

# BLOOD BULLETIN

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## Overview of Factor Xa Inhibitors: Evaluation, Bleeding Management, and What's Coming Next

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Until recently, warfarin and heparin were the primary options for prevention of thromboembolism in patients with high-risk conditions such as atrial fibrillation (AF). Now, factor Xa (FXa) inhibitors are available as an effective alternative. Currently apixaban (Eliquis), fondaparinux (Arixtra), and rivaroxaban (Xarelto) are licensed in the US. Like all medications, these drugs have advantages and side effects to consider. Benefits of this class of medication include standardized dosing, fewer food and drug interactions when compared with warfarin, and no need for regular lab monitoring due to more predictable pharmacokinetics. In the event of a serious bleed, however, reversal is challenging, as reliable monitoring methods are not established and currently no antidote is available.

FXa inhibitors act by directly inhibiting free Xa and prothrombinase activity. While they have no direct effect on platelet function, they indirectly inhibit platelet aggregation induced by thrombin.<sup>1</sup> The majority of FXa inhibitors are substrates for the P-glycoprotein and Cytochrome P-450 isoenzymes; thus, the concomitant administration of other potent CYP3A4 inhibitors can increase drug levels and lead to elevated bleeding risk.<sup>2</sup>

Severe bleeding or the need for emergent invasive procedures may require laboratory evaluation of FXa inhibition. The chromogenic anti-FXa activity assay accurately measures FXa inhibitor levels, but must be calibrated individually for each drug (e.g., rivaroxaban vs. apixaban).<sup>3</sup> Often, this test is not available in the acute care setting and, thus, it has limited use at this time. The international normalized ratio (INR) does not reflect changes in FXa levels and is not recommended.<sup>4</sup> The prothrombin time (PT) can be used to monitor overdose. Studies have found that rivaroxaban and apixaban will show a linear increase in PT at therapeutic levels or higher.<sup>5</sup> The PT, however, can only be used as a qualitative marker and should not be used to monitor for

### Key Points

- FXa inhibitors directly inhibit free Xa and prothrombinase activity.
- Anti-factor Xa activity assay is the only accurate measure. It must be calibrated for the specific drug and often is not available in the acute care setting.
- The PT can be used qualitatively for severe overdose or bleeding. INR is not useful.
- No clearly effective means for reversal exists; 3- or 4-factor PCCs, or activated PCCs, can be tried in urgent situations. Recommended dose is 25-to-50 units/kg.
- A potential antidote currently is being investigated.
- Several new FXa inhibitors are in development with various benefits, such as options for kidney-impaired patients.

sub-therapeutic values, as there is a high level of variability between the different reagents.<sup>4</sup>

Reversal of FXa inhibitors is problematic. Plasma is minimally effective and its use requires large-volume transfusions that are time-consuming and pose risk for volume overload.<sup>4</sup> Dialysis is generally ineffective, as these drugs are predominantly protein-bound. Therapeutic plasmapheresis may be considered in the event of life-threatening bleeding.<sup>5</sup>

The best options available for urgent reversal, in order of effectiveness, appear to be 4-factor prothrombin complex concentrates (PCCs), 3-Factor PCCs, and activated PCCs (e.g., FEIBA) – all of which rapidly replace factor X. The least effective is likely recombinant FVIIa.<sup>5</sup> Use of these plasma derivatives for this indication is off-label, but may be justified in an emergent situation. Clearly, though, better means for reversing this

anticoagulant class of medications are needed. Andexanet alfa is the first in a series of potential antidotes to FXa inhibitors and is being studied in a phase III trial. This drug is, in effect, an FXa “decoy,” which targets and irreversibly binds FXa inhibitors (both direct and indirect), preventing inhibition of native FXa<sup>6</sup>.

Comparison of FXa Inhibitors		
Drug		
Fondaparinux (Arixtra) Approved 2001 Subcutaneous	Rivaroxaban (Xarelto) Approved 2011 Oral	Apixaban (Eliquis) Approved 2012 Oral
Half-Life		
17-21 hours	5-9 hours (≤ 45 year-old) 11-13 hours (> 45 year-old)	12 hours
Metabolism		
Kidney (77%)	Kidney (33%) Liver (66%)	Kidney (27%) Liver (73%)
Indications		
DVT prophylaxis after hip/knee replacement or abdominal surgery. Treatment of DVT or acute pulmonary embolism (PE) when administered with warfarin.	DVT prophylaxis after hip/knee replacement surgery. Treatment and prevention of DVT or acute PE. Non-valvular AF; reduced risk of stroke and systemic embolism.	DVT prophylaxis after hip/knee replacement surgery. Treatment of DVT or PE. Non-valvular AF; reduced risk of stroke, and systemic embolism.
Precautions		
Dialysis can increase removal by 20%. Moderate to severe thrombocytopenia reported. Contraindicated in thrombocytopenia with a positive anti-platelet antibody test.	Concomitant aspirin use may increase bleeding risk. Concomitant clopidogrel prolongs bleeding time.	An increase of 50-60% in anti-FXa activity reported when combined with enoxaparin or naproxen.

### Future Developments

Several new FXa inhibitors are in development and are undergoing (or have completed) phase III trials.

*Idrabiotaparinux* is given as a subcutaneous injection, and has a half-life ( $t_{1/2}$ ) of 80 hours, thus making once a week dosing a possibility.<sup>6</sup>

*Betrixaban* is being studied through a phase III trial involving the prolonged treatment of deep venous thromboses (DVTs). This oral medication is intended to be used as a bridging medication for “hospital to home” therapy. It has a lower renal clearance than the currently licensed inhibitors, potentially expanding its applicability to those with reduced kidney function. Moreover, it is not metabolized by CYP3A4, which should reduce the likelihood of drug interactions.<sup>7</sup>

*Edoxaban* is a once-daily oral anticoagulant that has been used in Japan since 2011. Its manufacturer submitted an application to the Food and Drug

Administration in early 2014. Its  $t_{1/2}$  is 9 to 10 hours, and it is eliminated 49% through renal pathways. It was studied in both 30 mg and 60 mg doses – if both are approved, it will be the first of the FXa inhibitors to be offered in multiple dosing options.<sup>8</sup>

In summary, FXa inhibitors are popular because of their greater ease of use and enhanced safety as compared to traditional anticoagulants. There is no clearly effective means of urgent reversal, but 3- or 4-factor PCCs or activated PCCs may be of use. Several promising new FXa inhibitors are in development, which may permit more universal application of this class of medications.

### References

- Perzborn E, Strassburger J, et al. *In vitro* and *in vivo* studies of the novel antithrombotic agent BAY 59-7939—an oral, direct Factor Xa inhibitor. *J Thromb Haemost.* 2005 March; 3:514-521.
- Nutescu EA, Dager WE. Management of bleeding and reversal strategies for oral anticoagulants: Clinical practice considerations. *Am J Health-Syst Pharm* 2013 Nov; 70: 1914-1930.
- Steiner T, Böhm M, et al. Recommendations for the emergency management of complications associated with the new direct oral anticoagulants (DOACs), apixaban, dabigatran and rivaroxaban. *Clin Res Cardiol.* 2013 Jun;102:399-412.
- Mani H, Kasper A, Lindoff-Last E. Measuring the anticoagulant effects of target-specific oral anticoagulants—reasons, methods and current limitations. *J Thromb Thrombolysis* 2013 Aug; 36: 187-194
- Yates S, Sarode R. Novel Thrombin and Factor Xa inhibitors: Challenges to reversal of their anticoagulant effects. *Current Opin Hematology* 2013 Nov;6:552-557.
- Sanofi Website: [[http://en.sanofi.com/img/content/study/EFC10295\\_summary.pdf](http://en.sanofi.com/img/content/study/EFC10295_summary.pdf)] June 13, 2014.
- Portola Pharmaceuticals Website: [<http://www.portola.com/clinical-development/>] June 13., 2014.
- Ogata K, Mendell-Harary J, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol* 2010 Jul; 50:743-753.

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