



# The History of Anticoagulants

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## What are Anticoagulants?

Anticoagulants are designed to prevent coagulation (blood clotting). Anticoagulants have been used for more than 70 years to prevent and treat potentially deadly blood clots. However, widely used traditional therapies are associated with significant drawbacks.

## What are the Traditional Anticoagulants?

### ◆ Heparin (first launched in the 1930s)

Heparin (unfractionated) has been available for more than 70 years and is still used for the prevention and treatment of venous thromboembolism (VTE)<sup>1</sup>. It is effective if used correctly and has been the cornerstone of anticoagulation for many decades. However, it is associated with significant drawbacks:

- Heparins require administration by injection or infusion<sup>1</sup>, which can be inconvenient and cause discomfort
- Some patients taking heparin experience a negative reaction known as HIT (heparin-induced thrombocytopenia), which can lead to new or worsening thrombosis<sup>2</sup>

### ◆ Vitamin K Antagonists (VKAs – first launched in the 1940s)

VKAs, such as warfarin and acenocoumarol, were the first oral anticoagulants to be developed. Although they are very effective, they can be difficult to manage<sup>3,4</sup>:

- VKAs have a narrow therapeutic window (meaning there is a small gap between the dose that provides effective anticoagulation and a dose that increases bleeding events or can increase the rate of blood clots)<sup>5</sup>
- They are associated with a slow onset and offset of action<sup>5</sup>
- They also have many food and drug interactions<sup>5</sup>
- As a result, VKAs require regular coagulation monitoring and dose adjustments to maintain the optimal degree of anticoagulation
- These factors may contribute to the frequent underuse of warfarin, especially in elderly patients due to the higher risk of bleeding<sup>6</sup>





◆ **Low molecular weight heparins (LMWHs – first launched in the 1980s)**

LMWHs were developed to overcome some of the drawbacks of unfractionated heparin. One of the mainstays of current treatment, enoxaparin, was first launched in 1987. LMWHs do not require coagulation monitoring and have a lower risk of HIT than unfractionated heparin<sup>1</sup>

However, LMWHs:

- Must be administered by injection, which can be inconvenient and cause discomfort
- Can accumulate in patients with kidney impairment<sup>1</sup>

**What Are the New Oral Anticoagulants?**

New oral anticoagulants hold the promise of overcoming the limitations of traditional anticoagulants, thereby enabling their use to prevent and or treat more venous and arterial thromboembolic (VAT) conditions.

◆ **Indirect Factor Xa Inhibitors (first launched early 2000s)**

Indirect Factor Xa Inhibitors are selective for Factor Xa. Fondaparinux, an indirect Factor Xa inhibitor approved in the early 2000s, has been shown to be effective<sup>7</sup>, but is also administered by injection, which is inconvenient when long term use is required

◆ **Direct Thrombin Inhibitors (DTIs – first launched in 2004)**

DTIs inhibit the action of thrombin, the enzyme that promotes clot formation. Ximelagatran, the first oral DTI, was approved in Europe in 2004 but withdrawn in 2006 due to severe liver injuries in some patients. It was not approved in the U.S. Dabigatran, a new oral DTI, was introduced in 2008

◆ **Direct Factor Xa Inhibitors (first launched in 2008)**

In Europe two oral direct Factor Xa inhibitors have been approved for the prevention of venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery; once-daily Xarelto<sup>®</sup> (rivaroxaban) and twice-daily apixaban. In the U.S., only 'Xarelto' is available, following its approval in July 2011

- Oral direct Factor Xa inhibitors are direct and highly selective inhibitors of Factor Xa, an enzyme which acts at a pivotal stage in the blood-clotting (coagulation) process to prevent clot formation





- 'Xarelto' is currently approved in more than 110 countries worldwide for the prevention of venous thromboembolism (VTE) in adult patients undergoing total elective hip or knee replacement surgery including the U.S., where Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company) holds marketing rights for 'Xarelto'.

In November 2011, 'Xarelto' was also approved by the U.S. Food and Drug Administration (FDA) to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF)

- In September 2011, 'Xarelto' was recommended for European approval by the European Committee for Medicinal Products for Human Use (CHMP) for the prevention of stroke and systemic embolism in adult patients with non-valvular AF, as well as for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults

### Why is Factor Xa Important?

Coagulation occurs via a complex coagulation 'cascade'. Thrombin is an enzyme in the coagulation cascade that promotes the formation of blood clots.

One molecule of Factor Xa catalyses the formation of approximately 1,000 thrombin molecules via what is known as a 'thrombin burst'<sup>8,9</sup>.

Directly targeting and inhibiting Factor Xa can prevent the thrombin burst. Selectivity to Factor Xa has been proven to be clinically meaningful. Studies have demonstrated an increase in the anticoagulant efficacy of heparin-based drugs as their selectivity for Factor Xa increases<sup>7</sup>.

Based on preclinical and clinical trial data published to date, direct Factor Xa inhibitors, such as 'Xarelto', have the potential to advance the field of anticoagulant therapy. 'Xarelto' is a synthetic small molecule that selectively targets Factor Xa. By targeting Factor Xa at a pivotal stage in the coagulation cascade, 'Xarelto' inhibits thrombin generation rather than inhibiting the action of thrombin itself.





## References

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## About Rivaroxaban (Xarelto®)

Rivaroxaban is an oral anticoagulant that was discovered in Bayer HealthCare's Wuppertal laboratories in Germany, and is being jointly developed by Bayer HealthCare and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. It has a rapid onset of action with a predictable dose response and high bioavailability, no requirement for routine coagulation monitoring, and a limited potential for food and drug interactions.

Rivaroxaban is marketed under the brand name Xarelto® for VTE prevention in adult patients following elective hip or knee replacement surgery, and it is the only oral anticoagulant that has consistently demonstrated superior efficacy over enoxaparin in this indication. Rivaroxaban is approved in more than 110 countries worldwide and marketed outside the U.S. by Bayer HealthCare in this indication.

In the U.S., where rivaroxaban has been available since July 2011 for VTE prevention in adult patients following elective hip or knee replacement surgery, Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company) holds marketing rights. The Bayer HealthCare sales force is supporting Janssen Pharmaceuticals, Inc. in designated hospital accounts. On November 4, Xarelto® received further marketing approval in the U.S. for the prevention of stroke in patients with Atrial Fibrillation.

The extensive clinical trial programme supporting rivaroxaban makes it the most studied and widely published oral, direct Factor Xa inhibitor. The studies, reported and ongoing, involve over 75,000 patients for the prevention and treatment of venous and arterial thromboembolic (VAT) disorders across a broad range of acute and chronic conditions, including stroke prevention in patients with Atrial Fibrillation, DVT treatment and the prevention of recurrent DVT or PE, and the secondary prevention of Acute Coronary Syndrome.

**To learn more about thrombosis, please visit [www.thrombosisadviser.com](http://www.thrombosisadviser.com)  
To learn more about 'Xarelto' please visit [www.xarelto.com](http://www.xarelto.com)**

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