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ARISTOTLE RE-LYs on the ROCKET. What's new in stroke prevention in patients with atrial fibrillation?

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Abstract

Warfarin has long been considered the gold standard for stroke prevention in patients with atrial fibrillation (AF). Recently, three major trials comparing the efficacy and safety of new drugs: a thrombin inhibitor dabigatran and two inhibitors of factor Xa — rivaroxaban and apixaban, with that of warfarin, have been published. The aim of this paper is to present the main results of the RE-LY, ROCKET AF and ARISTOTLE trials, compare study populations and outcomes, and discuss clinical implications of their results for the long-term anticoagulation in patients with nonvalvular AF. (Cardiol J 2012; 19, 1: 4–10)

Key words: atrial fibrillation, stroke prevention, apixaban, dabigatran, rivaroxaban

Introduction

Atrial fibrillation (AF) is the commonest cardiac arrhythmia. AF is a major risk factor for stroke and systemic embolism. It causes an almost five-fold independent increase in the risk of ischemic stroke and is responsible for at least 20% of all strokes [1, 2]. AF-related strokes are associated with a high recurrence rate and worst survival [3]. The use of vitamin K antagonists (VKA) is the most effective standard therapy to prevent stroke and systemic events in patients with AF and is more beneficial than antiplatelet agents [4, 5]. VKA, first introduced about 60 years ago, were until recently the only available oral anticoagulants, and are recommended as the gold standard therapy by clinical guidelines [6]. Warfarin, the most commonly used VKA, reduces the risk of stroke by approximately 60% in patients with nonvalvular AF [5]. There are, however, several limitations to warfarin treatment. Warfarin therapy requires regular measurement of the international normalized ratio (INR). An INR value of 2.0–3.0 is the therapeutic range for stroke prevention [7]. Data from clinical trials show that patients with AF achieve the therapeutic INR range only during 60% of treatment time [8]. Multiple drug and food interactions, inter-individual and day-to-day variations in dose response require frequent laboratory monitoring and dose adjustment.

Importantly, treatment with warfarin significantly increases the risk of hemorrhage; about 2% of patients per year experience major bleeding [9]. The risk of bleeding is especially important in patients with AF after acute coronary syndromes and/or percutaneous interventions during triple anticoagulant therapy. High treatment inertion of warfarin (delayed onset of action, long half-life) often requires heparin bridging therapy before different interventional procedures, and increases the risk of bleeding during urgent surgical operations. Probably because of these limitations, only 54% of patients with indications for oral anticoagulants are actually treated with VKA; older patients (age > 80 years) and individuals with paroxysmal AF are especially undertreated [10].

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As a consequence of limitations related to warfarin treatment, attempts have been made to produce oral anticoagulant drugs targeting specific components of the coagulation cascade.

The process of coagulation is a complex proteinase cascade, comprising more than 30 different proteins. Both the intrinsic and extrinsic pathways of coagulation lead to the formation of thrombin (factor IIa) though the activation of factor X — the central element of the common coagulation pathway [11].

Of the many possible targets for the new drugs in the coagulation pathway, thrombin and factor Xa inhibitors have been tested. So far, large phase III clinical trials for the prevention of stroke in patients with AF have been completed for dabigatran, rivaroxaban and apixaban.

Among these new drugs, dabigatran, a specific thrombin inhibitor, has been already included in the US guidelines on the management of AF [12]. Dabigatran etexilate is a prodrug converted into the active principle dabigatran by blood esterases. Its metabolism is independent of the P450 cytochrome, and so far only a few drug interactions have been identified (amiodarone, varapamil, macrolides and tenophovir), with no known food interactions. It is eliminated mostly with urine, which makes the adjustment of dosage in patients with renal insufficiency necessary [13].

Rivaroxaban is a new oral direct factor Xa inhibitor, which has been recently approved in Europe for the treatment of AF. It has a rapid onset of action, with a half-life of 5–12 hours. Most of the drug is eliminated by the kidneys: one third in the unchanged, active form, and two thirds after being metabolized by the liver. The metabolites are also partly eliminated with feces. The only known interactions of rivaroxaban are with antimycotic azole drugs and protease inhibitors used in HIV therapy [14].

Apixaban, another oral direct Xa inhibitor, has a half-life of 9–14 hours, with elimination pathways that include metabolism and renal excretion. It is eliminated mostly by the liver [15].

Recently, three pivotal trials addressing the efficacy and safety of new oral anticoagulants in patients with non-valvular AF have been published. In RE-LY [16], two different doses of dabigatran were used, while ROCKET AF [17] and ARISTOTLE [18] studied rivaroxaban and apixaban, respectively.

The aim of this paper is to present the main results of ARISTOTLE, RE-LY and ROCKET AF, compare study populations and outcomes, and discuss clinical implications of their results for the long-term anticoagulation in patients with nonvalvular AF.

Characteristics and results of the studies

ARISTOTLE [18] was a double-blind, double-dummy, event-driven, phase III trial of stroke or systemic embolism prevention in patients with non-valvular AF; 18,201 patients were randomized to either a Xa inhibitor apixaban at a dose of 5 mg bid (2.5 mg bid with ≥ 2 of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine level ≥ 1.5 mg/dL), or dose-adjusted warfarin to a target INR of 2.0 to 3.0.

Patients had nonvalvular AF and ≥ 1 risk factors for stroke: previous stroke, transient ischemic attack (TIA) or systemic embolism, age ≥ 75 years, heart failure or left ventricular ejection fraction (LVEF) ≤ 40%, diabetes mellitus, or hypertension. The mean CHADS2 score [19] was 2.1; 19% of the patients had a previous stroke, systemic embolism or TIA. The primary efficacy end-point (stroke or systemic embolism) occurred in 212 patients in the apixaban arm (1.27%/year) and in 265 patients in the warfarin arm (1.6%/year). Apixaban not only proved to be non-inferior (HR 0.79; 95% CI 0.66–0.95; p < 0.001 for noninferiority), but also superior to warfarin (p = 0.01 for superiority) in the intention-to-treat (ITT) population. The primary safety end-point — major bleeding — occurred in 327 patients in the apixaban arm (2.13%/year) and in 462 patients in the warfarin arm (3.09%/year); HR 0.69; 95% CI 0.60–0.80; p < 0.001. Intracranial bleeding, other location bleeding, major or clinically relevant non-major bleeding and any bleeding were more common in the warfarin arm (warfarin *vs* apixaban 0.80%/year *vs* 0.33%/year, 2.27%/year *vs* 1.79%/year, 6.01%/year *vs* 4.07%/year and 25.8%/year *vs* 18.1%/year, respectively). The incidence of death from any cause was significantly lower in the apixaban arm (apixaban *vs* warfarin 3.52%/year *vs* 3.94%//year; HR 0.89; 95% CI 0.80–0.99; p = 0.047). Thus, ARISTOTLE showed that apixaban administration in patients with non-valvular AF and mean CHADS2 score of 2.1 was superior to warfarin in the prevention of stroke or systemic embolism, and resulted in less bleeding and lower mortality.

RE-LY [16] was a randomized, phase III trial of stroke or systemic embolism prevention, performed also in patients with non-valvular AF; 18,113 patients were randomized to receive, in a blinded fashion, fixed doses of a IIa inhibitor dabigatran —

either 110 mg or 150 mg bid — or, in an unblinded fashion, dose-adjusted warfarin to an INR of 2.0–3.0. Patients had AF and ≥ 1 of the following features: history of stroke or TIA, LVEF < 40%, NYHA class ≥ II, age ≥ 75 or age 65–74 plus diabetes mellitus, hypertension or coronary artery disease. The mean CHADS2 score was 2.1. History of previous stroke or TIA was present in 20.1% of patients. The primary efficacy end-point was the same as in ARISTOTLE (stroke or systemic embolism), and — after correction for additional events identified after publication of the primary paper [20] — occurred in 183 patients in the dabigatran 110 mg bid arm (1.54%/year), in 134 patients in the dabigatran 150 mg bid arm (1.11%/year), and in 202 patients in the warfarin arm (1.71%/year). Dabigatran at both doses was noninferior to warfarin (RR 0.90; 95% CI 0.74–1.10; p < 0.001 for noninferiority and RR 0.65; 95% CI 0.52–0.81; p < 0.001 for noninferiority, respectively) in the ITT population. The 150 mg bid dose of dabigatran was also superior to warfarin (RR 0.65; 95% CI 0.52–0.81; p < 0.001 for superiority). The primary safety end-point — major hemorrhage — occurred in 342 patients in the dabigatran 110 mg bid arm (2.87%/year), in 399 patients in the dabigatran 150 mg bid arm (3.32%/year), and in 421 patients in the warfarin arm (3.57%/year); RR 0.80; 95% CI 0.70–0.93; p = 0.003 and RR 0.93; 95% CI 0.81–1.07; p = 0.31, respectively. Major gastrointestinal (GI) bleedings were most common in the dabigatran 150 mg bid arm (dabigatran 150 mg bid *vs* warfarin 1.56%/year *vs* 1.08%/year). Life-threatening bleeding, intracranial bleeding, minor bleeding and major or minor bleeding occurred less frequently in the dabigatran arms (dabigatran 110 mg bid and 150 mg bid *vs* warfarin: 1.24%/year and 1.49%/year *vs* 1.80%/year; 0.23%/year and 0.30%/year *vs* 0.74%/year; 13.16%/year and 14.84%/year *vs* 16.37%/year; 14.62%/year and 16.42%/year *vs* 18.15%/year, respectively).

In summary, in RE-LY, dabigatran at a dose of 110 mg bid was noninferior to warfarin in the prevention of stroke or systemic embolism, causing less major bleeding. Dabigatran 150 mg bid, in the same population, was superior to warfarin in the prevention of stroke or systemic embolism, with no difference in the risk of major bleeding.

ROCKET AF [17] was a double-blind, double-dummy, event-driven, phase III trial of stroke or systemic embolism prevention in patients with non-valvular AF. The study randomized 14,264 patients to receive either rivaroxaban at a dose of 20 mg od (15 mg od in patients with creatinine clearance 30–49 mL/min) or dose-adjusted warfarin to a target INR of 2.5 (range 2.0–3.0 inclusive). In order to be included in the study, the patients had to have AF and a positive history for stroke, TIA or systemic embolism, or ≥ 2 additional risk factors for stroke: heart failure or LVEF ≤ 35%, hypertension, age ≥ 75, and diabetes mellitus. The mean CHADS2 score was 3.5. A majority of the patients (54.8%) had a previous stroke, systemic embolism or TIA. The primary efficacy end-point (stroke or systemic embolism) occurred in 188 patients in the rivaroxaban arm (1.7%/year) and in 241 patients in the warfarin arm (2.2%/year). Rivaroxaban proved to be noninferior to warfarin (HR 0.79; 95% CI 0.66–0.96; p < 0.001 for noninferiority) in the per protocol, as treated population. In the safety as treated population, the primary efficacy end-point occurred in 189 patients in the rivaroxaban arm (1.7%/year) and in 243 patients in the warfarin arm (2.2%/year); HR 0.79; 95% CI 0.65–0.95; p = 0.02 for superiority. In the ITT population, the primary efficacy end-point occurred in 269 patients in the rivaroxaban arm (2.1%/year) and in 306 patients in the warfarin arm (2.4%.year); HR 0.88; 95% CI 0.75–1.03; p < 0.001 for noninferiority; p = 0.12 for superiority. The principal safety end-point, a composite of major and non-major clinically relevant bleeding events, occurred in 1,475 patients in the rivaroxaban arm (14.9%/year) and in 1,449 patients in the warfarin arm (14.5%/year); HR 1.03; 95% CI 0.96–1.11; p = 0.44. Transfusion, decrease of hemoglobin ≥ 2.0 g/dL and major bleeding from gastrointestinal site occurred less frequently in the warfarin arm (warfarin *vs* rivaroxaban 1.3%/year *vs* 1.6%/year, 2.3%/year *vs* 2.8%/year and 2.2% *vs* 3.2%, respectively). Critical bleeding, fatal bleeding and intracranial hemorrhage were more common in the warfarin arm (warfarin *vs* rivaroxaban 1.2%/year *vs* 0.8%/year, 0.5%/year *vs* 0.2%/year and 0.7%/year *vs* 0.5%/year, respectively). In general, ROCKET AF showed that rivaroxaban was non-inferior to warfarin in the prevention of stroke or systemic embolism, with no difference in the risk of major and non-major clinically relevant bleeding. It is noteworthy that intracranial and fatal bleeding occurred less frequently in the rivaroxaban arm.

Comparison of the studies and outcomes

A comparison of the main characteristics of the three studies is presented in Table 1. The studies differed in a number of important respects.

ARISTOTLE and ROCKET AF were blinded in both arms, while in RE-LY warfarin therapy was open label.

Table 1. Comparison of main characteristics, end-points and definitions in the ARISTOTLE, RE-LY and ROCKET AF studies.

	ARISTOTLE [18]	RE-LY [16]	ROCKET AF [17]
Study drug	Apixaban	Dabigatran	Rivaroxaban
Comparator	←	Warfarin (INR 2–3)	→
N	18,201	18,113	14,264
Study design	Double-blind non-inferiority	Open-label (warfarin) non-inferiority	Double-blind non-inferiority
Dose of study drug	5 mg bid 2.5 mg bid for patients with ≥ 2 at baseline: age ≥ 80 years; weight ≤ 60 kg; serum creatinine ≥ 1.5 mg/dL	110 mg bid or 150 mg bid (randomized to two separate arms)	20 mg od 15 mg od for moderate renal impairment (CrCl 30–49 mL/min)
Primary efficacy end-point	←	Stroke and systemic embolism	→
Principal safety end-point	← Major bleeding	→	Composite of major and non-major clinically relevant bleeding
Definition of major bleeding	Clinically overt bleeding with: • ↓Hb ≥ 2 g/dL • Transfusion of ≥ 2 U of RBC • Fatal bleeding • Critical site bleeding	Bleeding associated with: • ↓Hb ≥ 2 g/dL • Transfusion of ≥ 2 U of blood • Symptomatic bleeding in a critical area or organ	Clinically overt bleeding associated with: • ↓Hb ≥ 2 g/dL • Transfusion of ≥ 2 U of RBC/whole blood • Fatal bleeding • Critical anatomic site bleeding • Permanent disability
Mean CHADS2 score	2.1	2.1	3.5

In ROCKET AF, CHADS2 score was higher than in the two other studies. This resulted in a higher all-cause mortality in the warfarin arm (4.95% per year in ROCKET AF *vs* 3.94 in ARISTOTLE and 4.13 in RE-LY), and also in a higher incidence of primary end-point events (2.4, 1.6 and 1.69% per year, respectively).

Also data analysis was not identical. In ARISTOTLE and RE-LY, primary analyses were carried out in the ITT population, while in ROCKET AF it was done in the per-protocol as treated and safety as treated cohorts; ITT data was, however, provided.

It is noteworthy that in ARISTOTLE data acquisition terminated when about 70% of subjects were still on the study drug, while in ROCKET AF all patients at that time had been switched over to warfarin.

Primary efficacy outcomes in the three studies are shown in Figure 1. All three drugs proved non-inferior compared to warfarin. There was a general trend in favor of study drugs, but the level of significance for superiority was only reached for apixaban, dabigatran 150 mg bid in the ITT and rivaroxaban in the as treated, but not in the ITT, analysis.

Figure 2 illustrates other efficacy and safety outcomes in the three trials. It is interesting that, except dabigatran at the dose of 150 mg bid, no study drug offered better ischemic stroke prevention than warfarin (Fig. 2A).

On the safety side, all three new drugs significantly reduced the incidence of hemorrhagic stroke and intracranial hemorrhage (Figs. 2B, E). This represents a clear advantage of apixaban, dabigatran and rivaroxaban over warfarin. Apparently, reduction in the number of hemorrhagic rather than ischemic strokes accounted for the superiority of the new drugs in some analyses, as described above. Interestingly, none of the trials directly reported the number of peripheral embolic events, the other primary outcome component. The RE-LY study was published first, and brought up a concern about a statistically marginal increase in the incidence of myocardial infarction with dabigatran (Fig. 2D). ARISTOTLE and ROCKET AF did not confirm this observation. Although all-cause mortality was significantly reduced in ARISTOTLE only, a similar trend was also observed in the two other studies (Fig. 2F).

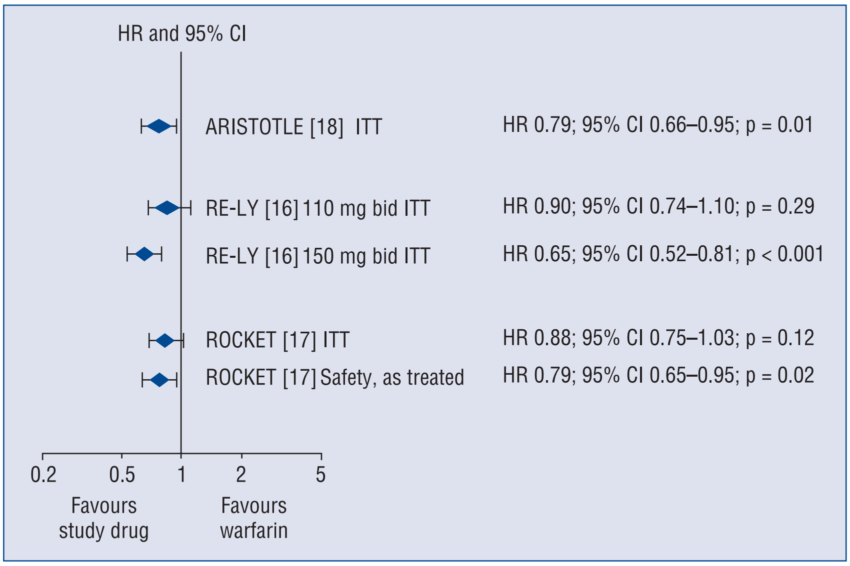

Figure 1. Primary efficacy end-point in ARISTOTLE, RE-LY and ROCKET AF; HR — hazard ratio; CI — confidence interval; ITT — intention to treat; p — level of significance for superiority.

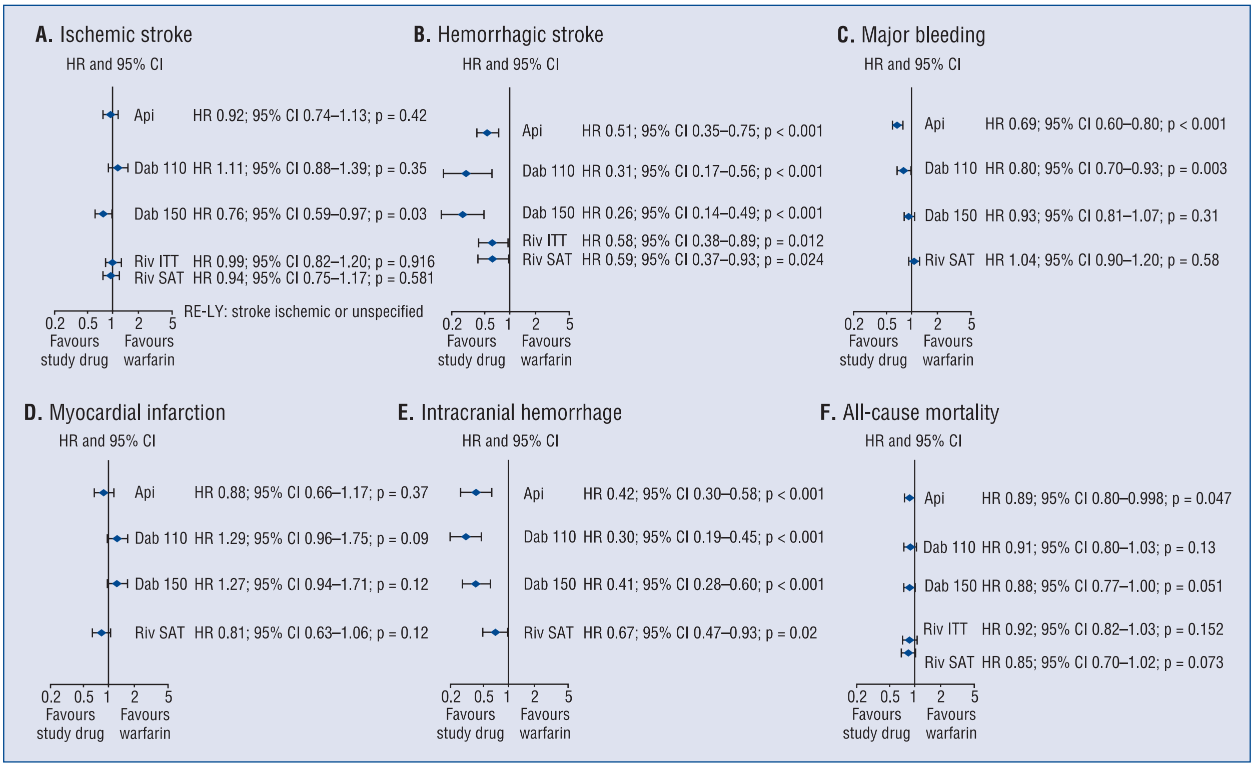

Figure 2. Other efficacy and safety outcomes in ARISTOTLE, RE-LY and ROCKET AF; Api — apixaban; Dab 110 — dabigatran 110 mg bid; Dab 150 — dabigatran 150 mg bid; Riv — rivaroxaban; HR — hazard ratio; CI – confidence interval; ITT — intention to treat; SAT — safety as treated; p — level of significance for superiority. Data from: Connolly et al. [16]; Patel et al. [17]; Granger et al. [18].

Clinical implications

Despite important differences, the general message from the three trials is consistent. Compared to warfarin, the three drugs have a potential to reduce stroke and systemic embolism, with similar or improved safety.

No need for laboratory control and no need for drug dose adjustment, as well as no food and very few drug interactions, are the major advantages of the novel oral anticoagulant drugs.

However, while the necessity to accurately monitor the INR with warfarin may be considered a disadvantage, it also gives the physician a possibility to control the drug compliance and hemostatic parameters of the patient. This is not possible with the new generation of anticoagulants, as no specific laboratory tests are known to monitor the levels of anticoagulation during their use. For rivaroxaban, a concentration-dependent prolongation of prothrombin time (PT), dilute PT, and activated partial thromboplastin time was observed; however, the results varied depending on the reagents and could not be standardized [21].

A secondary analysis of the RE-LY trial data showed that for all vascular events, non-hemorrhagic events and mortality, the advantages of dabigatran were greater at sites with poor than at those with good INR control, showing that the benefit of new treatments may depend on the local standards of care [22].

The efficacy and safety of the new drugs may differ for different subgroups. The beneficial effect of dabigatran is better expressed in patients aged < 75 years [23]. Special attention should be paid to patients with impaired renal function. In ARISTOTLE and ROCKET AF, the doses of apixaban and rivaroxaban were adjusted in patients with impaired glomerular filtration rate. The problem, however, is even more important with dabigatran. Recently, a concern has been expressed about an increased threat of bleeding and the need for initial, and thereafter systematic, renal function monitoring in patients receiving dabigatran [24].

A major disadvantage of the new drugs in cases of serious bleeding or where there is a need for emergency surgical intervention is the lack of specific antidotes to immediately correct the coagulation. This disadvantage may be soon overcome, at least in the case of the Xa inhibitors. Recently, Eerenberg et al. [25] evaluated the potential of prothrombin complex concentrate (PCC) to reverse the anticoagulant effect of rivaroxaban and dabigatran in healthy subjects. They found that PCC immediately and completely reverses the anticoagulant effect of rivaroxaban, but not that of dabigatran.

This example may reflect general differences between the IIa and Xa blockade [26].

Blockade of the Xa factor results in inhibition of new thrombin production, with no effect on the already existing thrombin. In addition, the physiological role of factor Xa is restricted to its action in both coagulation pathways, although it may also have a proinflammatory effect. Thrombin, on the other hand, apart from clot formation and inflammatory response, also plays a role as a mitogenic factor and coagulation promoter. Cessation of IIa factor blockade may result in a rebound thrombin overproduction. Therefore, factor Xa inhibition might be theoretically safer than thrombin blockade. It has to be emphasized, however, that direct comparisons of the two drug classes are lacking.

Finally, economic aspects have to be taken into consideration. Understandably, the direct costs of warfarin treatment are much lower than that of the new drugs. Initial data do however suggest that the new treatments may still be cost-effective [27].

Conclusions

Apixaban, rivaroxaban and dabigatran represent attractive alternatives to standard warfarin treatment in patients with nonvalvular AF. Their administration does not require regular laboratory monitoring. They are not only non-inferior to warfarin, but in many respects, including intracranial bleeds and hemorrhagic strokes, show superiority. Direct between-trial, and thus between-drug, comparison is difficult and requires further evaluation. The cost effectiveness of the new therapies needs further studies.

The introduction of the specific Xa and IIa inhibitors represents a major step forward in the treatment of patients with AF. Nonetheless, in patients with well controlled, stable INR values, warfarin may remain a valid treatment option.

Conflict of interest: M. Tendera was an investigator in the ROCKET-AF study and received honoraria from Bayer for scientific activities unrelated to rivaroxaban. M. Syzdół and Z. Parma declare no conflict of interest.

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