



The aim of a *Nature Milestone* is to describe the noteworthy discoveries that have advanced and defined a field of research or clinical practice. This *Milestone* plots the major developments that have furthered our scientific understanding of anticoagulants and the use of these drugs for medical therapy. This special supplement contains [14 Milestone articles](#) written by *Nature Reviews* editors, each highlighting an important breakthrough in its historical context and discussing its long-term influence on medical practice.

The Milestone articles begin just over 100 years ago, with the discovery and clinical application of heparin and warfarin. These drugs enabled physicians to prevent and treat venous thromboembolism and are still in routine use today. During the 1960s and 1970s, some of the earliest randomized, controlled clinical trials were performed to provide high-quality data supporting the efficacy of anticoagulant therapy within various medical settings. Nevertheless, these drugs have notable shortcomings, and the international normalized ratio was introduced to ensure that patients taking warfarin remained in the therapeutic range. The synthesis of low-molecular-weight heparins allowed out-of-hospital treatment of thrombosis, which was more convenient for patients than in-hospital care.

Research continued into drugs with a more specific target, yielding fondaparinux (a pentasaccharide anticoagulant targeting factor Xa) and ximelagatran (an oral direct thrombin inhibitor). Of note, these drugs could be given in fixed doses, without the need for routine monitoring, and they set the stage for the latest generation of anticoagulants, the non-vitamin K antagonist oral anticoagulants (NOACs). NOACs have revolutionized the practice of anticoagulation, and their clinical use is poised to be facilitated by the introduction of various reversal agents. Notwithstanding the huge progress that has been made, research and development continues into refining the duration of anticoagulant therapy, balancing the antithrombotic benefits with the associated risks of bleeding, exploring combined therapy with antiplatelet drugs to optimize the prevention of clotting, and resolving limitations such as preventing thrombosis induced by medical devices.

The Milestone articles are accompanied in this supplement by selected articles from the Nature Research archive, including a new Review on reversal agents for the NOACs. Online, the Milestones are presented on an interactive [Timeline](#), with animations, other multimedia content, and a much larger collection of reference articles. The selection of what to cover in this *Nature Milestone* could never be completely comprehensive, and the decision on what to include was made by the editors, but we are very grateful for the advice of our expert advisers who worked with us on this project. Finally, we acknowledge financial support from [Portola Pharmaceuticals, Inc.](#) As always, Springer Nature takes responsibility for the editorial content.

Gregory B. Lim, Chief Editor, *Nature Reviews Cardiology*