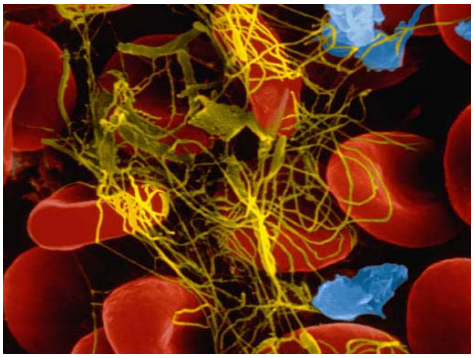
Understanding Blood Clotting and Anticoagulant Therapy

a. Blood clotting: an introduction

Blood clots form to prevent prolonged bleeding in response to damage to a blood vessel. When formed, the blood clot acts as a plug at the site of the blood vessel injury.

Conditions such as deep vein thrombosis (DVT) and pulmonary embolism (PE) arise when the blood clotting cascade is inappropriately activated leading to the formation of unnecessary blood clots which can subsequently block blood vessels. Several factors increase the risk of blood clots forming such as surgery, prolonged immobility and cancer.[1]

Blood clotting is a complex process, making it a challenge to identify the most effective point for anticoagulant therapies to target.



Blood clot forming in a damaged blood vessel

b. Current anticoagulant therapies

Currently available anticoagulant medications aim to interrupt the coagulation cascade to reduce the tendency of the blood to clot without thinning the blood so far as to risk causing bleeding. These treatments inhibit many different switches along the intricate blood-clotting cascade and some also have effects outside of the coagulation cascade.

Current anticoagulants have proved effective in treating and reducing the risk of occurrence of potentially life-threatening blood clots. However, they are associated with several drawbacks that limit their use and acceptability to patients and doctors alike. The different current treatment options have one or more of the following limitations:[2]

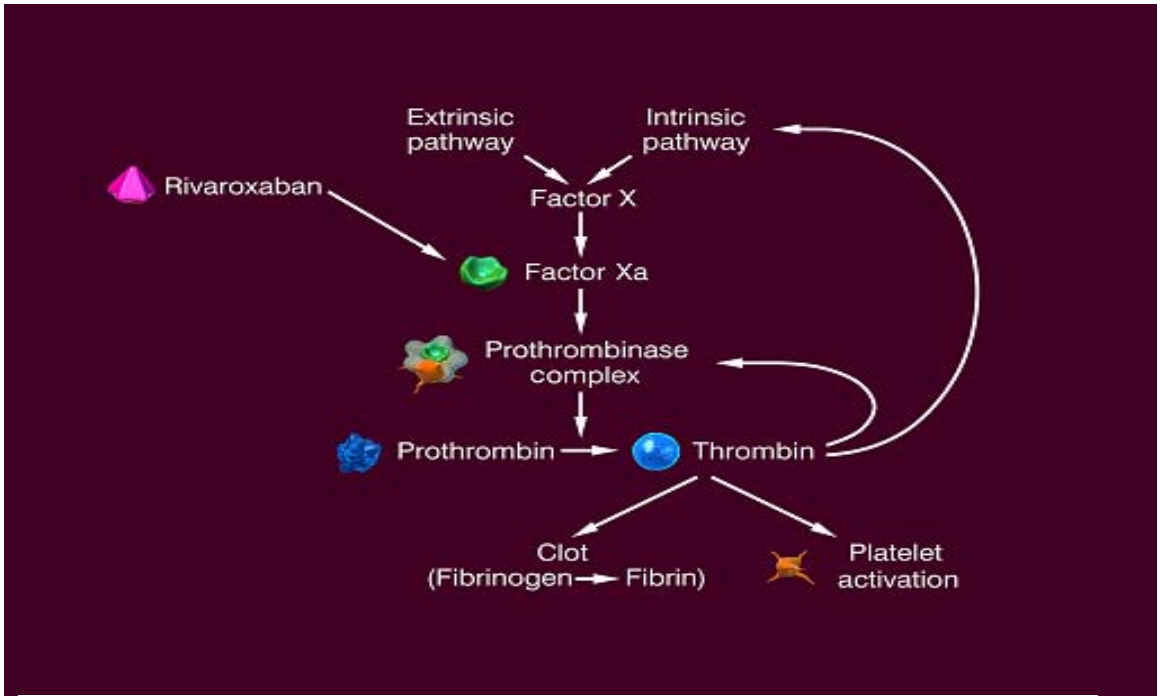
- The need for injections to administer the treatment
- Non-specific mechanism of action
- The requirement for frequent blood monitoring to avoid both undercoagulation and bleeding complications from overcoagulation
- The need to adjust the dose of anticoagulant on the basis of blood monitoring results and also other factors such as age, gender and weight
- Interactions of the anticoagulants with food and other medications

c. Direct Factor Xa therapies: a new era of oral anticoagulants

Medicines that directly inhibit Factor Xa represent a new era of medicines to prevent and treat blood clots. The development of direct Factor Xa inhibitors has been guided by the need for anticoagulants, which specifically target a pivotal point in the blood-clotting cascade. Therapies targeted to inhibit Factor Xa may eliminate the need for blood-clotting monitoring and dose adjustments.

Factor Xa has emerged as an attractive target for new anticoagulants[2] due to its central point in the blood-clotting cascade, where it stimulates the production of thrombin, the enzyme that promotes clot formation.[3] By regulating the production of thrombin, direct Factor Xa inhibitors control the blood-clotting process at a pivotal point in the coagulation cascade. One molecule of Factor Xa leads to the formation of about 1,000 thrombin molecules,[4] suggesting that direct Factor Xa inhibitors may be able to control the clotting process before it becomes too difficult to manage. The targeted action of direct Factor Xa inhibitors regulates thrombin generation rather than inhibiting the action of thrombin itself, which is required for maintaining blood coagulation in response to tissue damage.

Oral direct Factor Xa inhibitors also have the advantage that they may allow patients to be on the same treatment in the hospital and at home, where they may require treatment to deal with continued risk of developing life-threatening complications.



Simplified blood-clotting cascade and inhibition by Factor Xa inhibitors

References
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2. Turpie AGG. Arterioscler Thromb Vasc Biol 2007; 27: 1238-47.
3. Weitz J. J Thromb Haemost 2005; 3: 1843-53.
4. Mann KG. J Thromb Haemost 2003; 1: 1504-14.