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STATE-OF-THE-ART PAPER

New Oral Anticoagulants in Atrial Fibrillation and Acute Coronary Syndromes

ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease Position Paper

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Until recently, vitamin K antagonists were the only available oral anticoagulants, but with numerous limitations that prompted the introduction of new oral anticoagulants targeting the single coagulation enzymes thrombin (dabigatran) or factor Xa (apixaban, rivaroxaban, and edoxaban) and given in fixed doses without coagulation monitoring. Here we review the pharmacology and the results of clinical trials with these new agents in stroke prevention in atrial fibrillation and secondary prevention after acute coronary syndromes, providing perspectives on their future incorporation into clinical practice. In phase III trials in atrial fibrillation, compared with warfarin, dabigatran etexilate 150 mg B.I.D. reduced the rates of stroke/systemic embolism without any difference in major bleeding; dabigatran etexilate 110 mg B.I.D. had similar efficacy with decreased bleeding; apixaban 5 mg B.I.D. reduced stroke, systemic embolism, and mortality as well as major bleeding; and rivaroxaban 20 mg Q.D. was noninferior to warfarin for stroke and systemic embolism without a difference in major bleeding. All these agents reduced intracranial hemorrhage. Edoxaban is currently being evaluated in a further large phase III trial. Apixaban and rivaroxaban were evaluated in phase III trials for prevention of recurrent ischemia in patients with acute coronary syndromes who were mostly receiving dual antiplatelet therapy, with conflicting results on efficacy but consistent results for increased major bleeding. Overall, the new oral anticoagulants are poised to replace vitamin K antagonists for many patients with atrial fibrillation and may have a role after acute coronary syndromes. Although convenient to administer and manage, they present challenges that need to be addressed. (J Am Coll Cardiol 2012; 59:1413–25) © 2012 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

B.I.D. = twice daily
CI = confidence interval
CrCl = creatinine clearance
CYP = cytochrome P450
DTI = direct thrombin inhibitor
F = factor
HR = hazard ratio
INR = international normalized ratio
NSTE = non–ST-segment elevation
P-gp = P-glycoprotein
Q.D. = once daily
TIMI = Thrombolysis In Myocardial Infarction
TTR = time in therapeutic range
VKA = vitamin K antagonist

Preamble: Purposes and Scope of the Task Force

Drugs that interfere with blood coagulation (anticoagulants) are a mainstay of cardiovascular therapy. Until recently, vitamin K antagonists (VKAs) were the only available orally active anticoagulants. Although effective, VKAs have numerous limitations, which complicate their use (1). These limitations have prompted the introduction of new oral anticoagulants that target thrombin and factor (F) Xa, key enzymes in the coagulation pathway. The new oral anticoagulants, which can be given in fixed doses without routine coagulation monitoring, overcome many of the problems associated with VKAs.

This document, produced by a committee appointed by the European Society of Cardiology Working Group on Thrombosis and assembling a group of coagulation experts and clinical cardiologists, aims to: 1) review the mechanism of action, pharmacologic properties, and side effects of the new anticoagulants; and 2) describe and comment on the results of recently completed clinical trials in 2 specific cardiac conditions, atrial fibrillation and acute coronary syndromes.

This document is intended to follow and complement the Task Force Document on the use of Antiplatelet Agents in Atherothrombotic Diseases (2) and is an update of a previous document (1).

Mechanism of Action of Novel Anticoagulants

A rational classification of all currently available anticoagulants is based on their route of administration (parenteral vs. oral) and their mechanism of action (direct vs. indirect). Targets of the novel anticoagulants under development or in initial clinical use for long-term therapy are depicted in Figure 1. These agents inhibit a single step in coagulation, at major variance from VKAs, which block multiple steps because they reduce the synthesis of the vitamin K–dependent coagulation factors.

The direct thrombin inhibitors (DTI) (gatrans) bind to thrombin and block its capacity to convert fibrinogen to fibrin; to amplify its own generation through activation of FV, FVIII, and FIX; and to serve as a potent platelet agonist

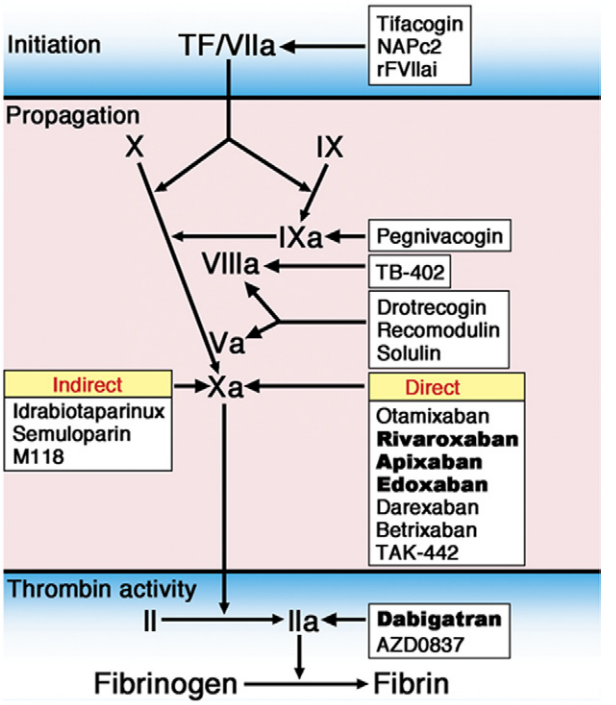

Figure 1 Targets of Novel Anticoagulants for Long-Term Use

Besides the indirect thrombin inhibitors (unfractionated heparin [UFH] and low molecular weight heparin [LMWH]), direct thrombin inhibitors bind directly to thrombin and prevent fibrin formation as well as thrombin-mediated activation of factor (F) V, FVIII, FXI, and FXIII. They also prevent thrombin-mediated activation of platelets, inflammation, antifibrinolysis, and the anticoagulant protein C/protein S/thrombomodulin pathway. Parenteral direct thrombin inhibitors include hirudin, bivalirudin, and argatroban. Oral direct thrombin inhibitors are prodrugs that generate an active compound able to bind directly to the catalytic site of thrombin: examples include ximelagatran (withdrawn from development), AZD0837, now under evaluation, and dabigatran etexilate. Drugs that target coagulation proteases that drive the propagation phase include agents that block FIXa (such as the DNA aptamer pegnivacogin), FVIIIa (TB-402), or jointly FVa/FVIIIa, cofactors that are critical for the generation of thrombin (drotrecogin, which is a recombinant form of human activated protein C and recomodulin and solulin, both of which are recombinant soluble derivatives of human thrombomodulin). Blockers of the propagation phase also include FXa inhibitors. At variance from the parenteral indirect FXa inhibitors, such as UFH, LMWH, and pentasaccharide derivatives (fondaparinux, idrabiotaparinux), which exert their effects equally on thrombin and FXa (UFH), prevalently on FXa (LMWH), or exclusively on FXa (fondaparinux, biotaparinux), all by potentiating the natural inhibitor antithrombin (AT) (AT III), a number of oral direct (i.e., non–AT-mediated) FXa inhibitors are in clinical trials. To target the initiation of coagulation, inhibitors toward the tissue factor/FVIIa complex have been developed, such as recombinant TFPI (tifacogin), recombinant nematode anticoagulant protein (NAP)C2, active site–inhibited recombinant (r) FVIIa inhibitors (rFVIIai) and monoclonal antibodies against TF. Figure illustration by Craig Skaggs.

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