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

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).

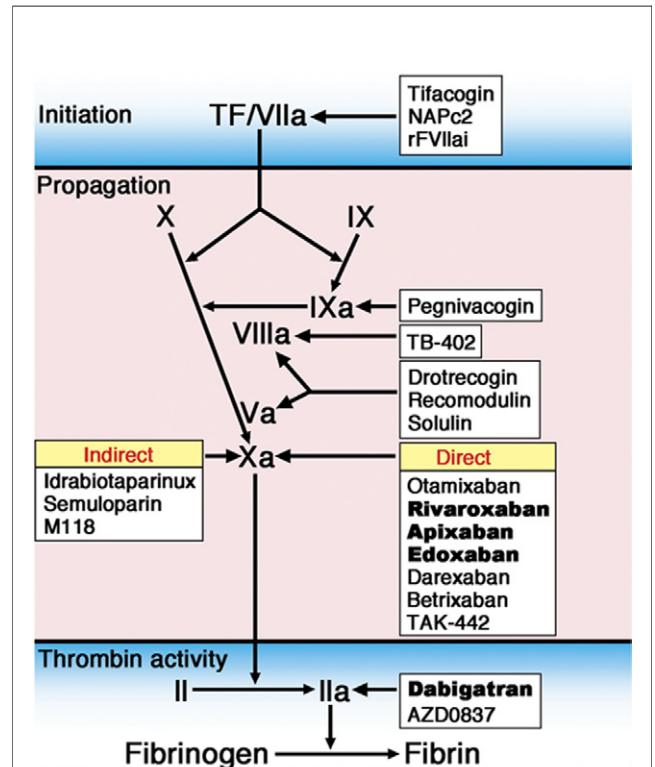## Mechanism of Action of Novel Anticoagulants

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.

(3). In contrast to indirect thrombin inhibitors, such as heparin, DTIs not only inhibit free thrombin, but also inhibit thrombin bound to fibrin (4). Currently, only 1 DTI (dabigatran etexilate) has completed phase III clinical evaluation for stroke prevention in atrial fibrillation.

Drugs that target coagulation proteases that drive the propagation phase also decrease thrombin generation and 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; recomodulin and solulin, both recombinant soluble derivatives of human thrombomodulin) (4) (Fig. 1). None of these new drugs have yet reached phase III development with cardiological indications. The largest family of new anticoagulants for long-term use is the FXa inhibitors. Parenteral synthetic pentasaccharides mediate indirect, antithrombin-dependent inhibition of FXa. The prototype of such drugs, fondaparinux, has been in clinical use for the treatment of acute coronary syndromes for a number of years. Idrabiotaparinux, a hypermethylated derivative of fondaparinux that possesses a biotin moiety to enable reversal, has been evaluated for the treatment of venous thromboembolism and as an alternative to warfarin for stroke prevention in patients with atrial fibrillation. The atrial fibrillation trial was stopped early, and the future of this agent is uncertain. Consequently, idrabiotaparinux is not further reviewed here. A large series of compounds is now being developed to target FXa directly (*direct* FXa inhibitors, xabans), most of which are orally active. Only 3 such compounds (apixaban, rivaroxaban, edoxaban) have, however, completed or are now undergoing phase III clinical development for stroke prevention in atrial fibrillation. Rivaroxaban and apixaban have also undergone phase III clinical trials for the prevention of recurrent ischemia in acute coronary syndromes.

New Anticoagulants: General Pharmacology

Dabigatran etexilate. Dabigatran etexilate is a synthetic low molecular weight peptidomimetic that binds directly and reversibly to the catalytic site of thrombin (5). Dabigatran etexilate is a prodrug that has ~6% bioavailability after oral administration. Once absorbed, the compound is rapidly and completely biotransformed to the active compound dabigatran by esterase-mediated hydrolysis. Pharmacokinetic data in healthy volunteers show peak plasma levels 2 to 3 h after oral administration of dabigatran etexilate–containing capsules filled with micropellets of the drug surrounding a tartaric acid core. Tartaric acid is used because drug absorption is enhanced with an acidic microenvironment (6). After reaching peak plasma concentrations, dabigatran clearance exhibits a biexponential decline with a mean terminal half-life of approximately 11 h in healthy elderly subjects. After administration of multiple doses, a terminal half-life of ~12 to 14 h was observed,

independent of the dose (7). Dabigatran is eliminated unchanged primarily by the kidneys; therefore plasma concentrations are increased in patients with moderately impaired renal function (creatinine clearance [CrCl] <50 ml/min). The therapeutic window, however, is fairly wide, and the drug has been tested in fixed doses in patients with CrCl >30 ml/min (5). Close clinical surveillance is recommended in patients with renal impairment. No dose adjustment is necessary for patients with mild renal impairment (CrCl of 50 to 80 ml/min). For patients with moderate renal impairment (CrCl of 30 to 50 ml/min), the recommended dose is 300 mg taken as one 150-mg capsule twice daily. However, for patients with a high risk of bleeding, including patients 75 to 80 years of age, a dose reduction to 220 mg taken as one 110-mg capsule twice daily should be considered. The lower dose is mandatory for patients older than 80 years of age. No dose adjustment is needed with concomitant use of the P-glycoprotein (P-gp) inhibitor amiodarone, but in patients receiving verapamil the dose should be reduced to 110 mg B.I.D., and both drugs should be taken at the same time. Exposure to dabigatran is higher (by 1.7- to 2-fold) when it is coadministered with dronedarone. Dronedarone should therefore not be coadministered with dabigatran. Concomitant administration of potent P-gp inducers (such as rifampicin, St. John's wort, carbamazepine, and phenytoin) can decrease dabigatran plasma concentrations and should be avoided. A summary of the main pharmacologic characteristics of dabigatran etexilate compared with the new FXa inhibitors in phase III clinical development is shown in Table 1.

There is currently no specific reversal agent or antidote for dabigatran. In case of an overdose, oral administration of activated charcoal may be helpful for adsorbing drug from the stomach, whereas hemodialysis may be effective for removing dabigatran from the blood. Because it is a thrombin inhibitor, administration of coagulation factors (fresh frozen plasma, prothrombin complex concentrates) may not be wholly effective in reversing its effects. However, even though prothrombin complex concentrate has little effect on dabigatran-induced prolongation of the activated partial thromboplastin time in volunteers (8) or animals, it attenuates dabigatran-induced bleeding in animals in a dose-dependent fashion. Therefore, in cases of uncontrolled bleeding, unactivated or activated prothrombin complex concentrates or recombinant activated FVII may be helpful.

The mid- and long-term treatment with dabigatran etexilate has already been evaluated in >45,000 patients for the prevention and treatment of venous thromboembolism and in >500,000 patients with atrial fibrillation (including post-marketing surveillance). There is no evidence of liver toxicity with the drug.

Rivaroxaban. Rivaroxaban is a highly selective, reversible direct oral FXa inhibitor, rapidly absorbed after oral administration with a maximum concentration after 2 to 4 h. The absolute bioavailability of rivaroxaban at a dose of 20 mg in the fasting state is approximately 66%, but it increases with

Table 1	Pharmacological Characteristics of Oral Direct Thrombin Inhibitors and Oral Direct Factor Xa Inhibitors in Phase III Clinical Development			
	Dabigatran Etexilate	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Mechanism of action	Selective direct FIIa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor
Oral bioavailability, %	6.5	80–100	50	62
Half-life, h	12–17	5–13	8–15	6–11
Renal elimination, %	85	66 (36 unchanged and 30 inactive metabolites)	27	50§
Time to maximum inhibition, h	0.5–2	1–4	1–4	1–2
Potential metabolic drug interactions	Inhibitors of P-gp:verapamil, reduce dose; dronedarone: avoid Potent inducers of P-gp†: avoid	Potent inhibitors of CYP3A4 and P-gp*: avoid Potent inducers of CYP3A4‡ and P-gp: use with caution	Potent inhibitors of CYP3A4 and P-gp*: avoid Potent inducers of CYP3A4‡ and P-gp† use with caution	Potent inhibitors of P-gp*: reduce dose Potent inducers of P-gp†: avoid

*Potent inhibitors of CYP3A4 include antifungals (e.g., ketoconazole, intraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin, and protease inhibitors (e.g., ritonavir, atanazavir). P-gp inhibitors include verapamil, amiodarone, quinidine, and clarithromycin. †P-gp inducers include rifampicin, St. John's wort (*Hypericum perforatum*), carbamazepine, and phenytoin. ‡Potent CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital, and St. John's wort. §Of the absorbed drug.

CYP = cytochrome P450 isoenzyme; F = factor; P-gp = P-glycoprotein.

food, thus prompting the recommendation to take the tablets with food. About one-third of the drug is excreted renally, two-thirds are metabolized. With a CrCl of 15 to 29 ml/min, rivaroxaban exposure is 1.5-fold higher than that with values >80 ml/min (9). There are limited clinical data on patients with a CrCl of 15 to 29 ml/min; consequently, rivaroxaban should be used with caution in such patients. The drug is not recommended in patients with a CrCl of <15 ml/min. The half-life of the drug is 5 to 13 h, and the drug has been administered once daily for atrial fibrillation and twice daily in the setting of acute coronary syndromes, mostly in combination with antiplatelet drugs. The drug is metabolized in the liver via cytochrome P450 (CYP)−dependent and −independent mechanisms. Because rivaroxaban is metabolized via CYP3A4 and CYP2J2 and is a substrate of P-gp, it is not recommended in patients receiving strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics and HIV protease inhibitors (Table 1).

There is currently no specific reversal agent or antidote for rivaroxaban. In case of an overdose, administration of oral activated charcoal may be helpful for adsorption of active drug in the stomach; hemodialysis is unlikely to be helpful because rivaroxaban is highly protein bound. Being an upstream inhibitor of coagulation, the administration of coagulation factors (fresh frozen plasma, prothrombin complex concentrates, or activated FVII) may reverse its effects; in volunteers, prothrombin complex concentrate reverses rivaroxaban-induced prolongation of the prothrombin time (8). Whether it attenuates rivaroxaban-induced bleeding is unknown.

Apixaban. Apixaban is a highly selective, reversible direct FXa inhibitor. Maximum plasma concentrations are obtained 3 to 4 h after oral administration, and the bioavailability of the drug is ~50% for doses as high as 10 mg. Apixaban has a half-life of 8 to 15 h (Table 1) and has been given twice daily for all indications. Apixaban is metabolized in the liver via CYP3A4-dependent and -independent mechanisms, and ~25% of the dose administered is ex-

creted unchanged in the urine. There are limited clinical data in patients with a CrCl of 15 to 29 ml/min; consequently, apixaban should be used with caution in such patients. Apixaban is not recommended for patients with impaired renal function (CrCl <15 ml/min). The usual recommended dose of apixaban for stroke prevention in atrial fibrillation is 5 mg B.I.D.; a 2.5-mg B.I.D. dose is recommended for patients with ≥2 of the following criteria: age 80 years and older, body weight <60 kg, or a serum creatinine level of ≥1.5 mg/dl (133 μmol/l). Apixaban is not recommended in patients receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole antimycotics and human immunodeficiency virus protease inhibitors (Table 1). The drug should be used with caution in patients receiving concomitant treatment with strong CYP3A4 and P-gp inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital).

There is currently no specific reversal agent or antidote for apixaban. In case of an overdose, the same considerations as for rivaroxaban apply (see Rivaroxaban, above).

Edoxaban. Edoxaban is also an oral selective direct FXa inhibitor. The drug has an oral bioavailability of 62%, and absorption is not influenced by food. Peak plasma concentrations are achieved 1 to 3 h after oral administration (Table 1), and the half-life is 7 to 10 h. About 50% of the absorbed drug is excreted unchanged in the urine. The drug is metabolized in the liver <4% via a CYP3A4-dependent pathway. Metabolism is, however, mostly influenced by P-gp inhibitors or inducers (Table 1). Patients with a CrCl of 30 to 50 ml/min, a body weight <60 kg, and receiving potent P-gp inhibitors (such as verapamil, quinidine, or dronedarone) will have increased drug exposure and require halving of the dose (10). There is currently no specific reversal agent or antidote for edoxaban. In case of an overdose, the same considerations as for rivaroxaban apply (see Rivaroxaban, above).

A phase II study comparing the safety of 4 fixed-dose regimens of edoxaban (30 mg every day [Q.D.], 30 mg B.I.D., 60 mg Q.D., 60 mg B.I.D.) with warfarin in 1,146

Table 2	**Overview of Design of the Pivotal Phase III Trials of New Oral Anticoagulants Compared With Warfarin in Nonvalvular Atrial Fibrillation**			
	RELY	**ROCKET**	**ARISTOTLE**	**ENGAGE AF**
Sample size	18,113	14,264	18,201	21,107
New treatment and dose	Dabigatran 110 mg B.I.D.	Rivaroxaban 20 mg	Apixaban 5 mg	Edoxaban 30 mg Q.D.
	Dabigatran 150 mg B.I.D.	Q.D.	B.I.D.	Edoxaban 60 mg Q.D.
Dose adjustment	No	At randomization	At randomization	During trial
Design	Noninferiority	Noninferiority	Noninferiority	Noninferiority
	PROBE	Double blind	Double blind	Double blind
Patients	CHADS$_2$ score ≥1	CHADS$_2$ score ≥2	CHADS$_2$ score ≥1	CHADS$_2$ score ≥2
Primary outcome	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism
Safety outcome	Major bleeding	Major bleeding	Major bleeding	Major bleeding

CHADS$_2$ score = a score to evaluate thromboembolic risk, taking into account congestive heart failure (C), hypertension (H), age ≥75 years (A), diabetes (D) (with each such factors scoring 1) and previous stroke/systemic embolism (S), the latter scoring 2 (S$_2$); PROBE = prospective, randomized, open-label with blinded event adjudication. Major bleeding definition included critical bleed or hemoglobin drop ≥2 g/dl or ≥2 U of packed red cell transfusion (in ROCKET AF and ARISTOTLE, the latter 2 items had to be associated with clinically overt bleeding). B.I.D. = twice daily; Q.D. = once daily.

patients with nonvalvular atrial fibrillation in a 12-week, parallel-group, multicenter, multinational study demonstrated that the safety profiles of edoxaban 30 and 60 mg Q.D. in such patients were similar to those of warfarin. In contrast, the edoxaban B.I.D. regimens were associated with more bleeding than warfarin (11). For these reasons, both the 30 and the 60 mg Q.D. regimens were carried forward in the now ongoing phase III ENGAGE AF–TIMI 48 (Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation–Thrombolysis In Myocardial Infarction-48) study (see Edoxaban section).

New Anticoagulants in Atrial Fibrillation

Dabigatran etexilate. The dose-ranging phase II trial PETRO (Prevention of Embolic and ThROmbotic events) (12) and its long-term extension (PETRO-Ex) (13) suggested that a dose regimen of 150 mg B.I.D. of dabigatran etexilate might provide an optimal efficacy/safety balance. The pivotal RE-LY (Randomised Evaluation of Long term anticoagulant therapY) trial was a prospective, randomized, open-label clinical phase III trial comparing 2 blinded doses of dabigatran etexilate (110 mg B.I.D. [D110] or 150 mg B.I.D. [D150]) with open-label, adjusted-dose warfarin aiming for a target international normalized ratio (INR) of 2.0 to 3.0 (14,15) (Table 2). A total of 18,113 patients with nonvalvular atrial fibrillation and at least 1 risk factor for stroke were included. Patients with a stroke during the last 14 days or with a CrCl of <30 ml/min were excluded. By trial design, half of the patients were warfarin-naïve, as defined by a maximum of 60 days use of warfarin before randomization. The mean CHADS$_2$ score (a score to evaluate thromboembolic risk, taking into account congestive heart failure [C], hypertension [H], age 75 years and older [A], diabetes [D] [with each such factor scoring 1] and previous stroke/systemic embolism [S], the latter scoring 2 [S$_2$]) was 2.1, and 31.9% of the patients had a CHADS$_2$ score of 0 to 1, 35.6% had a score of 2, and 32.5% had a score of 3 to 6. Median treatment duration was 2 years. The mean and median times in therapeutic range (TTR) for the warfarin-treated patients was 64% and 67%,

respectively. Evaluation of outcome events was centrally blinded.

The results showed a reduction of the primary outcome of stroke or systemic embolism from 1.71% in the warfarin group to 1.54% per year in the D110 group (hazard ratio [HR]: 0.90; 95% confidence interval [CI]: 0.74 to 1.10; p < 0.001 for noninferiority) and 1.11% per year in the D150 group (HR: 0.65; 95% CI: 0.52 to 0.81; p < 0.001 for superiority) (Fig. 2). The rate of major bleeding was 3.57% per year in the warfarin group compared with 2.87% per year in the D110 group (p = 0.003) and 3.32% in the D150 group (p = 0.31) (Fig. 3). Rates of hemorrhagic stroke and intracranial bleeding were lower with both doses of dabigatran etexilate (annual intracranial bleeding rate: 0.1% with both D110 and D150 vs. 0.4% with warfarin; p < 0.001). Gastrointestinal bleeding, however, was increased from 1.0% per year on warfarin to 1.5% per year with D150 (p < 0.001). There was a trend toward higher rates of myocardial infarction with both dabigatran doses (15,16). Total mortality was 4.13% per year for warfarin compared with 3.75%
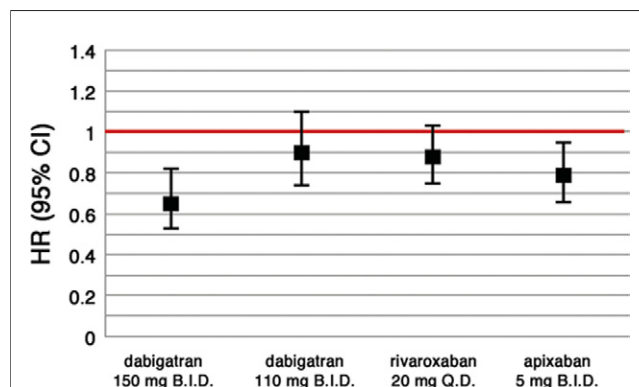
| **Figure 2** | **Comparable Primary Efficacy Endpoints of Stroke or Systemic Embolism** |

Hazard ratios and 95% confidence intervals of the primary outcome in the 3 pivotal trials comparing new oral anticoagulants with warfarin in nonvalvular atrial fibrillation (14,18,20). B.I.D. = twice daily; CI = confidence interval; HR = hazard ratio; Q.D. = once daily.

Figure 3   **Comparable Primary Safety Endpoints of Major Bleeding**

Hazard ratios and 95% confidence intervals of the primary safety outcome (major bleeding) in the 3 pivotal trials comparing new oral anticoagulants with warfarin in nonvalvular atrial fibrillation (14,18,20). Abbreviations as in Figure 2.
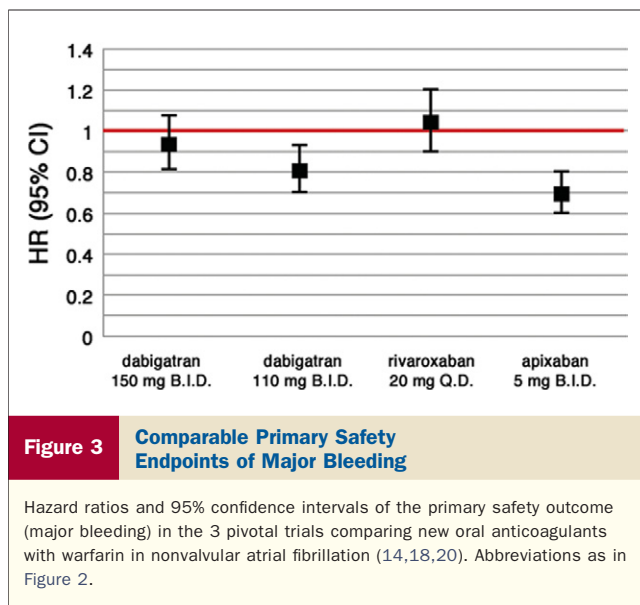
per year for D110 (p = 0.13) and 3.64% per year for D150 (p = 0.051). The rates of discontinuation at 2 years were higher with D150 (20.7%) and D110 (21.2%) than with warfarin (16.6%). A post-randomization subgroup analysis found no significant interaction between mean center TTR and the effects of D150 or D110 concerning the primary outcome, but significant interactions with the effects on mortality, major bleeding, and the composite of ischemic and bleeding outcomes, indicating a greater benefit of dabigatran at centers with poor INR control (17). Based on the results of the RE-LY trial, dabigatran etexilate has been approved as an alternative to VKAs for stroke prevention in nonvalvular atrial fibrillation by the U.S. Food and Drug Administration, the European Medicinal Agency, and health authorities in many countries worldwide. Although the U.S. Food and Drug Administration has approved the 150 mg B.I.D. dose regimen (as well as 75 mg B.I.D. for patients with severe renal impairment, the group excluded from the RE-LY trial, based not on efficacy and safety data, but on pharmacokinetic and pharmacodynamic modeling), the Canadian regulatory authority, the European Medicinal Agency, and many other authorities worldwide have approved both the 150 mg B.I.D. and the 110 mg B.I.D. dose regimens.

Rivaroxaban. The ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) (18) included patients with nonvalvular atrial fibrillation at high risk of stroke, as evidenced by a $CHADS_2$ score of ≥2. This trial randomized 14,264 patients to double-blind treatment with rivaroxaban 20 mg Q.D. (15 mg daily for CrCl of 30 to 49 ml/min) or warfarin. The population was at higher risk of stroke than in most other atrial fibrillation trials, with a mean $CHADS_2$ score of 3.5. Eighty-seven percent of patients had a $CHADS_2$ score of ≥3 and 44% a $CHADS_2$

score of ≥4, and 55% had a history of stroke, transient ischemic attack, or systemic embolism. The warfarin treatment aimed at an INR level between 2.0 and 3.0. However, the mean TTR was 55% (median 58%), which is lower than in other randomized trials. The primary objective was to demonstrate noninferiority of rivaroxaban versus warfarin for the occurrence of stroke or systemic embolism. The study was event driven and ended after approximately 2 years (707 days) median follow-up.

The results concerning the primary objective showed a yearly rate of stroke and systemic embolism of 2.12% in the rivaroxaban group and of 2.42% in the warfarin group (HR with rivaroxaban: 0.88; 95% CI: 0.74 to 1.03; p < 0.001 for noninferiority and p = 0.117 for superiority) (Fig. 2), but with no reduction in ischemic stroke. The total mortality was 4.5% in the rivaroxaban group and 4.9% in the warfarin group (p = 0.15). The yearly rate of major bleeding was 3.60% in the rivaroxaban group and 3.45% in the warfarin group (p = 0.58) (Fig. 3). There was a lower rate of intracranial bleeding (0.5%/year vs. 0.7%/year; p = 0.02) and thereby fewer fatal bleeding events (0.2%/year vs. 0.5%/year; p = 0.003) with rivaroxaban versus warfarin. However, there were more patients with bleeding requiring transfusion and more gastrointestinal bleeding with rivaroxaban. There was numerically a nonsignificantly lower rate of myocardial infarction in the rivaroxaban group. Premature discontinuation of treatment was more common with rivaroxaban (23.9%), than with warfarin (22.4%). The conclusions of the trial were that in patients with nonvalvular atrial fibrillation and a high risk of stroke, rivaroxaban was noninferior compared with warfarin concerning the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding. The complementary results with Q.D. reduced-dose rivaroxaban compared with reduced-intensity warfarin in Japanese patients with atrial fibrillation at risk of stroke (the J-ROCKET AF study) were recently announced to be consistent with the results in the main ROCKET-AF trial, although this trial was underpowered for efficacy endpoints.

Apixaban. The first published results on the efficacy of FXa inhibitors for stroke prevention in atrial fibrillation come from the AVERROES (Apixaban VERsus acetylsalicylic acid to pRevent strOkE in atrial fibrillation patientS who have failed or are unsuitable for vitamin K antagonist treatment) trial (19). This trial included patients with nonvalvular atrial fibrillation and at least 1 risk factor for stroke, but who were not suitable candidates for or were unwilling to take a VKA. The study randomized 5,599 such patients to double-blind, double-dummy treatment with either apixaban (5 mg B.I.D., with reduction to 2.5 mg B.I.D. for patients who met ≥2 of the following criteria: age 80 years and older, a body weight of ≤60 kg, or a serum creatinine level of ≥1.5 mg/dl (133 μmol/l) or aspirin (81 to 324 mg Q.D.). After 1.1-year median follow-up, the Data and Safety Monitoring Board recommended early termination of the study because of a clear benefit of apixaban.

Concerning efficacy, there was a reduction in the primary outcome events of stroke or systemic embolism from 3.7% per year in the aspirin group to 1.6% per year in the apixaban group (HR: 0.45; 95% CI: 0.32 to 0.62; p < 0.001). Mortality tended to be reduced from 4.4% per year in the aspirin group to 3.5% per year in the apixaban group (p = 0.07). Major bleeding was similar: 1.2%/year with aspirin versus 1.4%/year with apixaban (p = 0.57), as were intracranial bleeding rates: 0.4%/year versus 0.4%/year. At 2 years, the rates of permanent discontinuation of the study medication were 20.5%/year in the aspirin group versus 17.9%/year in the apixaban group (p = 0.03). The conclusions of the trial were that in patients with nonvalvular atrial fibrillation at increased risk of stroke and who were unsuitable for VKA treatment, apixaban substantially reduced the risk of stroke or systemic embolism compared with aspirin, without significantly increasing the risk of major or intracranial bleeding.

The ARISTOTLE (Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial [20] was a randomized double-blind double-dummy phase III trial comparing apixaban (5 mg B.I.D., with reduction to 2.5 mg B.I.D. for patients who met ≥2 of the following criteria: age 80 years and older, body weight of ≤60 kg, or serum creatinine level of ≥1.5 mg/dl (133 μmol/l) with dose-adjusted warfarin aiming at an INR of 2.0 to 3.0 (Table 2). A total of 18,201 patients with nonvalvular atrial fibrillation documented in the 12 months before randomization and at least 1 additional risk factor for stroke were included. Patients with a stroke during the past 7 days or with a CrCl of <25 ml/min were excluded. By trial design, 43% of the patients were warfarin naïve, as defined by ≤30-day use of warfarin before randomization. The mean $CHADS_2$ score was 2.1; 34.0% of the patients had a $CHADS_2$ score of 0 to 1, 35.8% had a score of 2, and 30.2% had a score of 3 to 6. Median treatment duration was 1.8 years with a minimum of 1-year follow-up. The mean TTR for the warfarin-treated patients was 62.2% (median, 66.0%).

The results showed a reduction of the primary outcome of stroke or systemic embolism from 1.60%/year in the warfarin group to 1.27%/year in the apixaban group (HR: 0.79; 95% CI: 0.66 to 0.95; p = 0.01 for superiority) (Fig. 2). The rate of major bleeding was 3.09%/year for patients in the warfarin group compared with 2.13%/year in the apixaban group (p < 0.001) (Fig. 3). Rates of hemorrhagic stroke and intracranial bleeding were significantly lower in patients treated with apixaban than with warfarin (intracranial bleeding 0.33/year vs. 0.80%/year, p < 0.001). Gastrointestinal bleeding was similar between the treatment arms. There was a numerically nonsignificantly lower rate of myocardial infarction with apixaban. Total mortality was 3.94%/year for warfarin compared with 3.52%/year for apixaban (p = 0.047). There was no significant difference in the incidence of ischemic stroke. Pre-defined subgroup analyses in the ARISTOTLE trial found no significant

interaction between the TTR with warfarin treatment and any of the other efficacy or safety outcomes. The results were consistent across a large number of pre-defined subgroups, including the Asian-Pacific subpopulations, which were integrated as parts of the trial. Apixaban was better tolerated than warfarin, with fewer early discontinuations (25.3% vs. 27.5%). The conclusions of the trial were that in patients with nonvalvular atrial fibrillation and increased risk of stroke, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

Edoxaban. The results of the edoxaban trial against warfarin (ENGAGE AF–TIMI 48) [10] are expected in 2012. ENGAGE AF–TIMI 48 is a phase III, randomized, double-blind, double-dummy, multinational, noninferiority design trial comparing 2 exposure strategies of edoxaban versus warfarin. A total of 21,107 subjects have been randomized to edoxaban high exposure (60 mg Q.D., adjusted for drug clearance), edoxaban low exposure (30 mg Q.D., adjusted for drug clearance), or warfarin titrated to an INR of 2.0 to 3.0. The edoxaban strategies provide for dynamic dose reductions in subjects with anticipated increased drug exposure. Blinded treatment is maintained through the use of sham INRs in patients receiving edoxaban. Eligibility criteria include recent (≤12 months) electrocardiographic documentation of nonvalvular atrial fibrillation and a $CHADS_2$ score of ≥2. Randomization is stratified by $CHADS_2$ score and anticipated drug exposure. The primary objective is to determine whether edoxaban is noninferior to warfarin for the prevention of stroke and systemic embolism. The primary safety endpoint is major bleeding according to a modified International Society on Thrombosis and Haemostasis definition. The expected median follow-up is 24 months [10].

Comparative appraisal of treatment alternatives for stroke prevention in atrial fibrillation: VKA versus oral direct thrombin inhibitors versus oral FXa inhibitors. When trying to compare the utility of these new alternatives with one another, the potential pitfalls of cross-trial comparisons need to be emphasized. Thus, the moderate-risk populations in RE-LY and ARISTOTLE trials with dabigatran etexilate and apixaban are different from the high-risk population included in the ROCKET-AF trial with rivaroxaban. The studies also have a different distribution of participating countries, with more patients from lower income countries and a lower average level of TTR in the ROCKET AF trial and possibly other differences in the standards of care. Furthermore, it cannot be excluded that the open-label design of the RE-LY trial may have led to some advantages concerning individualized warfarin dosing and INR control and disadvantages concerning blinding of event evaluation compared with the double-blind ROCKET-AF and ARISTOTLE trials. There were also differences in follow-up periods because only the ROCKET-AF trial included events up to 30 days after study drug discontinuation. In addition, the ROCKET-AF trial pre-specified an

on-treatment analysis instead of the conventional intention-to-treat analysis for the primary testing of noninferiority. Also, the end of study treatment differed among the trials: most dabigatran etexilate–treated patients in the RE-LY trial continued with the same blinded dose of the drug as part of the RELY-ABLE (Long-Term Multicenter Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed RE-LY Trial) trial, whereas there was a switch from the double-blind study drug to open-label VKAs in the ROCKET-AF and ARISTOTLE trials.

Based on the currently available results from the individual trials (Figs. 2 and 3), it is clear that both the oral direct thrombin inhibitor dabigatran etexilate and the oral FXa inhibitors apixaban and rivaroxaban are attractive alternatives to warfarin or aspirin in patients with nonvalvular atrial fibrillation and an increased risk of stroke. Apixaban 5 mg (with dose reduction to 2.5 mg in specific cases) B.I.D. is currently the best documented alternative to both warfarin and aspirin for stroke prevention in a broad population with atrial fibrillation and increased risk of stroke based on 2 independent large scale trials (ARISTOTLE and AVERROES). Apixaban has been shown to be superior compared with warfarin concerning the reduction of stroke and mortality in combination with a reduction in major bleeding, with a bleeding risk similar to that of low-dose aspirin, and with better tolerability than both these alternatives, albeit with no reduction in ischemic stroke compared with warfarin. Dabigatran etexilate 150 mg B.I.D. is also a well-documented alternative to warfarin based on its reduction of hemorrhagic stroke as well as of ischemic stroke and systemic embolism, with a similar risk of major bleeding and a reduced risk of intracranial bleeding. Dabigatran etexilate 150 mg B.I.D., however, is associated with some specific side effects, such as an increased rate of dyspepsia and gastrointestinal bleeding, a trend toward an increased risk of myocardial infarction, and a dependence on normal or only moderately impaired renal function for its elimination. The availability of the dabigatran 110 mg B.I.D. and, in some countries, the 75 mg B.I.D. dose regimen(s) allows for tailoring of treatment in older patients and/or those with poor renal function. Rivaroxaban 20 mg (with dose adjustment to 15 mg in specific cases) Q.D. is a third alternative to warfarin for stroke prevention in patients with nonvalvular atrial fibrillation with a high risk of stroke. Rivaroxaban is documented to be noninferior concerning stroke prevention and major bleeding, with a lower risk of intracranial but a higher rate of gastrointestinal bleeding in this population. Rivaroxaban has the advantage of a convenient once-daily regimen, which may improve adherence.

The relative efficacy and/or safety advantages of the new anticoagulants versus VKAs appear to depend, to a large extent, albeit not only, on the quality of anticoagulation with VKAs. Patients already on long-term VKA treatment, with well-controlled INR (TTR >70%) and handling VKA treatment and laboratory monitoring without problems,

derive therefore still uncertain overall advantages from switching to the new oral anticoagulants, and the arguments for changing treatment in such patients appear weaker than for other patient categories. There are also several remaining conditions in which VKA may still be needed, such as intolerance of the new anticoagulants, very poor renal function, other needs for close monitoring of anticoagulation, and clinical settings in which we currently lack documentation on the efficacy and safety of anticoagulation with the new agents.

New Oral Anticoagulants in Acute Coronary Syndromes

The management of acute coronary syndromes has improved significantly in recent years with the introduction of interventional treatment strategies, potent platelet inhibitory drugs, and secondary risk-modifying drug treatment regimens. Incorporation of these therapies has resulted in reduced mortality and morbidity (21). However, the risk of recurrent ischemic events is still high at 30 days and long term (22). VKAs have been shown to reduce the risk of recurrent ischemic events, both as monotherapy and in combination with aspirin (23). Evidence regarding the efficacy and safety of VKA when used in combination with dual antiplatelet therapy (aspirin and clopidogrel, so-called triple therapy) is limited, but registry data indicate a high risk of major bleeding (24). The efficacy and safety of VKAs in combination with the new potent P2Y12 antagonists prasugrel and ticagrelor have not been investigated.

Despite proven efficacy, VKAs are rarely used in patients with acute coronary syndromes because management is cumbersome. The new oral anticoagulants are more convenient to administer than VKAs and therefore may offer advantages in this setting.

Four of the novel oral anticoagulants have been tested in placebo-controlled phase II trials, including patients with ST-segment elevation myocardial infarction and non–ST-segment elevation (NSTE) acute coronary syndrome (Table 3): the oral DTI dabigatran etexilate (RE-DEEM [Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome], patient inclusion within 14 days after index event) (25) and the FXa inhibitors rivaroxaban (AT-LAS ACS–TIMI 46 [Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 46]) (26), apixaban (APPRAISE [Apixaban for Prevention of Acute Ischemic and Safety Events] trial) (27), and darexaban (RUBY-1 [Study Evaluating Safety, Tolerability and Efficacy of YM150 in Subjects With Acute Coronary Syndromes]) (28) that were tested in patients within 7 days after the index event. The trials were powered to evaluate safety, with drug exposure either once or twice daily, using multiple doses, for a period of 6 months. In all studies, most patients received dual antiplatelet therapy with aspirin and clopidogrel.

Table 3	Phase II Double-Blind, Placebo-Controlled, Dose-Escalation Trials of New Anticoagulants in Acute Coronary Syndromes			
	Dabigatran Etexilate	**Rivaroxaban**	**Apixaban**	**Darexaban**
Acronym	RE-DEEM	ATLAS	APPRAISE	RUBY-1
n	1,861	3,491	1,715	1,279
STEMI/NSTEMI ACS, %	60/40	52/48	61–67/33–39	71/29
Dual platelet inhibition, %	99	Stratum 1: 0; stratum 2: 100	76	97
Duration of therapy, months	6	6	6	6
Dosage	50–150 B.I.D.	5–20 mg Q.D.	10–20 mg Q.D./2.5–10 mg B.I.D.	10–60 mg Q.D./5–30 mg B.I.D.
Safety outcome, HR (95% CI)	50 mg: 1.82 (0.77–4.29)	Stratum 1:	2.5 mg B.I.D.: 1.78 (0.91–3.48)	10 mg Q.D.: 1.78 (0.68–4.60)
	75 mg: 2.44 (1.05–5.65)	5 mg: 0.81 (0.09–7.23)	10 mg B.I.D.: 2.45 (1.31–4.61)	30 mg Q.D.: 1.83 (0.71–4.75)
	110 mg: 3.36 (1.60–7.91)	10 mg: 3.40 (0.91–12.65)	10-mg B.I.D. and 20-mg Q.D. arms terminated because of a high bleeding* risk	60 mg Q.D.: 2.43 (0.98–5.97)
	150 mg: 3.88 (1.73–8.74)	20 mg: 6.43 (1.94–21.37)		5 mg B.I.D.: 2.05 (0.81–5.15)
		Stratum 2:		15 mg B.I.D.: 2.27 (0.92–5.59)
		5 mg: 2.17 (0.91–5.18)		30 mg B.I.D.: 3.80 (1.66–8.68)
		10 mg: 3.34 (2.15–5.19)		
		15 mg: 3.41 (1.97–5.89)		
		20 mg: 4.56 (2.83–7.33)		

*Bleeding definition: International Society on Thrombosis and Haemostasis major and clinically relevant nonmajor bleeding for dabigatran etexilate, apixaban, and darexaban; Thrombolysis In Myocardial Infarction major, Thrombolysis In Myocardial Infarction minor, or bleeding requiring medical attention for rivaroxaban.

ACS = acute coronary syndrome(s); B.I.D. = twice daily; CI = confidence interval; HR = hazard ratio; NSTEMI = non–-ST-segment elevation myocardial infarction; Q.D. = once daily; STEMI = ST-segment elevation myocardial infarction.

In the RE-DEEM trial (25), with >99% of patients receiving dual platelet inhibition, a dose-dependent increase in clinically relevant bleeding events was observed, with highest rates with the dabigatran etexilate 110 mg and 150 mg B.I.D. currently used in atrial fibrillation (Table 3). The most frequently reported bleeding events were gastrointestinal bleeding and epistaxis. The study was not powered to demonstrate an efficacy difference in cardiovascular death, nonfatal myocardial infarction or nonhemorrhagic stroke, but a numerically lower proportion was attained in the 2 higher dabigatran doses (110 mg B.I.D., 3.0%; 150 mg B.I.D., 3.5%) compared with the lower doses (50 mg B.I.D., 4.6%; 75 mg B.I.D., 4.9%) and the placebo group (3.8%).

The ATLAS ACS–TIMI 46 trial (26) demonstrated a rivaroxaban dose-dependent increased risk of clinically significant bleeding complications both in patients receiving aspirin alone (stratum 1) and, even more so, in patients receiving dual platelet inhibition (stratum 2) (Table 3). In addition, both patients receiving once and twice daily dosing had a dose-dependent increased risk of bleeding. Compared with placebo, rivaroxaban was associated with an HR of 0.53 (95% CI: 0.33 to 0.84) for death, myocardial infarction, stroke, or severe recurrent ischemia requiring revascularization in stratum 1 and an HR of 0.99 (95% CI: 0.69 to 1.42) in stratum 2 (p for interaction = 0.034).

The APPRAISE trial (27) demonstrated a dose-dependent increased risk of bleeding complications with apixaban 2.5 mg B.I.D. and 10 mg Q.D. (27) (Table 3). The 2 higher doses, 10 mg B.I.D. and 20 mg Q.D., were associated with the highest rates of clinically relevant bleeding and were prematurely terminated. The most frequent types of bleeding were subcutaneous bruising and hematomas, epistaxis and gingival bleeding, hematuria, and gastrointestinal bleeding. The incidence of cardiovascular death,

myocardial infarction, severe recurrent ischemia, or ischemic stroke was numerically, but not significantly, lower in patients assigned to apixaban 2.5 mg B.I.D. or 10 mg Q.D. compared with placebo, with greater benefits of apixaban among patients on aspirin alone or nonrevascularized.

The RUBY-1 trial (28) evaluated the safety, tolerability, and most promising regimen of darexaban (YM150) for the prevention of ischemic events in acute coronary syndromes. Darexaban (5 mg B.I.D., 10 mg Q.D., 15 mg B.I.D., 30 mg Q.D., 30 mg B.I.D., or 60 mg Q.D.), when added to dual antiplatelet therapy, produced an expected dose-related 2- to 4-fold increase in bleeding versus placebo (Table 3), with no other safety concerns, but also with no signal of efficacy.

After the phase II trials, 2 phase III studies were conducted (Tables 4 and 5). The APPRAISE-2 trial (29) was prematurely terminated because of an excess of bleeding with apixaban and no evidence of benefit. The ATLAS ACS 2–TIMI 51 (30) was conversely concluded and met its primary objective (31).

In the APPRAISE 2 trial, 7,392 patients with an acute coronary syndrome (40% ST-segment elevation myocardial infarction; 60% NSTE acute coronary syndromes) and at least 2 additional risk factors for recurrent ischemic events were randomized at a median 6 days after the index event to apixaban 5 mg B.I.D. (2.5 mg B.I.D. in patients with a CrCl of <40 ml/min) or placebo for a mean follow-up of 241 days (29). The majority of patients (81%) received dual antiplatelet therapy with aspirin and clopidogrel (Table 4). The primary efficacy composite outcome of cardiovascular death, myocardial infarction, or ischemic stroke was 13.2 per 100 patient-years with apixaban and 14.0 per 100 patient-years with placebo (HR: 0.95; 95% CI: 0.80 to 1.11) at the early termination of the trial. The primary safety outcome of major bleeding according to the Thrombolysis In Myocardial Infarction (TIMI) definition occurred more

Table 4	APPRAISE-2 Versus ATLAS-2: Baseline Characteristics/Concomitant Medications/Follow-up	
	APPRAISE-2 (N = 7,392)	**ATLAS-2 (N = 15,526)**
Age, yrs	67 (median)	62 (mean)
Diabetes mellitus, %	47.8	32.0
Heart failure or LVEF <40% associated with index ACS event, %	40.2	—
Previous cerebrovascular disease, %	10.0	Excluded
Renal function	28.9% with impaired renal function	Median CrCl 85 ml/min (interquartile range: 68–105)
Index ACS event type		
STEMI, %	39.6	50.3
NSTEMI, %	41.6	25.6
Unstable angina, %	18.2	24.0
Aspirin, %	97	99
Thienopyridine, %	81 (dual)	93
Follow-up	8.0 months (median)	13.1 months (mean duration of treatment with a study drug)

CrCl = creatinine clearance; LVEF = left ventricular ejection fraction; other abbreviations as in Table 3.

often with apixaban (2.4 events per 100 patient-years) than with placebo (0.9 events per 100 patient-years; HR: 2.59, 95% CI: 1.50 to 4.46). Apixaban was associated with more intracranial hemorrhage (0.6 compared with 0.2 per 100 patient-years; HR: 4.06; 95% CI: 1.15 to 14.38), and with a numerical increase in fatal bleeding (5 vs. 0 events during the trial). The overall efficacy/safety balance considerations prompted the Data and Safety Monitoring Board to terminate the trial before completing enrollment of the planned 10,800 patients. Consequently, the efficacy of apixaban remains uncertain because the wide CIs allow for either benefit or harm (Table 5).

In the ATLAS ACS-2–TIMI 51 (ATLAS-2) trial, 15,526 patients with an acute coronary syndrome were randomized 1:1:1 to placebo or rivaroxaban 2.5 mg B.I.D. or 5 mg B.I.D. (30,31). Patients with previous gastrointestinal bleeding, previous ischemic stroke or transient ischemic attack, and poor renal function were excluded from the higher exposure arm in this trial. The mean duration of treatment with a study drug was 13.1 months. Rivaroxaban compared with placebo significantly reduced the primary efficacy composite of cardiovascular death, myocardial infarction, or stroke with respective rates of 8.9% and 10.7% in the study period (HR in the rivaroxaban group: 0.84; 95% CI: 0.74 to 0.96; p = 0.008), with significant improvement for both the 2.5-mg B.I.D. dose (9.1% vs. 10.7%, p = 0.02) and the 5-mg B.I.D. dose (8.8% vs. 10.7%; p = 0.03). The 2.5-mg, but not the 5-mg B.I.D. dose, reduced the rates of death during the study period from cardiovascular causes (2.7% vs. 4.1%; p = 0.002) and from any cause (2.9% vs. 4.5%; p = 0.002), whereas 5 mg B.I.D., but not 2.5 mg B.I.D., reduced myocardial infarction. Over the study period, the 2 doses of rivaroxaban combined increased the rates of TIMI major bleeding (not related to coronary artery bypass grafting) to 2.1% compared with 0.6% (HR: 3.96; 95% CI: 2.46 to 6.38; p < 0.001) and intracranial hemorrhage to 0.6% compared with 0.2% (HR: 3.28; 95% CI: 1.28 to 8.42; p = 0.009), without a significant increase in fatal bleeding (0.3% vs. 0.2%; HR: 1.19; 95% CI: 0.54 to 2.59; p = 0.66). The 2.5 mg B.I.D. dose resulted in

significantly fewer fatal bleeding events than the 5 mg B.I.D. dose (0.1% vs. 0.4% in 13.1 months; p = 0.04) (Table 5).

Critical appraisal of oral FXa inhibitor treatment in acute coronary syndromes. The 2 trials of oral FXa inhibitors after acute coronary syndrome show a lack of consistency in the efficacy outcomes, with a significant reduction compared with placebo in the ATLAS-2 trial but not in the APPRAISE-2 trial. This discrepancy is not well explained by a difference in the rates of bleeding, which was increased to a fairly similar extent in both trials. One potential reason for this pattern relates to the differences in the inclusion criteria; compared with the ATLAS-2 population, the APPRAISE-2 population was older and more commonly had diabetes, renal dysfunction, and previous stroke, and more frequently had myocardial infarction versus unstable angina and NSTE acute coronary syndromes versus ST-segment elevation myocardial infarction as the index event (Table 4). The higher risk population included in the APPRAISE-2 study was reflected by a higher rate of the primary efficacy outcome, part of which might have had a different pathophysiology—and eventually be less related to thrombotic events and thereby less responsive to anticoagulant treatment—than in the ATLAS-2 trial. Another potential reason for differences in outcome is that the FXa inhibition potency of the studied doses was different: APPRAISE-2 used the same 5 mg B.I.D. apixaban dose tested in atrial fibrillation (20), whereas ATLAS-2 used 2 doses, 2.5 mg B.I.D. and 5 mg B.I.D., that were one fourth to one half of the total daily dose of rivaroxaban (20 mg Q.D.) tested in atrial fibrillation (18). Better efficacy with a lower level of FXa inhibition would seem logical if the bleeding rates had also been lower. However, the risks of TIMI major (non–coronary artery bypass graft related) bleeding were not lower, but rather actually numerically higher, with both rivaroxaban doses in ATLAS-2 (HR: 3.46; 95% CI: 2.08 to 5.77; p < 0.001 for rivaroxaban 2.5 mg B.I.D. versus placebo; HR: 4.47; 95% CI: 2.71 to 7.36; p < 0.001 for rivaroxaban 5 mg B.I.D. vs. placebo) than in APPRAISE-2 (HR: 2.59; 95% CI: 1.50 to 4.46; p = 0.001)

Table 5 APPRAISE-2 Versus ATLAS-2: Efficacy and Safety Outcomes

	APPRAISE-2*			ATLAS-2†			HR (95% CI)		
	Apixaban (n = 3,705)	Placebo (n = 3,687)	HR (95% CI)	Rivaroxaban 2.5 mg B.I.D. (n = 5,114)	Rivaroxaban 5 mg B.I.D. (n = 5,115)	Placebo (n = 5,113)	2.5 mg B.I.D. vs. Placebo	5 mg B.I.D. vs. Placebo	Rivaroxaban Combined vs. Placebo
Efficacy outcomes									
CV death	105 (2.8)	109 (3.0)	0.96 (0.73–1.25)	94 (2.7)‡	132 (4.0)	143 (4.1)	0.66 (0.51–0.86)	0.94 (0.75–1.20)	0.80 (0.65–0.99)
Myocardial infarction	182 (4.9)	194 (5.3)	0.93 (0.76–1.14)	205 (6.1)	179 (4.9)	229 (6.6)	0.90 (0.75–1.09)	0.79 (0.65–0.97)	0.85 (0.72–1.00)
Ischemic stroke	23 (0.6)§	34 (0.9)	0.68 (0.40–1.15)	30 (1.0)	35 (0.9)	34 (1.0)	0.89 (0.55–1.45)	1.05 (0.65–1.68)	0.97 (0.66–1.47)
Stent thrombosis	35 (0.9)‖	48 (1.3)	0.73 (0.47–1.17)	47 (2.2)	51 (2.3)#	72 (2.9)	0.65 (0.45–0.94)	0.73 (0.51–1.04)	0.69 (0.51–0.93)
Safety outcomes									
ICH	12 (0.3)**	3 (0.1)	4.06 (1.15–14.38)	14 (0.4)††	18 (0.7)‡‡	5 (0.2)	2.83 (1.02–7.86)	3.74 (1.39–10.07)	3.28 (1.28–8.42)
Fatal bleeding	5 (0.1)	0 (0)	NA	6 (0.1)	15 (0.4)	9 (0.2)	0.67 (0.24–1.89)	1.72 (0.75–3.92)	1.19 (0.54–2.59)

Values are n (%) unless otherwise specified. *Rates of events during the median follow-up of 241 days. †Rates of events as Kaplan-Meier estimates through 24 months. Although rates are not comparable due to the different time durations of the studies, HRs are comparable. ‡p = 0.002. §p = 0.14. ‖p = 0.15. ¶p = 0.02. #p = 0.08. **p = 0.03. ††p = 0.04. ‡‡p = 0.005.

B.I.D. = twice daily; CV = cardiovascular; ICH = intracranial hemorrhage; NA = not applicable; other abbreviations as in Table 3.

for apixaban 5 mg B.I.D. versus placebo. This allows for the alternative hypothesis that a lower, rather than a higher, level of FXa inhibition per se may have a better antithrombotic effect. Although this did occur also in phase II studies with the parenteral indirect FXa inhibitor fondaparinux (32) and with the oral Xa blocker darexaban (28), this hypothesis is counterintuitive and needs verification in other trials. In the ATLAS-2 trial, with all the limits of subgroup analysis, there was also a significant reduction in mortality but not in myocardial infarction in the 2.5 mg B.I.D. arm versus placebo and a reduction in myocardial infarction but not mortality in the 5 mg B.I.D. arm versus placebo, which, if true, are still lacking a consistent explanation. A third possible reason for the differences in efficacy outcomes is that the lack of significance of the reduction in ischemic events in the APPRAISE-2 trial is due to the play of chance because the trial was prematurely terminated and the fairly wide CIs for efficacy do not exclude a remaining potential for a reduction in event rates.

The 3- to 4-fold excess in major and intracranial bleeding events with the addition of any dose of FXa inhibitors in addition to current antiplatelet treatment occurred continuously throughout the whole treatment period in both trials. The gain in ischemic events in the ATLAS-2 trial was, in contrast to previous trials of antithrombotic agents, greater later rather than earlier during the follow-up, which does not suggest an option for short-term anticoagulant treatment to avoid the accrual of major bleeding events in the long term. The excess of bleeding was even larger in patient groups at higher risk of bleeding (e.g., older age, female sex, lower body weight, or reduced renal function, which are more common in real life than in the trial populations). Therefore, the unavoidable excess in major and intracranial bleeding is a major concern when considering the addition of oral FXa inhibitors to current antiplatelet treatment for long-term treatment in patients after an acute coronary syndrome.

According to the most recent European Society of Cardiology guidelines for the treatment of NSTE acute coronary syndrome (33), the more effective P2Y12 inhibitors prasugrel and ticagrelor are now the preferred antiplatelet agents in combination with aspirin. In the joint American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions Guideline for Percutaneous Coronary Interventions, prasugrel and ticagrelor are considered at the same level as clopidogrel for percutaneous coronary intervention treatment in acute coronary syndromes (Class I Recommendation, Level of Evidence: B) (34). Long-term treatment with either prasugrel or ticagrelor is associated with a reduction in ischemic events compared with clopidogrel (ticagrelor also with lower mortality) and with only a relatively small (30%) increase in the risk of major bleeding compared with the 3- to 4-fold increase observed with FXa inhibitors. Therefore, the use of any of these new antiplatelet agents (prasugrel or ticagrelor) instead of clopidogrel

appears preferable to adding an FXa inhibitor, with its considerably greater added risk of major (including intracranial) bleeding without proven greater gains in efficacy. It is unknown whether low doses of any of the novel anticoagulants might provide incremental benefit and/or be tolerable in the presence of any of these new and more effective antiplatelet agents. Therefore, the present results of FXa inhibitors after acute coronary syndromes may not lead to changes of clinical practice. They still, however, open up a new avenue for research because of the proof that they may reduce ischemic events in patients with coronary heart disease. The challenge for future trials will be therefore to identify the combination of antithrombotic agents that provides the largest reduction in thrombotic events with the smallest risk of bleeding (e.g., by testing combinations of 1 single antiplatelet agent with a FXa inhibitor).

Conclusions and Implications

The availability, as of now, of 3 new treatment alternatives for stroke prevention in patients with nonvalvular atrial fibrillation is a great step forward to further improve outcomes and quality of life. Compared with warfarin, these new alternatives have important advantages, with their lower risk of intracranial bleeding, no clear interactions with food, fewer interactions with medications, and no need for frequent laboratory monitoring and dose adjustments. Therefore, these new oral anticoagulants will be preferred alternatives to VKAs for many patients with atrial fibrillation and an increased risk of stroke. However, still further information is needed on how to prioritize the patients deriving greater benefits from the novel agents. More information is also needed on the transition between different agents, interruption for procedures and/or surgery, anticoagulation during cardioversion and ablation procedures, and dosing in renal failure. There is also a need for more information on how to manage patients with bleeding because there are no specific antidotes for any of the new agents. Generally available tools to determine the anticoagulant effect (e.g., thrombin time or anti-Xa activity) may be needed when these compounds become widely used. Adherence might be a larger issue in the real-life setting than in clinical trials. Therefore, there needs to be agreement on how these patients should be followed on an individual level and how the efficacy and safety of these new treatments can be determined at a health care system level. Because these are lifelong treatments, there is also a need for assessing long-term efficacy and safety over decades in the real-life setting. The cost of the drug at the patient level might be an obstacle to their use, although the cost-effectiveness at a societal level might be tolerable in comparison with other recently accepted novel treatments. Finally, complementary trials will be needed to determine the utility of these agents in combination with antiplatelet treatments after myocardial infarction and percutaneous coronary intervention and in patients with other indications for anticoagulation, such as mitral stenosis, mechanical prosthetic valves, stroke without atrial fibrillation, and cancer.

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