The History of Anticoagulants

The first line of defence against the consequences of a blood clot, including deep vein thrombosis, pulmonary embolism, stroke arising from atrial fibrillation, and acute coronary syndrome, is an anticoagulant. Anticoagulants have been used for more than 70 years to prevent and treat these potentially deadly blood clots. However, widely used traditional therapies are associated with significant drawbacks.

Traditional Anticoagulants

1930s

Heparin (Unfractionated)

Heparin (unfractionated) is still used for the prevention and treatment of venous thromboembolism (VTE)[1] and is effective if used correctly. However:

- Heparins require administration by injection or infusion[1], which can be inconvenient and cause discomfort
- Some patients experience an adverse reaction known as HIT (heparin-induced thrombocytopenia)[2]

1940s

Vitamin K Antagonists (VKAs)

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[3,4]:

- VKAs have a narrow therapeutic window and require regular monitoring[5]
- They are associated with a slow onset and offset of action[5]
- They have many food and drug interactions[5]

1980s

Low Molecular Weight Heparins (LMWHs)

LMWHs were developed to overcome some of the drawbacks of unfractionated heparin[1]. However:

- LMWHs must still be administered by injection
- Can also accumulate in patients with kidney impairment[1]

Novel Oral Anticoagulants (OACs) can overcome the limitations of traditional anticoagulants to prevent and or treat venous and arterial thromboembolic (VAT) conditions

Novel Oral Anticoagulants (OACs)

2000s

Indirect Factor Xa Inhibitors

Indirect Factor Xa Inhibitors are selective for Factor Xa but require antithrombin (ATIII) molecules to work.

- **Fondaparinux** approved in the early 2000s

Fondaparinux has been shown to be effective[6], but is also administered by injection, which is inconvenient when long term use is required

Direct Thrombin Inhibitors (DTIs)

DTIs inhibit the action of thrombin, the enzyme that promotes clot formation.

- **Ximelagatran:**
  - Approved in Europe in 2004
  - Withdrawn in 2006 due to severe liver damage in some patients
- **Dabigatran** approved in Europe in 2008 for the prevention of VTE in patients undergoing hip or knee replacement

Direct Factor Xa Inhibitors

Highly selective inhibitors of Factor Xa.

- **Xarelto® (rivaroxaban)** became the first Direct Factor Xa Inhibitor to be approved for the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery in 2008. Since then, 'Xarelto' has been approved to protect patients across more VAT diseases than other novel oral anticoagulants
- **Apixaban** approved in 2011

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.

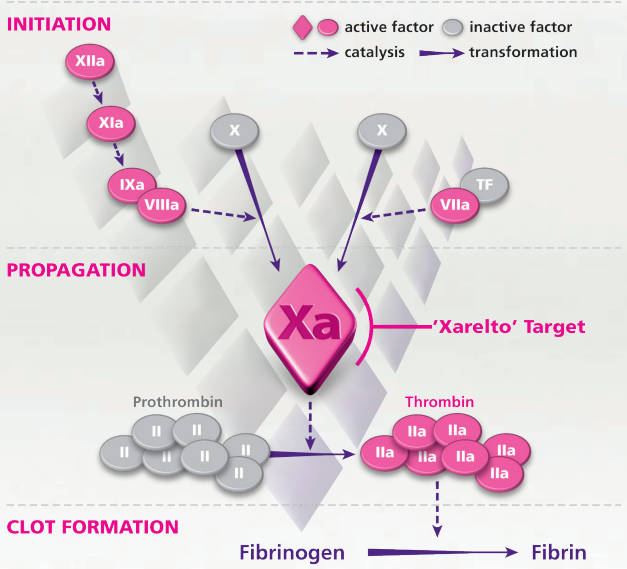
One molecule of Factor Xa catalyses the formation of approximately 1,000 thrombin molecules via what is known as a 'thrombin burst'[7,8].

Directly targeting and inhibiting Factor Xa prevents 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[7].

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 and directly 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.

Targeting Factor Xa to Inhibit Thrombin Generation



The History of Anticoagulants continued...

About 'Xarelto'

Rivaroxaban is the most broadly indicated novel oral anticoagulant and is marketed under the brand name Xarelto®. To date, 'Xarelto' is approved for five indications across seven distinct areas of use, consistently protecting patients across more venous and arterial thromboembolic (VAT) conditions than any other novel OAC:

- The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors
- The treatment of deep vein thrombosis (DVT) in adults
- The treatment of pulmonary embolism (PE) in adults
- The prevention of recurrent DVT and PE in adults
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip replacement surgery
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective knee replacement surgery
- The prevention of atherothrombotic events (cardiovascular death, heart attack or stroke) after an Acute Coronary Syndrome in adult patients with elevated cardiac biomarkers when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus a thienopyridine (clopidogrel or ticlopidine)

Whilst licences may differ from country to country, across all indications 'Xarelto' is approved in more than 120 countries.

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 very high priority for Bayer, and the company has developed a Prescribers Guide for physicians and a 'Xarelto' Patient Card for patients to support best practice. To learn more, please visit: https://prescribe.xarelto.com.

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

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