

## **Oral Antithrombin and Anti Xa Agents and Their Impact in the Management of Thrombosis and Cardiovascular Disease**

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Interest in the development of synthetic parenteral antithrombin agents has led to the development of such anticoagulant drugs as hirudin, bivalirudin and argatroban. More recently this interest has shifted to the development of oral antithrombin and anti-Xa drugs as potential replacements for heparins and oral anticoagulants. Currently several oral anti-Xa and anti IIa drugs are in clinical development for the management of thrombosis and cardiovascular diseases. These agents have been compared with warfarin and exhibit distinct pharmacological actions. Not only are these agents distinct, but each of these drugs can be differentiated within its own class.

Rivaroxaban (Xarelto) has been extensively investigated in several clinical trails for the management of post surgical and medical venous thromboembolism. In addition, this agent has also been investigated in the management of atrial fibrillation and acute coronary syndrome. It is approved for the post-surgical prophylaxis venous thrombosis in the European Community and in Canada; in the United States it remains under review by the FDA.

Apixaban represents another factor Xa inhibitor that has undergone extensive clinical trials for the management of venous thrombosis, atrial fibrillation and stroke. In addition, this drug is also being evaluated for the management of acute coronary syndrome in combination with aspirin and clopidogrel. Edoxaban and TK 442, along with several other agents, are being pursued for similar indications. Most of these oral factor Xa inhibitors have been found to be more effective than standard of care. However, safety considerations, such as bleeding, elevation of liver enzymes and drug interactions require further investigation.

Dabigatran represents a specific, reversible thrombin inhibitor that has been clinically evaluated in similar patient groups as the factor Xa inhibitors. Dabigatran is approved in the European Community and in Canada for the management of venous thromboembolism after hip and knee surgery, and has also been tested in patients with atrial fibrillation or acute coronary syndrome. Dabigatran is used at a relatively high dosage in comparison to the factor Xa inhibitors

While there is no specific antidote available for the neutralization of these agents at this time, more recently a molecularly modified lacking catalytic and membrane binding activities has been developed that can neutralize the effect of factor Xa inhibitors and low molecular weight heparins. Both the oral anti-Xa and anti-IIa drugs maybe useful in the management of heparin and warfarin compromised patients. However, because of the single target actions, these drugs may have a limited therapeutic spectrum in comparison to heparin and warfarin. Like warfarin these anti-Xa and anti-IIa drugs cross placental and other membrane barriers. Furthermore, unlike heparin, these drugs do not release TFPI from the endothelium. Moreover, drug and food interactions and

pharmacogenomic considerations in special population groups require further investigations.

Regardless of some of the developmental considerations requiring additional trials, these drugs offer new opportunities for the management of thrombosis and cardiovascular disease, which maybe of major value in heparin and warfarin compromised patients. Additional clinical indications for their use include prolonged management of medical thrombosis, heparin induced thrombocytopenia, thrombophilic conditions and cancer-associated thrombosis.