THE HISTORY OF ANTICOAGULANTS

FAST FACTS

- Anticoagulants have been used for more than 70 years to prevent and treat potentially deadly blood clots
- Older treatments, including heparins and vitamin K antagonists, have long been the mainstays of treatment. These agents, although effective if managed properly, have significant limitations
- Improvements in understanding how the clotting process works have led to the development of anticoagulants that are increasingly specific and act against the *right* targets, to achieve the optimal balance between efficacy, safety and convenience
- The next evolution of anticoagulant medicines – oral, direct Factor Xa inhibitors, such as rivaroxaban – target a pivotal enzyme that carefully pinpoints a 'switch' to control the clotting process at the crucial moment

1930s: The advent of heparin

Heparin (unfractionated) has been available for more than 60 years but requires injection, which makes it inconvenient for use out of the hospital setting. It also requires coagulation monitoring, and is associated with heparin-induced thrombocytopoenia (known as HIT or reduced platelet count associated with an increased bleeding risk) and osteopoenia (low bone mineral density).[1]

1940s: The first oral anticoagulants

Vitamin K Antagonists (VKAs), such as warfarin and acenocoumarol, were the first oral anticoagulants. They are highly effective, but difficult to manage well, requiring frequent monitoring and dose adjustment to limit adverse consequences, multiple food and drug interactions and to address variable pharmacology (response to treatment). These factors, in addition to an increased risk of bleeding and other adverse effects, may contribute to the frequent underuse of warfarin, especially in elderly patients, and low patient satisfaction.[2,3] In addition, VKAs have a slow onset of action, and when used for VTE treatment, where the patient is at immediate risk of clots, bridging therapy with injected anticoagulants with a fast onset of action is required.

1980s: Overcoming the drawbacks of unfractionated heparin

The low molecular weight heparins (LMWHs) were developed to overcome some of the drawbacks of unfractionated heparin. One of the mainstays of current treatment, enoxaparin, first emerged in 1987. LMWHs do not require monitoring and have lower risk of HIT,[4] but they must be administered by injection, and can accumulate in patients with kidney impairment.[1]

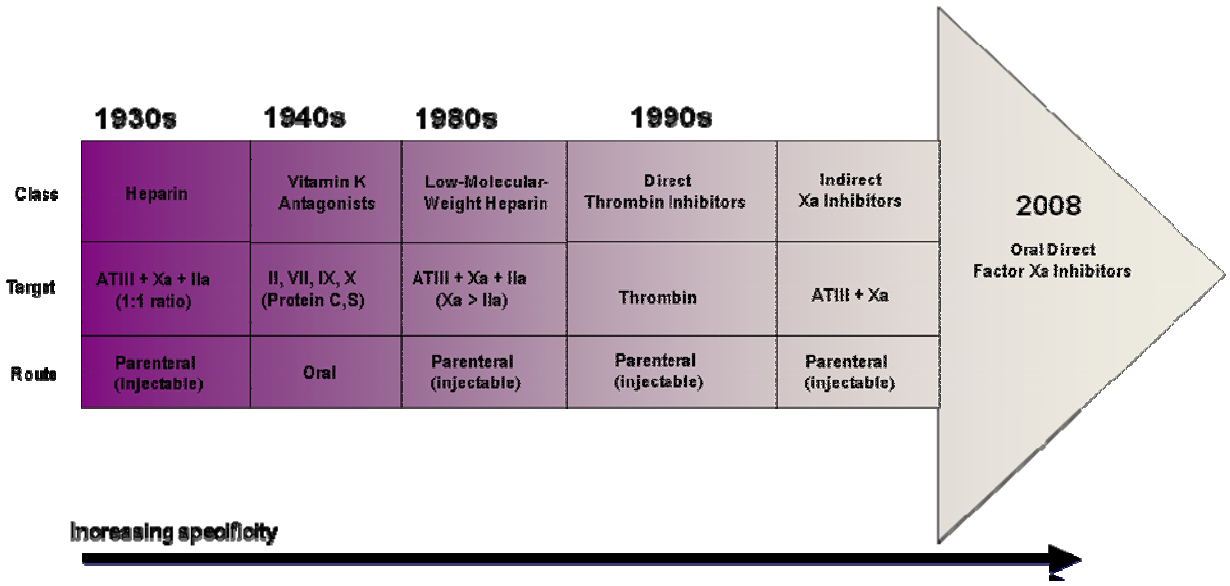
1990s: DTIs and indirect Factor Xa inhibitors developed

Fondaparinux, an indirect Factor Xa inhibitor, has been shown to be effective, but is also administered by injection, which is inconvenient when long-term use is required. Direct thrombin inhibitors (DTIs) were first used in 1990s. DTIs inhibit the action of thrombin, the enzyme that promotes clot formation. Ximelagatran, the first oral DTI, was never approved in the U.S. and withdrawn from the European market in 2006. Dabigatran, a new oral DTI, was introduced in 2008.

2008: Development of the first oral, direct Factor Xa inhibitor

Rivaroxaban is a new, oral anticoagulant in advanced clinical development. It is a direct Factor Xa inhibitor, thought to be the next evolution of oral anticoagulant medicines. Directly inhibiting Factor Xa is thought to be more effective than targeting thrombin. In fact, one molecule of Factor Xa results in the generation of more than 1000 thrombin molecules.[5] Also, regulating the production of thrombin, rather than inhibiting the action of thrombin itself, aims to ensure that the natural clotting process, important for wound healing following surgery, can occur as intended.

The data from three pivotal Phase III trials in VTE prevention in patients undergoing total hip or knee replacement surgery showed superior efficacy of rivaroxaban both in head-to-head comparisons with enoxaparin (RECORD1 & 3) and when comparing extended-duration (35 +/- 4 days) rivaroxaban with short-duration (10-14 days) enoxaparin followed by placebo (RECORD2). In all three trials, both rivaroxaban and enoxaparin had similar rates of major bleeding.



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