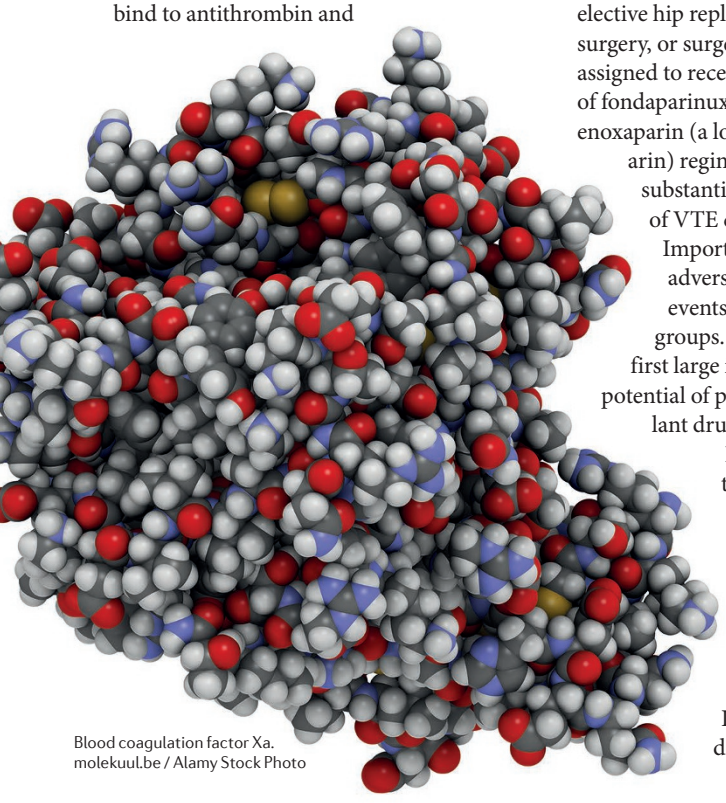
MILESTONE 8

Targeting the Xa factor

After the discovery in the 1960s that heparin and vitamin K antagonists (VKAs) were effective for the treatment of acute pulmonary embolism (MILESTONE 3), these agents were the main anticoagulant drugs for decades. However, heparin and VKAs must be administered in hospital, because they require blood monitoring and dose adjustments. A low-molecular-weight heparin that could be given to out-patients was developed (MILESTONE 7), but even this drug must be administered subcutaneously. Therefore, improved anticoagulant therapeutic agents were still needed. In 2002, Turpie and colleagues published a meta-analysis of four studies that showed the anticoagulant potential of a new class of synthetic, pentasaccharide antithrombotic agents that specifically target factor Xa.

In the coagulation cascade, prothrombin is converted to the key clotting factor thrombin by factor Xa; this conversion is inhibited by antithrombin, which targets both factor Xa and thrombin. Heparin enhances the capacity of antithrombin to inactivate thrombin and factor Xa, whereas VKAs reduce the clotting activity of key factors downstream of the vitamin K pathway. Fondaparinux belonged to a new class of synthetic pentasaccharides that bind to antithrombin and specifically inhibit factor Xa without directly acting on thrombin. This specific inactivation of factor Xa inhibits the generation of thrombin.



Blood coagulation factor Xa.
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> “As a result of these landmark studies … clinicians today have a safe and effective class of anticoagulant drugs that do not require dose adjustment”

A major complication of orthopaedic surgery is the development of venous thromboembolism (VTE). The first dose-ranging study that Turpie and colleagues performed in 2001 in patients undergoing surgery established that a single dose of fondaparinux could be given daily, without the need for dose monitoring. Subsequently, in a meta-analysis of 7,344 patients enrolled across four randomized, double-blind, phase III clinical trials, Turpie *et al.* investigated the efficacy of fondaparinux for the prevention of VTE after major orthopaedic surgery. Patients undergoing elective hip replacement, elective major knee surgery, or surgery for hip fracture were assigned to receive either a once-daily dose of fondaparinux sodium or an approved enoxaparin (a low-molecular-weight heparin) regimen. Of note, fondaparinux substantially reduced the incidence of VTE compared with enoxaparin. Importantly, the incidence of adverse clinically relevant bleeding events was similar across both groups. This meta-analysis was the first large investigation to show the potential of pentasaccharides as anticoagulant drugs in humans.

In the early 2000s, unfractionated heparin was the standard treatment for pulmonary embolism, which is a life-threatening condition that contributes to up to 10% of deaths among patients in hospital. In 2003, the Matisse Investigators published details of an open-label trial, which enrolled 2,213 patients with acute symptomatic pulmonary embolism and randomly assigned patients to the standard heparin treatment or treatment with fondaparinux. A once-daily, subcutaneously administered dose of fondaparinux was shown to be as safe and effective as unfractionated heparin in the treatment of pulmonary embolism. This finding was important because, unlike heparin, fondaparinux can be administered without monitoring. In 2004, Büller *et al.* published the results of a randomized, double-blind study of 2,205 patients with deep-vein thrombosis from 154 centres; these results demonstrated that fondaparinux is as safe and effective as enoxaparin for the treatment of patients with this condition.

In patients with acute coronary syndromes, a combination of anticoagulants, antiplatelet agents, and invasive coronary procedures used to be the standard approach to reduce the risk of ischaemic coronary events. However, these treatments also increase the risk of bleeding. In 2006, the OASIS-5 investigators assessed whether treatment with fondaparinux could reduce the risk of ischaemic events without increasing bleeding. A total of 20,078 patients with acute coronary syndromes were randomly assigned to treatment with fondaparinux or enoxaparin. Remarkably, treatment with fondaparinux substantially reduced the risk of major bleeding and improved long-term morbidity and mortality, in addition to providing a similar level of protection from ischaemic events to treatment with enoxaparin.

As a result of these landmark studies, which showed unequivocally that factor Xa is a good target for antithrombotic therapy and that fondaparinux is effective in targeting factor Xa, clinicians today have a safe and effective class of anticoagulant drugs that do not require dose adjustment.

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FURTHER READING Stashenko, G. J. & Tapson, V. T. Prevention of venous thromboembolism in medical patients and outpatients. *Nat. Rev. Cardiol.* **6**, 356–363 (2009)