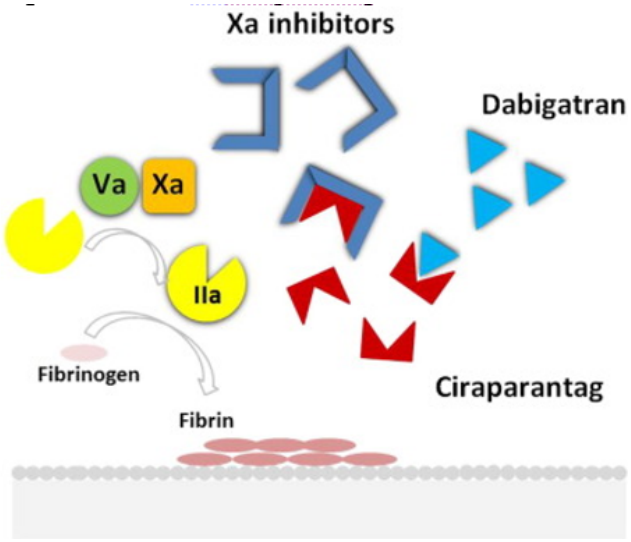

Fig. 6: Action of ciraparantag

3. Vital Trials With Factor Xa inhibitors

ARISTOTLE study : In patients with atrial fibrillation and at least one additional risk factor for stroke, the use of apixaban, as compared with warfarin, significantly reduced the risk of stroke or systemic embolism by 21%, major bleeding by 31%, and death by 11%.[13]

Record 1 and 2 are similar, The only difference concerns the duration of the prophylaxis in the comparator arm: 5 weeks in the Record 1 , 2 weeks in the Record 2 **:** Extended thromboprophylaxis with rivaroxaban was significantly more effective than short-term enoxaparin plus placebo for the prevention of venous thromboembolism, including symptomatic events, in patients undergoing total hip arthroplasty.[14]

The ATLAS ACS 2 – TIMI 51 trial found rivaroxaban reduced the risk for the composite endpoint of death from cardiovascular causes, MI or stroke vs. placebo (8.9% vs. 10.7%, respectively. Improvements were seen with both 2.5 mg and 5 mg dose.[15]

ROCKET AF Clinical Trials: In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism.[16]

Once-daily regimens of Edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes. Edoxaban is licensed in Japan for VTE prophylaxis after elective hip or knee arthroplasty[17]

An updated meta analysis has shown that Dabigatran, rivaroxaban, and apixaban appear to be superior to warfarin in both efficacy and safety in Asians with non-valvular AF.

4. Newer Factor Xa Inhibitors

Otamixaban a phenylpyridine, is an experimental injectable anticoagulant direct factor Xa inhibitor that was investigated for the treatment for acute coronary syndrome, Iintermediate doses of otamixaban — 0.105 or 0.140 mg/kg per hour — resulted in a 40% decrease in the rate of the primary endpoint. Patients in the intermediate doses had 46% reduction in risk for death or MI.[18]

Darexaban is a potent direct factor Xa inhibitor Decreases blood clot formation in a dose dependent manner. A phase II dose-finding study has found that the new oral Factor Xa inhibitor darexaban was associated with a two to four-fold increase in bleeding when added to dual antiplatelet therapy in patients following an acute coronary syndrome Darexaban decrease the incidence and severity of stroke in patients with atrial fibrillation by preventing the formation of blood clots. Darexaban when added to dual antiplatelet therapy after Acute coronary syndrome produces an expected dose-related two- to four-fold increase in bleeding, with no other safety concerns.[19]

Table 5: Advantages of factor Xa inhibitors are

Dose-dependent inhibition of Factor Xa activity and prolongation of Prothrombin time
Absence of food interactions and few drug interactions
They have rapid onset of action
Reducing thrombosis and fatal bleeding
Low potential of pharmacodynamic interaction which allows broad range of co-medications
Low potential for pharmacokinetic interactions – CYP 3A4 inhibitors may be of clinical relevance
Short half-time
Absence of the need for laboratory monitoring,

Betrixaban (PRT-054,021) is an anticoagulant drug which acts as a direct factor Xa inhibitor. It is potent, orally active and highly selective for factor X a It has undergone human clinical trials for prevention of embolism afterknee surgery and prevention of stroke following atrial fibrillation. Betrixaban at doses of 40–80 mg per day was well tolerated in AF (Atrial Fibrillation) patients at risk for stroke with a risk of bleeding that was similar to, or lower than, that of well-managed warfarin. Similar efficacy and safety were observed in all groups, with a favourable safety profile.[20]

5. Conclusion

The important indications for Factor Xa inhibitors are the treatment of DVT and PE, and the prevention of recurrent DVT and PE in adults

DOAC (Direct oral anticoagulants) are not appropriate in some patients, such as who have liver or kidney disease. They are also contraindicated in hepatic disease associated with coagulopathy and clinically relevant risk. Dabigatran, rivaroxaban, and apixaban appear to be superior to warfarin

in both efficacy and safety in Asians with non-valvular AF and are associated with a lower rate of gastrointestinal bleeding. There is dosing difference. Rivaroxaban is given twice daily for 3 weeks, then once daily; apixaban is given twice daily with a dose change after 7 days; whereas edoxaban is a once daily medication. Another anticoagulant, Dabigatran is an oral factor II a (thrombin) inhibitor. By binding reversibly to the active site of factor IIa, dabigatran attenuates thrombin activity and reduces fibrin formation. In a Norwagian study, statistically significant differences between dabigatran and apixaban were both associated with significantly lower risk of major bleeding compared with rivaroxaban. However, the number of patients studied in clinical trials and Post-marketing trials globally done are significant with Rivaroxaban, which makes it the most sought factor Xa inhibitor in clinical practice.

6. Source of Funding

None.

7. Conflict of Interest

None.

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