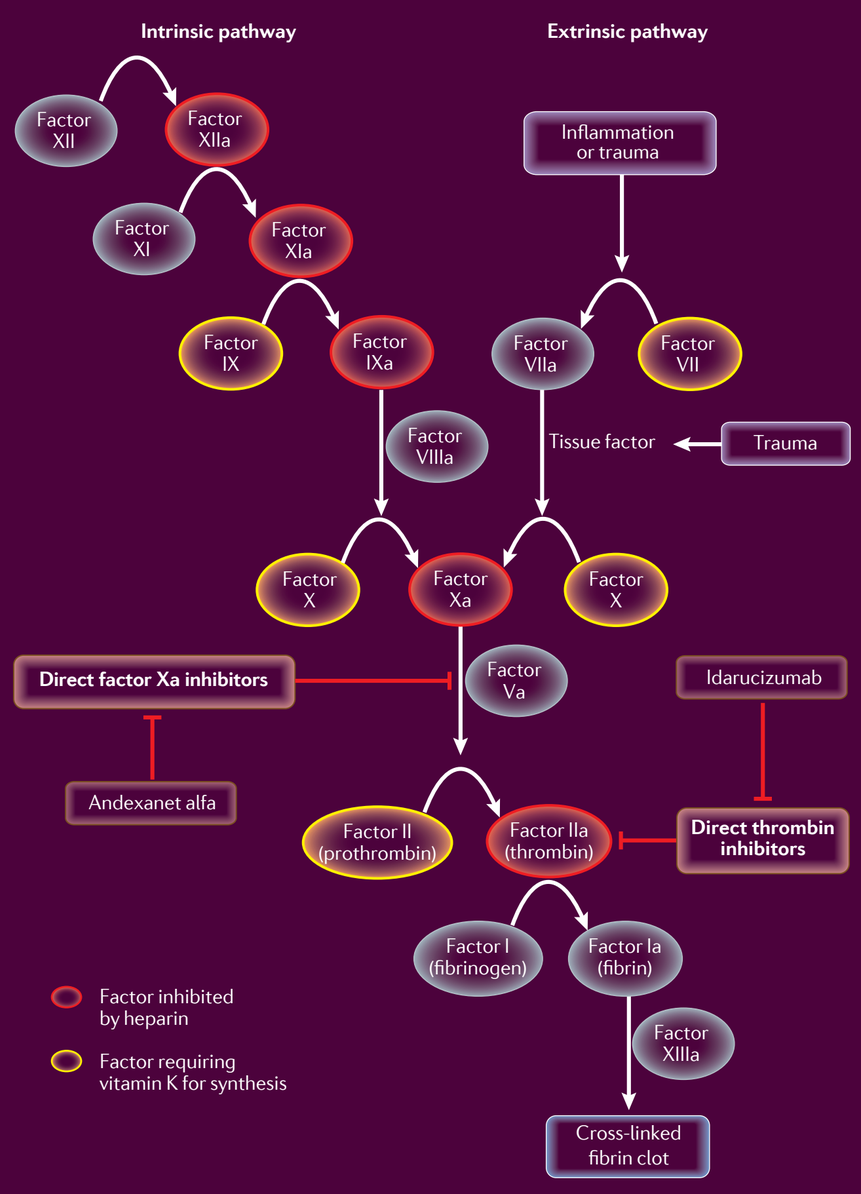
nature REVIEWS
CARDIOLOGY

Anticoagulant drugs

Eduardo Ramacciotti and Jawed Fareed

Anticoagulant drugs are used to prevent and treat venous and arterial thrombosis—cardiovascular diseases that combined are the leading cause of death in the world. Heparin, the first clinically available anticoagulant drug, was serendipitously discovered by a medical student 100 years ago, and is still widely used. Other parenteral anticoagulants developed after the discovery of heparin, such as LMWHs and synthetic pentasaccharides, are also important agents in the management of thrombosis. Warfarin, the first oral anticoagulant, is a vitamin K antagonist that was initially developed as a rat poison in the 1950s. Owing to drawbacks of warfarin (such as risk of bleeding, drug–drug interactions, need for periodic monitoring, and slow onset of action), NOACs were developed, and their use is increasing. In 2010, dabigatran, a direct thrombin inhibitor, was the first NOAC approved for clinical use in the USA. Direct factor Xa inhibitors, such as apixaban, edoxaban, and rivaroxaban, are also widely studied and have been approved for various indications. However, NOACs also have some shortcomings including monitoring issues, pharmacodynamic differences, cost, bleeding complications, and interactions with other drugs. The development and approval of specific reversal agents for these compounds (idarucizumab for dabigatran, and andexanet alfa for anti-factor Xa agents) are underway, which is likely to revolutionize the clinical practice of oral anticoagulation.

Coagulation cascade



Unfractionated heparin

In 1916, Jay McLean serendipitously discovered heparin while working as a medical student in the physiology laboratory of William Henry Howell at Johns Hopkins University Hospital in Baltimore, MD, USA. McLean was using dog liver in a search for a procoagulant—not an anticoagulant—substance. Howell continued the research and named the natural, complex polysaccharide 'heparin'. Therapeutic (unfractionated) heparin is a biological product isolated from mammalian tissues, most commonly porcine intestinal mucosa or bovine lung. Heparin is synthesized in these tissues and in mast cells as part of a high-molecular-weight proteoglycan. The anticoagulant effect of heparin is primarily attributed to inhibition of the serine protease coagulation factors mediated through heparin binding to plasma proteins known as serine protease inhibitors (serpins). The most important anticoagulant activities are the inhibition of the coagulation factors thrombin and factor Xa by heparin complexed to antithrombin.

Low-molecular-weight heparins

LMWHs (approximately 5 kDa) are prepared by controlled depolymerization of heparin. In addition to reducing molecular weight, depolymerization reduces the number of antithrombin binding sites on the heparin chains and alters the biological activity of the drug. Whereas unfractionated heparin has equal potency against thrombin and factor Xa, LMWHs have much higher anti-factor Xa activity. LMWHs have been the drugs of choice for prophylaxis and treatment of thrombosis owing to their high bioavailability, long duration of action, and low need for monitoring.

Pentasaccharide

Fondaparinux was the first of a new class of antithrombotic agents distinct from heparin and LMWHs. The drug is a synthetic pentasaccharide that mimics the active site of heparin that binds to antithrombin. Fondaparinux has only factor Xa inhibitory activity, which in turn inhibits thrombin generation. Fondaparinux inhibits factor Xa indirectly by combining with the naturally occurring cofactor antithrombin; this complex then effectively binds with the active site of factor Xa. In contrast to heparin and LMWH, plasma anti-factor Xa activity corresponds directly to levels of fondaparinux. Tissue factor pathway inhibitor is not released. Bioavailability is almost 100% via the subcutaneous route, onset of action is rapid, half-life is prolonged via both intravenous and subcutaneous dosing regimens (14–20 h), and the drug is not metabolized before renal excretion.

New targets for anticoagulation

Factor XI inhibitors

Impairment of intrinsic coagulation by selective inhibition of factor XI leaves the extrinsic and common pathways of coagulation intact, making factor XI an attractive drug target. Moreover, human deficiency of factor XI results in a milder bleeding disorder compared with other coagulation-factor deficiencies, and an elevated level of factor XI is a risk factor for thromboembolic disease. An antisense oligonucleotide (ISIS-FXI$_{Rx}$) that inhibits factor XI as well as other synthetic anti-factor XIa agents are in phase II clinical trials.[5]

Factor XII inhibitors

Inhibition of factor XII activity is an attractive approach for the treatment and prevention of thrombotic diseases. However, the few existing factor XII inhibitors have low selectivity; new factor XIIa inhibitors are in the early stages of development.

Non-vitamin K oral anticoagulants

Direct thrombin inhibitors

Dabigatran, a direct thrombin (factor IIa) inhibitor, was the first NOAC to be approved for clinical use in the USA.[1] Dabigatran etexilate is a low-molecular-weight prodrug with no pharmacological activity. After oral administration, dabigatran etexilate is converted to its active form, dabigatran—a potent, competitive, and reversible direct inhibitor of the active site of thrombin, the final effector in blood coagulation. By inhibiting thrombin, dabigatran prevents the conversion of fibrinogen to fibrin, positive feedback amplification of coagulation activation, crosslinking of fibrin monomers, platelet activation, and inhibition of fibrinolysis.

Direct factor Xa inhibitors

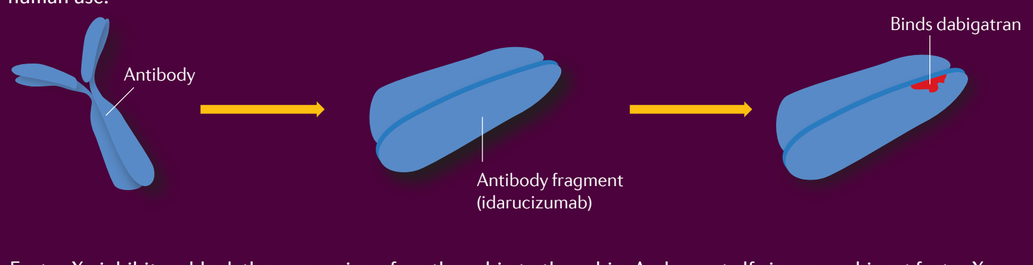
Apixaban, edoxaban, and rivaroxaban are orally active, direct, selective inhibitors of coagulation factor Xa. These drugs reversibly bind to the active site of factor Xa and exert anticoagulant and antithrombotic effects by diminishing the conversion of prothrombin to thrombin. These compounds directly inhibit free and clot-bound factor Xa. As the common mediator of both extrinsic and intrinsic activation of coagulation, factor Xa is the sole physiological mediator of thrombin formation. Thrombin, through its actions on fibrin formation and platelet activation, is an important mediator of thrombosis in both venous and arterial circulation. Inhibition of thrombin generation, therefore, produces antithrombotic effects in a variety of pathological conditions.

Vitamin K antagonists

Warfarin and other vitamin K antagonists block the cyclic interconversion of vitamin K and vitamin K epoxide. Vitamin K is a cofactor for the carboxylation of various 'vitamin K-dependent' proteins, including the coagulation factors II, VII, IX, and X. By inhibiting the vitamin K conversion cycle, warfarin causes the hepatic formation of partially decarboxylated proteins with reduced activity in the coagulation cascade. Food, genetic polymorphisms, medications, and various clinical conditions that alter levels of vitamin K in the blood or interfere with the activity or metabolism of warfarin can alter the anticoagulant effects of warfarin. Warfarin is still widely used because of its low cost, but has been progressively replaced by NOACs.

Reversal agents for NOACs

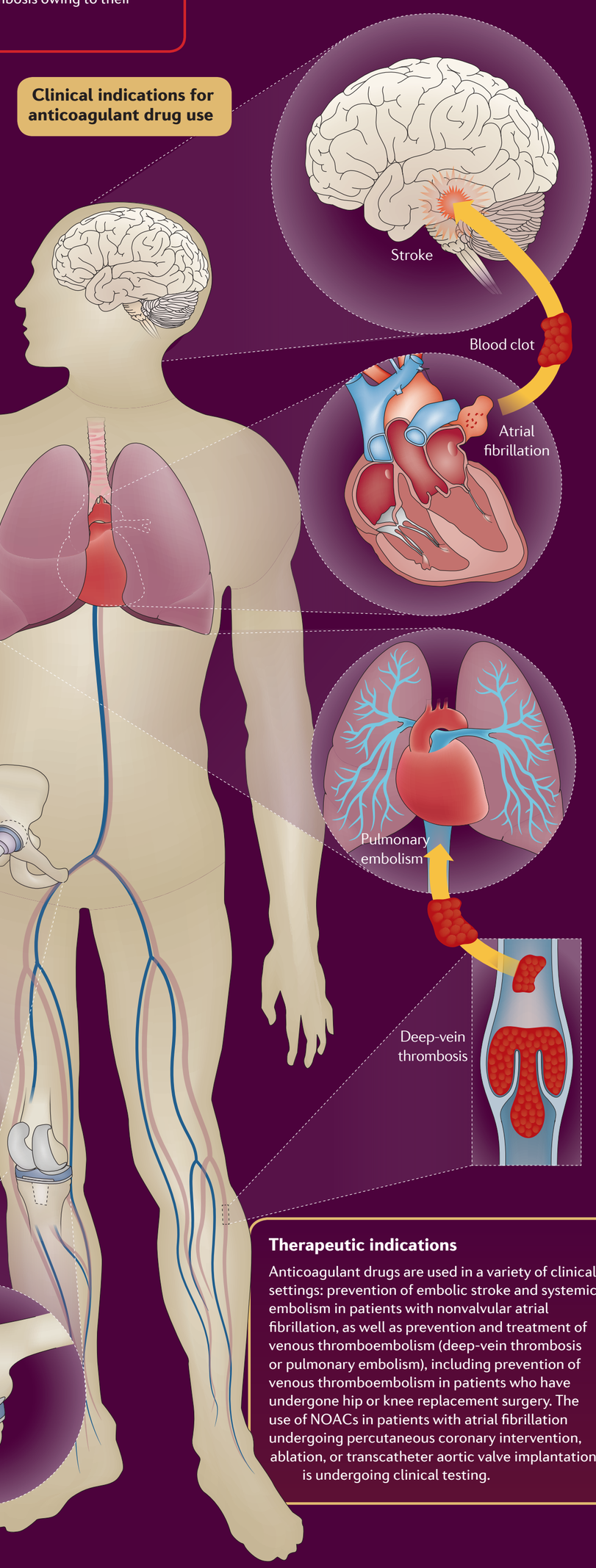
Antidotes to reverse the effects of NOACs are undergoing clinical testing.
A humanized monoclonal antibody fragment (idarucizumab) against dabigatran has been approved by the FDA for human use.[2,3]



Factor Xa inhibitors block the conversion of prothrombin to thrombin. Andexanet alfa is a recombinant factor Xa derivative that binds to factor Xa inhibitors, but lacks catalytic and membrane-binding activity.

A small-molecule antidote for edoxaban, PER977, is also undergoing clinical testing.

Clinical indications for anticoagulant drug use



Therapeutic indications

Anticoagulant drugs are used in a variety of clinical settings: prevention of embolic stroke and systemic embolism in patients with nonvalvular atrial fibrillation, as well as prevention and treatment of venous thromboembolism (deep-vein thrombosis or pulmonary embolism), including prevention of venous thromboembolism in patients who have undergone hip or knee replacement surgery. The use of NOACs in patients with atrial fibrillation undergoing percutaneous coronary intervention, ablation, or transcatheter aortic valve implantation is undergoing clinical testing.

References

1. Connolly, S. J. *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **361**, 1139–1151 (2009).
2. Pollack, C. V. Jr *et al.* Idarucizumab for dabigatran reversal. *N. Engl. J. Med.* **373**, 511–520 (2015).
3. U.S. Food and Drug Administration. *FDA approves Praxbind, the first reversal agent for the anticoagulant Pradaxa* [online], http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm467300.htm (2015).
4. Siegal, D. M. *et al.* Andexanet alfa for the reversal of factor Xa inhibitor activity. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1510991.
5. Büller, H. R. *et al.* Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N. Engl. J. Med.* **372**, 232–240 (2015).

Abbreviations

LMWH low-molecular-weight heparin
NOAC non-vitamin K oral anticoagulant

Further reading

Baber, U., Mastoris, I. & Mehran, R. Balancing ischaemia and bleeding risks with novel oral anticoagulants. *Nat. Rev. Cardiol.* **11**, 693–703 (2014).

Affiliations and competing interests

Department of Vascular Surgery, Albert Einstein Israeli Hospital, Rua das Palmeiras 32, Santo Andre-SP, 09080-160, Brazil (E.R.). The Hemostasis and Thrombosis Research Laboratories, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153, USA (E.R., J.F.).

The authors declare no competing interests.

Edited by Gregory B. S. Lim; designed by Tom Wilson.
The poster content is peer-reviewed and editorially independent.
© 2015 Nature Publishing Group. http://www.nature.com/nrcardio/posters/anticoagulation