nature REVIEWS
DRUG DISCOVERY

The 50-year quest to replace warfarin

Jeffrey Weitz

Anticoagulants are used for the prevention and treatment of venous and arterial thrombosis, the leading cause of morbidity and mortality in the Western world. Warfarin — the prototype oral anticoagulant — is a vitamin K antagonist that has been in clinical use since the 1950s. Although they are effective, vitamin K antagonists have several drawbacks, the most notable of which is the propensity to cause bleeding. Other limitations include a slow onset of action, interactions with multiple other drugs and interpatient variability in drug response. As a result, regular monitoring is required to check that the appropriate level of anticoagulation is reached and maintained in patients receiving warfarin. Consequently, warfarin is underused, and the level of anticoagulation is often suboptimal even when it is administered. These drawbacks highlight the need for new oral anticoagulants. The first drug to be approved — in 2010 — as an alternative to warfarin was dabigatran, a direct thrombin inhibitor. Clinical studies of the direct factor Xa inhibitors rivaroxaban and apixaban have been completed and could form the basis for regulatory approval as alternatives to warfarin.

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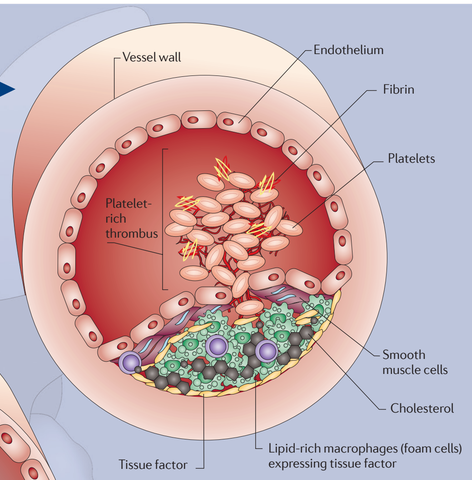
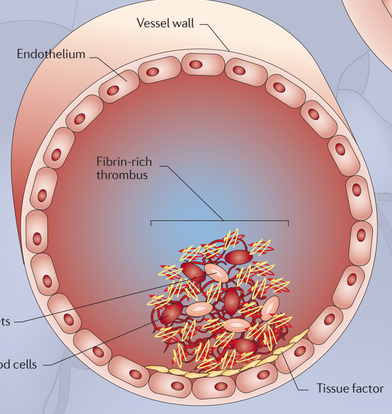
Venous and arterial thrombosis

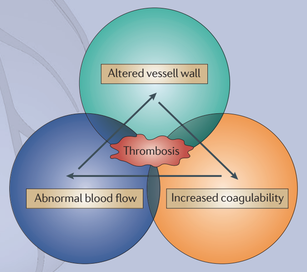
Arterial thrombosis. The primary trigger of this is rupture of an atherosclerotic plaque, which exposes material that activates platelets and triggers coagulation. The coagulation cascade (see far right) is initiated by tissue factor, which is expressed by lipid-rich macrophages that are exposed in the core of the ruptured plaque. Activated platelets clump together to form aggregates that are held together by fibrin. The resultant platelet-rich thrombus can then occlude the artery and block blood flow.



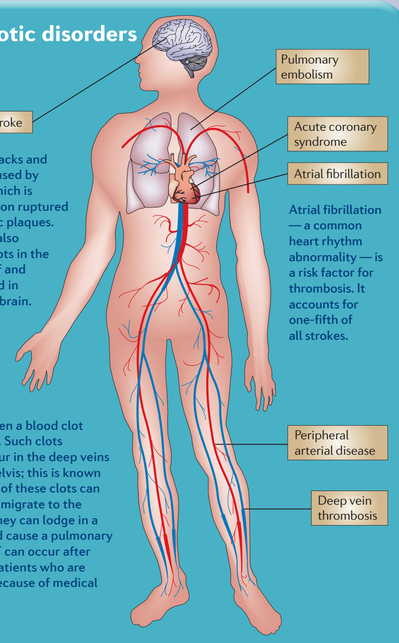


Venous thrombosis. Venous thrombi are rich in fibrin and contain fewer platelets than arterial thrombi. They form in areas where blood flow is sluggish. Such altered blood flow activates the endothelium, which triggers coagulation and subsequent fibrin generation.

Virchow's triad. Named after the German physician Rudolf Virchow (1821–1902), this triad describes the three conditions that contribute to thrombosis.



Thrombotic disorders



Most heart attacks and strokes are caused by thrombosis, which is superimposed on ruptured atherosclerotic plaques.

Strokes can also occur when clots in the heart break off and become lodged in arteries in the brain.

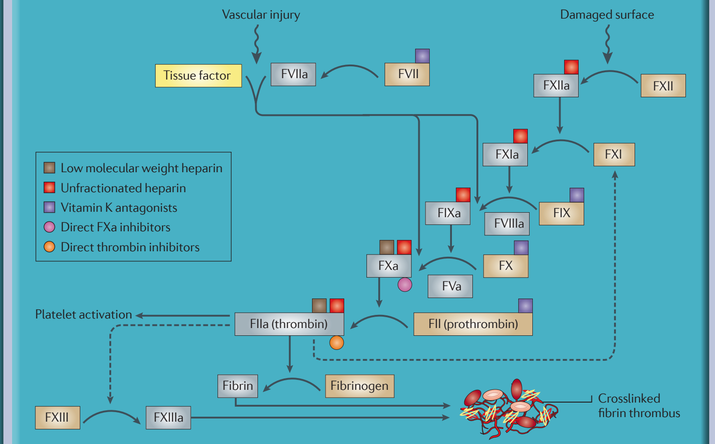
Atrial fibrillation — a common heart rhythm abnormality — is a risk factor for thrombosis. It accounts for one-fifth of all strokes.

VTE occurs when a blood clot forms in a vein. Such clots commonly occur in the deep veins of the leg or pelvis; this is known as a DVT. Parts of these clots can break free and migrate to the lungs, where they can lodge in a lung artery and cause a pulmonary embolism. DVT can occur after surgery or in patients who are immobilized because of medical illnesses.

For over 50 years, anticoagulants such as warfarin and other vitamin K antagonists have been used to prevent or treat many of these disorders. The new oral anticoagulants can overcome many of the limitations of vitamin K antagonists. By simplifying long-term anticoagulation therapy, more patients could be treated with the new agents. In addition, because novel oral anticoagulants produce a more predictable level of anticoagulation than warfarin, they are easier to administer and are potentially safer and more efficacious.

The coagulation cascade

This is classically divided into three pathways. The extrinsic pathway (also known as the tissue factor pathway) initiates coagulation. This pathway is triggered when vessel injury exposes tissue factor, or when endothelial cell activation results in the tethering of tissue factor-bearing monocytes or cell fragments known as microparticles. Tissue factor binds to activated factor VII (FVIIa) and this complex then activates FX and FIX.



The intrinsic pathway (also known as the contact pathway) amplifies FX activation. In addition to direct activation of FX, the tissue factor–FVIIa complex also activates FIX. FIXa, together with its cofactor FVIIIa, then activates FX to generate additional FXa. Both of these pathways converge at the final common pathway. FXa, together with its cofactor FVa, forms prothrombinase, a complex that efficiently activates prothrombin (FII) to generate thrombin (FIIa). Thrombin converts fibrinogen, a soluble protein, into fibrin monomers that polymerize to form fibrin strands. FXIIIa crosslinks the fibrin strands to stabilize the thrombus.

This panel shows the target points of various anticoagulants. Of note, vitamin K antagonists — such as warfarin — target multiple factors, as do the heparins (unfractionated heparin and LMWH, which are given by injection when an immediate anticoagulant effect is needed). By contrast, the new anticoagulants specifically target either FXa or thrombin.

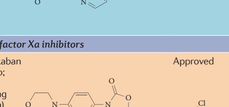
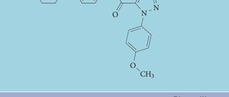
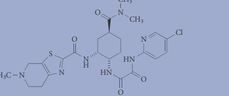
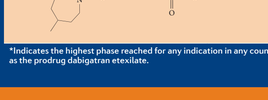
Comparative pharmacology of new oral anticoagulants compared to warfarin

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Prodrug	No	Yes	No	No	No
Bioavailability	Over 90%	6%	80%	60%	50%
Dosing	Once daily	Once or twice daily	Once or twice daily	Twice daily	Once daily
Half-life	36–42 hours	12–14 hours	7–11 hours	12 hours	9–11 hours
Renal excretion	None	80%	66% (33% unchanged and 33% as inactive metabolites)	25%	35%
Coagulation monitoring	Yes	No	No	No	No
Drug–drug interactions	Numerous	P-gp	CYP3A4 and P-gp	CYP3A4	CYP3A4 and P-gp
Antidote(s)	Vitamin K, plasma, prothrombin concentrates	None	None	None	None

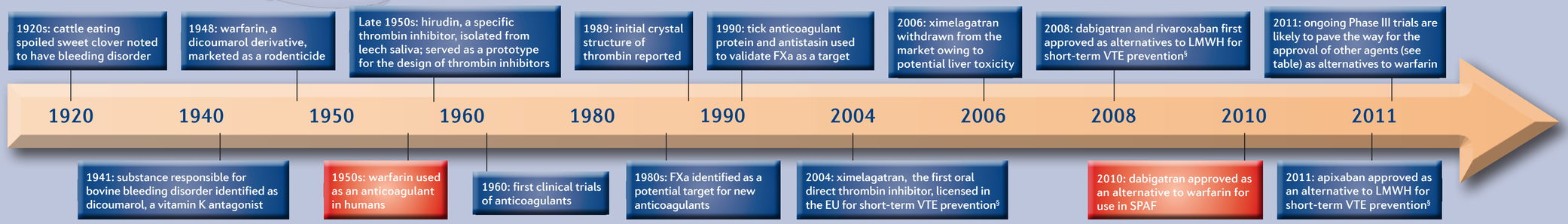
Advantages of new oral anticoagulants and their clinical implications

Advantage	Clinical implications
Rapid onset of action	No need for bridging therapy
Predictable anticoagulant effect	No need for routine coagulation monitoring
Specific coagulation enzyme targeted	Low risk of off-target adverse effects
Low potential for food interactions	No dietary precautions needed
Low potential for drug interactions	Few drug restrictions

Oral anticoagulants in Phase III clinical trials and beyond

Drug	Structure	Highest phase*	Indications (acronym of key Phase III trials)
Direct thrombin inhibitors			
Dabigatran‡ (Pradaxa; Boehringer Ingelheim)		Approved	• VTE prevention (RE-NOVATE I and II; RE-MODEL; RE-MOBILIZE) • VTE treatment (RE-COVER I and II; RE-MEDY; RE-SONATE) • SPAF (RE-LY; RELY-ABLE)
Direct factor Xa inhibitors			
Rivaroxaban (Xarelto; Bayer Schering Pharma)		Approved	• VTE prevention (RECORD1–4) • VTE treatment (EINSTEIN-DVT; EINSTEIN-PE; EINSTEIN-EXT) • SPAF (J-ROCKET AF; ROCKET-AF) • ACS (ATLAS-TIMI-51)
Apixaban (Eliquis; Bristol-Myers Squibb/ Pfizer)		Approved	• VTE prevention (ADVANCE 1–3; ADOPT) • VTE treatment (AMPLIFY; AMPLIFY-EXT) • SPAF (AVERROES; ARISTOTLE) • ACS (APPRAISE-2; study terminated)
Edoxaban		Phase III	• VTE treatment (HOKUSAI) • SPAF (ENGAGE-AF TIMI-48)
Darexaban (YM150)		Phase II/III	• VTE prevention • ACS

*Indicates the highest phase reached for any indication in any country. ‡Dabigatran is administered as the prodrug dabigatran etexilate.



About Boehringer Ingelheim GmbH. Research into an oral direct thrombin inhibitor began in the early 1990s on the Research and Development Campus of Boehringer Ingelheim in Biberach, Germany. Dabigatran etexilate was first synthesized in 1996. This was the starting point for an unprecedented development program, including extensive Phase III clinical testing investigating Pradaxa® in multiple indications requiring anticoagulation. Among these, RE-LY® was the largest atrial fibrillation (AF) study ever completed, which compared two doses of dabigatran etexilate (110mg and 150mg bid), administered in a blinded manner, with open label warfarin. The RE-LY® trial demonstrated superiority of the 150 mg dose and non-inferiority of the 110 mg dose of Pradaxa® over the 50-year old standard of care, warfarin, in preventing stroke in AF. This was achieved without additional overall bleeding with the higher dose and significantly less bleeding with the lower dose. Importantly, significantly less intracranial bleeding with both doses was seen.

In contrast to warfarin, Pradaxa® does not require routine coagulation monitoring or dose adjustments, is not affected by food and has a low potential for drug–drug interactions. Dabigatran etexilate is approved for clinical use in stroke risk reduction in non-valvular AF in many countries around the globe, including the USA, Canada, Europe and Japan. It is also approved in 83 countries for prevention of venous thromboembolic events in adults undergoing elective total hip or knee replacement surgery. Boehringer Ingelheim is one of the world's 20 leading pharmaceutical companies (http://www.boehringer-ingelheim.com). Since its inception in 1885, the family-owned company is committed to researching, developing, manufacturing and marketing novel products of high therapeutic value for human and veterinary medicine. Headquarters are in Ingelheim, Germany, and it operates globally with 145 affiliates and over 42,000 employees.

Abbreviations

ACS, acute coronary syndrome; CYP3A4, cytochrome P450 3A4; DVT, deep vein thrombosis; EU, European Union; LMWH, low molecular weight heparin; P-gp, P glycoprotein; SPAF, stroke prevention in atrial fibrillation; VTE, venous thromboembolism. §After orthopaedic surgery.

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