



# 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 an adverse 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 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 also 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 Novel Oral Anticoagulants?**

**Novel oral anticoagulants** hold the promise of overcoming the limitations of traditional anticoagulants 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 damage in some patients. It was not approved in the U.S. Another oral DTI, dabigatran, was approved in Europe in 2008 for the prevention of venous thromboembolism in patients undergoing hip or knee replacement.

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

Oral direct Factor Xa inhibitors are highly selective inhibitors of Factor Xa, an enzyme which acts at a pivotal stage in the blood-clotting (coagulation) process to prevent clot formation. In 2008, Xarelto<sup>®</sup> (rivaroxaban) became the first Factor Xa to be approved for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. In 2011, apixaban was also approved for these patients. Since then, 'Xarelto' has been approved to protect patients from blood clots across more venous and arterial thromboembolic diseases than other novel oral anticoagulants





## 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>8</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', protects against blood clots by selectively targeting Factor Xa, the pivotal point in the coagulation process. By targeting Factor Xa, 'Xarelto' inhibits thrombin generation rather than inhibiting the action of thrombin itself.

## References

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**RIVAROXABAN**



## About Xarelto® (Rivaroxaban)

Rivaroxaban is the most broadly indicated novel oral anticoagulant and is marketed under the brand name Xarelto®. To date, Xarelto has been approved for use in the following venous arterial thromboembolic (VAT) indications:

- The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors in more than 70 countries worldwide
- The treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) in adults in more than 70 countries worldwide
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery in more than 120 countries worldwide

Since the first approval of Xarelto in 2008 in the orthopaedic setting, more than two and a half million patients worldwide have received Xarelto in daily clinical practice in this indication alone.

Rivaroxaban was discovered by Bayer HealthCare, and is being jointly developed with Janssen Research & Development, LLC. Xarelto is marketed outside the U.S. by Bayer HealthCare and in the U.S. by Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company).

Anticoagulant medicines are potent therapies used to prevent or treat serious illnesses and potentially life threatening conditions. Before initiating therapy with anticoagulant medicines, physicians should carefully assess the benefit and risk for the individual patient.

Responsible use of Xarelto is a high priority for Bayer, and the company has developed a [Prescribers Guide](#) for physicians and a [Xarelto Patient Card](#) for patients to support best practices. To learn more, please visit: <https://prescribe.xarelto.com>.

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