About the History of Anticoagulants

Fast facts

- **Anticoagulants have been used for more than 70 years to prevent and treat potentially deadly blood clots**
- **Older compounds, including heparins and vitamin K antagonists (VKAs), have long been the mainstays of treatment. These agents, although effective if managed properly, have significant drawbacks**
- **By targeting Factor Xa at a pivotal stage in the blood-clotting process, Xarelto® (rivaroxaban) inhibits thrombin generation rather than inhibiting the action of thrombin itself**

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 thrombocytopenia (known as HIT, or reduced platelet count) and osteopenia (reduced bone mineral density).[1]

1940s: The first oral anticoagulants

Vitamin K Antagonists (VKAs), such as warfarin and acenocoumarol, were the first oral anticoagulants on the market. They are highly effective, but difficult to manage. For example, these therapies require frequent monitoring and dose adjustment to limit adverse consequences and they have multiple food and drug interactions. These factors, in addition to a 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. When used for VTE treatment, where the patient has a clot at risk of progressing further, 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 a lower risk of HIT,[4] but they must be administered by injection, and can accumulate in patients with kidney impairment.[1]

1990s-2000s: DTIs and indirect Factor Xa inhibitors developed

Fondaparinux, an indirect Factor Xa inhibitor approved in the early 2000s, 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 introduced in the 1990s. DTIs inhibit the action of thrombin, the enzyme that promotes clot formation. Ximelagatran, the first oral DTI, was not approved in the US and was withdrawn from the European market in 2006 primarily due to severe liver injuries in some patients. Dabigatran, a new oral DTI, was introduced in the European Union and other countries in 2008.

2008: The first oral direct Factor Xa inhibitor

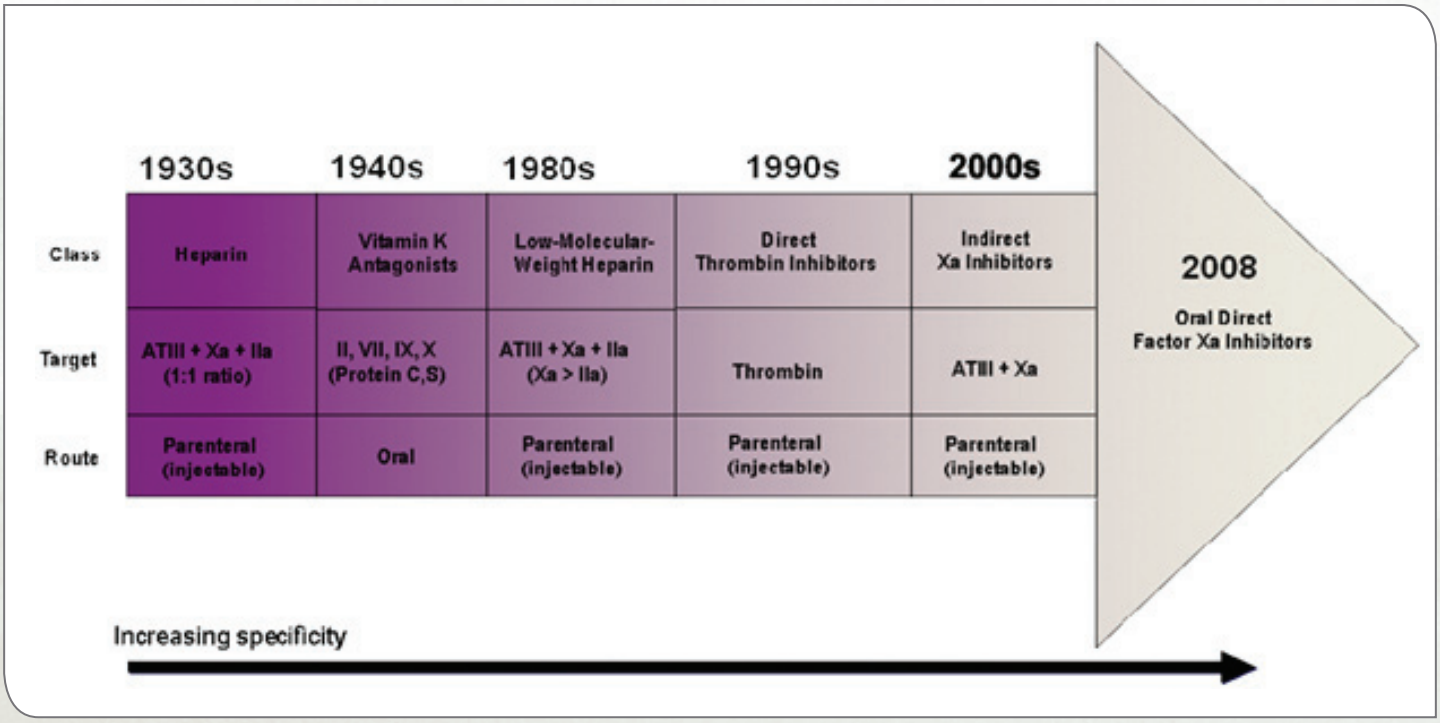
Xarelto® (rivaroxaban), a once-daily, oral direct Factor Xa inhibitor, has been shown to be safe and effective for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

By targeting Factor Xa at a pivotal stage in the blood-clotting process, rivaroxaban inhibits thrombin generation rather than inhibiting the action of thrombin itself. Thrombin is an enzyme in the blood clotting cascade that promotes the formation of blood clots.

Data from four distinct Phase III trials within the RECORD program for VTE prevention following elective (planned) hip or knee replacement surgery showed superior efficacy of rivaroxaban, both in head-to-head comparisons with enoxaparin (RECORD1, 3 and 4) and when comparing

extended-duration (5 weeks) rivaroxaban with short-duration (2 weeks) enoxaparin (RECORD2). In all four trials, 'Xarelto' and enoxaparin had comparable safety profiles, including low rates of major bleeding.[5,6,7,8]

On September 30, 2008, the European Commission granted marketing approval for rivaroxaban for the prevention of VTE in adult patients undergoing elective (planned) hip or knee replacement surgery.



References

1 Hirsh J, Anand S, Halperin JL and Fuster V. Guide to Anticoagulant Therapy: Heparin : A Statement for Healthcare Professionals From the American Heart Association. *Circulation.* 103 (2001);2994-3018

2 Ansell J, Hirsh J, Poller L, et al. The Pharmacology and Management of the Vitamin K Antagonists. *Chest.* 126 (2004);204S-233S

3 Dantas GC, Thompson BV, Manson JA, et al. Patients' perspectives on taking warfarin: qualitative study in family practice. *BMC Family Practice.* 5 (2004);15

4 AG, Turpie. Oral, direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. *Arterioscler Thromb Vasc Biol*. 2007;27(6):1238-47

5 Kakkar AK, Brenner B, Dahl OE et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty; A double-blind, randomised controlled trial. *Lancet*. 2008;372:31-9

6 Lassen MR, Angeno W, Borris LC et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med*. 2008;358:2776-86

7 Turpie AG, Lassen MR, Davidson BL et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomized trial. *Lancet*. 2009;373:1673-80

8 Eriksson BI, Borris LC, Friedman RJ et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Eng J Med* 2008;358:2765-75

To learn more about thrombosis please visit www.thrombosisadviser.com
To learn more about 'Xarelto' please visit www.xarelto.com

Bayer HealthCare
Bayer Schering Pharma

RIVAROXABAN

MEDIA BACKGROUNDER
FOR EX-US AND EX-UK USE ONLY

August 2010