REVIEW ARTICLE

A new era for anticoagulation in atrial fibrillation

Which anticoagulant should we choose for long-term prevention of thromboembolic complications in patients with atrial fibrillation?

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KEY WORDS

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ABSTRACT

For more than 60 years, vitamin K antagonists have been the only available oral anticoagulants for the prevention of stroke and systemic embolism in atrial fibrillation (AF). Several new molecules, with a favorable pharmacokinetic profile and avoiding routine monitoring, have been recently developed, opening a new era in anticoagulation. The oral direct thrombin inhibitor, dabigatran, and the oral activated factor X inhibitors, rivaroxaban and apixaban, are the novel oral anticoagulants with data from large randomized clinical trials showing that these drugs are noninferior to warfarin in the prevention of stroke and thromboembolic complications of AF, with the advantage of less hemorrhagic stroke and intracranial bleeding. While these trial data are extremely encouraging, several practical issues (e.g., lack of specific antidote, safety of long-term treatment or cost-effectiveness in "real-life" clinical practice) still need to be elucidated.

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Introduction Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice with an overall prevalence of 5.5%, increasing with advanced age up to 17.8% among individuals over 85 years old.[1] AF carries a nearly 5-fold increased risk of stroke[2] with a 30-day mortality rate of 24% in the absence of treatment.[3]

Oral anticoagulants are the most effective antithrombotic treatment, since they reduce stroke risk by 64% compared with only 22% reduction of antiplatelet drugs, or a nonsignificant 19% reduction with aspirin.[4] Thus, oral anticoagulants are recommended in AF patients at moderate-high risk for stroke and thromboembolism.[5]

For the past 60 years, vitamin K antagonists (VKAs), mainly warfarin, have been the only available oral anticoagulants, but they have important limitations. The variable anticoagulant response, the food and drug interaction, and the narrow therapeutic window explain the requirement for frequent anticoagulation monitoring through international normalized ratio (INR).[6]

In the last decade, several novel oral anticoagulants (NOACs) have been developed: the direct thrombin inhibitors (dabigatran etexilate, AZD-0837) and activated factor X (FXa) inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban, eribaxaban, LY517 717, YM150, TAK-442).[7] These agents have a low potential for food and drug interactions and a predictable anticoagulant effect, which allow fixed dosing regimens without the need for routine monitoring. The short half-life may help to prevent overdosage and bleeding events, but requires strict patient compliance to assure accurate anticoagulation levels. Reversal of action in the event of a major bleeding is still an issue with NOACs, as no specific antidote is currently available. Furthermore, there are no standardized tests to monitor the anticoagulant status of each patient.[8] **TABLE 1** provides an overview of advantages and disadvantages of NOACs compared with VKAs.

Ximelagatran was the first oral thrombin inhibitor to be marketed; nonetheless, it was

TABLE 1 Comparative features of vitamin K antagonists and novel oral anticoagulants

VKAs	NOACs
need for regular anticoagulation monitoring – food and drug interactions – narrow therapeutic window – inter- and intraindividual variability in dose response	fixed dose regimen without need for routine monitoring – low potential for food and drug interactions – wider therapeutic window – predictable anticoagulant effect
delayed onset of action	rapid onset of action
long half-life	short half-life
mainly hepatic metabolism	mainly renal clearance
available antidote	no available antidote
anticoagulant monitoring through INR	no standardized monitoring test

Abbreviations: INR – international normalized ratio, NOACs – novel oral anticoagulants, VKAs – vitamin K antagonists

withdrawn in 2006 because of severe hepatic toxicity.[9] The only NOACs to have completed phase III randomized controlled trials for stroke prevention in AF are dabigatran, rivaroxaban, and apixaban. This review will focus on the pharmacological properties and clinical results of these new drugs.

Dabigatran **Pharmacodynamics** Dabigatran is a direct inhibitor of thrombin, the final pathway in the coagulation cascade, which catalyzes the conversion of fibrinogen into fibrin and leads to thrombus formation. By interacting directly and exclusively with the active site of the thrombin molecule, dabigatran inactivates both free and clot-bound thrombin. This is a peculiar property because fibrin-bound thrombin is protected from inhibition by heparin and, moreover, is a trigger of thrombus expansion.[10] Dabigatran has also been demonstrated to decrease endogenous and tissue-factor-induced thrombin generation.[11]

Pharmacokinetics Dabigatran is administered orally as a prodrug, dabigatran etexilate, which is rapidly absorbed and converted by ubiquitous esterases into its active metabolite. After oral administration, it has an absolute bioavailability of only 6.5%, which is not influenced by coadministration of food.[10] Peak plasma concentrations are reached within 0.5 to 2 hours and elimination half-life is 12 to 14 hours after multiple doses.[10] Dabigatran is not metabolized by cytochrome P450 isoenzymes, being substantially unaffected by mild-to-moderate hepatic impairment.[11] The clearance occurs for about 80% via renal excretion of unchanged drug, while only 20% is excreted through the biliary system, making dabigatran contraindicated in severe renal impairment.[10] Because of low plasma protein binding, in case of required rapid reversal, dabigatran may be dialyzable.[12]

Dabigatran etexilate, but not dabigatran, is a substrate for P-glycoprotein (P-gp), so any potential interactions are restricted to drug absorption.[10] Coadministration of potent P-gp inducers (e.g., rifampicin or some antiepileptic drugs) should be avoided because they may reduce plasma dabigatran levels.[13]

Potent P-gp inhibitors may increase plasma concentrations of dabigatran, and thus azole-antimycotics, immunosuppressants, and human immunodeficiency virus protease inhibitors are contraindicated.[13] Also, verapamil amplifies the exposure to dabigatran only if present in the gastrointestinal tract when the drug is administered,[10] and its concomitant use necessitates a dose reduction, although no dose adjustment is required for amiodarone or quinidine.[13] **TABLE 2** provides a summary of the properties of NOACs in more advanced stages of development.

Trials Dabigatran has been investigated for prevention of thromboembolic complications of AF in the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy).[14] RE-LY enrolled 18,113 patients with nonvalvular AF and at least one of the following risk factors: previous stroke or transient ischemic attack (TIA), symptomatic heart failure or left ventricular ejection fraction <40%, age ≥75 years or age 65–74 years associated with diabetes mellitus, hypertension, or coronary artery disease. Patients were randomized to 2 blinded doses of dabigatran, 110 or 150 mg bid, or open-label warfarin dose adjusted to target INR 2.0–3.0. Main features and results are summarized in **TABLE 3**.

Dabigatran 110 mg bid was noninferior to warfarin in the primary efficacy outcome of stroke and systemic embolism (1.54% vs. 1.71% per year, P <0.001 for non-inferiority, P = 0.30 for superiority) and was superior with respect to the primary safety outcome of major bleeding (2.87% vs. 3.57% per year, P = 0.003). Dabigatran 150 mg was rather superior to warfarin for the primary efficacy outcome (1.11% vs. 1.71% per year, P <0.001 for superiority) and was associated with a similar rate of major bleeding (3.32% vs. 3.57% per year, P = 0.32). This trend was also evident between the 2 dabigatran doses.[14]

Considering subtypes of bleeding in the overall trial, intracranial hemorrhages were lower with both dosages of dabigatran, while major gastrointestinal bleeds were higher with dabigatran 150 mg compared both with warfarin and with dabigatran 110 mg.[15] A recent subanalysis according to age revealed that in patients <75 years both

TABLE 2 Characteristics of novel oral anticoagulants in more advanced stages of development compared with warfarin

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
mechanism of action	inhibition of factor II (thrombin)	inhibition of FXa	inhibition of FXa	reduced synthesis of vitamin K dependent coagulation factors (II, VII, IX, X, protein C and S)
dosing	bid	qd	bid	qd
bioavailability	~6%	66%–100%[a]	>50%	>95%
time to maximum plasma concentration	0.5–2 h	2–4 h	1–4 h	90 min[b]
half-life	12–14 h	5–9 h (young) 11–13 h (elderly)	8–13 h	36–42 h
route of clearance	80% renal	66% renal	25% renal	multiple[c]
plasma protein binding	35%	~90%	~90%	99%
cytochrome P450 metabolism	no	minor (mainly CYP3A4/5)	minor (mainly CYP3A4/5)	yes (mainly CYP2C9)
drug interactions	P-gp strong inhibitors and inducers	combined P-gp and CYP3A4 strong inhibitors and inducers	combined P-gp and CYP3A4 strong inhibitors and inducers	many different mechanisms of interaction
antidote	not available (suggested hemodialysis)	not available (suggested PCCs)	not available (suggested PCCs)	rapid reversal with PCCs or FFP, slow reversal with vitamin K

Abbreviations: FFP – fresh-frozen plasma, FXa – activated factor X, PCCs – prothrombin complex concentrates, P-gp – P-glycoprotein

a depending on dosage and fasting status
b however for peak action required 4–5 days
c almost entirely hepatic transformation into inactive metabolites, then mainly renal excretion

dosages of dabigatran were associated with lower major bleeding, whereas in patients ≥75 years intracranial hemorrhages were lower but extracranial bleeding were similar or higher (for 110 mg and 150 mg dose, respectively).[15]

A large number of cardioversions were performed during the RE-LY trial (1983 in 1270 patients). In a post-hoc analysis, the rates of thromboembolic and bleeding events at 30 days were low and comparable to those on warfarin; therefore, suggesting dabigatran as a reasonable alternative to warfarin in patients requiring cardioversion.[16] The benefit of dabigatran compared with warfarin, in primary efficacy and safety outcomes, was proven also in secondary prevention[17] and irrespective of previous VKA exposure[18] or type of AF.[19] Dabigatran resulted particularly advantageous, with regard to all vascular events and mortality, at site with poor INR control, while it was comparable to warfarin in those with good INR control (time within therapeutic range [TTR] >72%), though the analysis was performed on center's mean TTR and not on individual TTR.[20,21]

The only significant side effect of dabigatran was dyspepsia, consistently observed not only in the open-label RE-LY trial but also in the double-blind RE-COVER trial for treatment of acute venous thromboembolism (VTE).[22,23] This symptom and the associated greater risk of gastrointestinal bleeding may be partly explained by the formulation of dabigatran, which contains a tartaric acid core coated with dabigatran. The tartaric acid creates an acidic environment in order to enhance absorption of the drug, independently of gastric pH.[23]

Dabigatran has also been indirectly compared with antiplatelets.[24] The higher dosage (150 mg bid) showed nearly a two-third reduction of stroke compared with both monotherapy and double antiplatelet therapy, without increasing the risk of intracranial or extracranial bleeding. The lower dosage (110 mg bid) almost halved the relative risk of stroke compared with aspirin and aspirin plus clopidogrel, but the latter was borderline statistically significant. Furthermore, there was a trend towards reduction of bleeding events.[24]

License Dabigatran was approved in the European Union in 2008 for VTE prevention after total knee or hip arthroplasty.[13] In view of the results of the RE-LY trial, this compound has been included in the European guidelines for management of AF[5] and recently licensed by the European Medicines Evaluation Agency (EMEA) at 2 dosages (110 and 150 mg bid) depending on the balance between thromboembolic and bleeding risk factors.[5,13] The U.S. Food and Drug Administration (FDA) has rather approved only the 150 mg bid dosage, which should be reduced to 75 mg bid in selected cases (e.g., creatinine clearance 15–30 ml/min),[25] even if the latter has not been tested in the setting of AF.

Rivaroxaban **Pharmacodynamics** Rivaroxaban is an oral direct inhibitor of FXa. It can bind not only free FXa but also prothrombinase-bound and clot-associated FXa, without the need of antithrombin as cofactor.[26] FXa plays a critical role in the coagulation cascade, lying at the convergence

TABLE 3 Summary of phase III randomized clinical trials evaluating novel anticoagulants vs. vitamin K antagonists in atrial fibrillation

Trial	Patients (N)	Characteristics	Intervention	Duration of follow-up	Primary outcome: stroke or systemic embolism, %/y (n/N)	Rate ratio (95% CIs) [*P* value]	Major bleeding, %/y (n/N)	Rate ratio (95% CIs) [*P* value]
RE-LY[14]	18,113	nonvalvular AF ≥1 risk factor (previous stroke/TIA, symptomatic HF or LVEF <40%, age ≥75 y, age 65–74 y + DM or HTN or CAD) age 71 y (mean) men 63.6% $CHADS_2$ 2.1 (mean) TTR 64% (mean)[a]	warfarin	2.0 y (median)	1.71%/y (202/6022)		3.57%/y (421/6022)	
			dabigatran 110 mg bid		1.54%/y (183/6015)	0.90 (0.74–1.10) [0.30][b]	2.87%/y (342/6015)	0.80 (0.70–0.93) [0.003][b]
			dabigatran 150 mg bid blinded dosage of dabigatran, unblinded warfarin assignment		1.11%/y (134/6076)	0.65 (0.52–0.81) [<0.001][b]	3.32%/y (399/6076)	0.93 (0.81–1.07) [0.32][b]
ROCKET-AF[30]	14,264	nonvalvular AF history of stroke/TIA/SE or ≥2 risk factors (symptomatic HF or LVEF ≤35%, HTN, age ≥75 y, DM) age 73 y (median) men 60.3% $CHADS_2$ 3.5 (mean) TTR 55% (mean)[a]	warfarin	1.9 y (median)	2.4%/y (306/7090)		3.4%/y (386/7125)	
			rivaroxaban 15–20 mg od double blind, double dummy		2.1%/y (269/7081)	0.88 (0.75–1.03) [0.12][c]	3.6%/y (395/7111)	1.04 (0.90–1.20) [0.58][c]
ARISTOTLE[31]	18,201	nonvalvular AF or flutter ≥1 risk factor (age ≥75 y, previous stroke/TIA/SE, symptomatic HF or LVEF ≤40%, DM, HTN) age 70 y (median) men 64.7% $CHADS_2$ 2.1 (mean) TTR 62.2% (mean)[a]	warfarin	1.8 y (median)	1.60%/y (265/9081)		3.09%/y (462/9052)	
			apixaban 2.5–5 mg bid double blind, double dummy		1.27%/y (212/9120)	0.79 (0.66–0.95) [0.01][c]	2.13%/y (327/9088)	0.69 (0.60–0.80) [<0.001][c]

Abbreviations: AF – atrial fibrillation, CAD – coronary artery disease, CHADS2 score – cardiac heart failure, hypertension, age ≥75 years, diabetes mellitus (1 point each), previous stroke or transient ischemic attack or systemic embolism (2 points), CIs – confidence intervals, DM – diabetes mellitus, HF – heart failure, HTN – hypertension, LVEF – left ventricular ejection fraction, RCTs – randomized controlled trials, SE – systemic embolism, TIA – transient ischemic attack, TTR – time within therapeutic range INR, others – see TABLE 1

a the definition of TTR differed in the trials: RE-LY excluded INRs during first week and after discontinuation of study drug; ROCKET-AF included all INRs during the study and for 7 days after warfarin interruption; ARISTOTLE excluded INRs of the first 7 days after randomization and during study drug interruptions

b risk ratio

c hazard ratio

of intrinsic and extrinsic pathways and leading to thrombin generation.

Pharmacokinetics The absolute bioavailability of rivaroxaban after oral administration is dose-dependent, being from 80% to 100% for the 10 mg dose and 66% for the 20 mg dose in the fasting state.[27] Food results in delayed but increased absorption;[28] therefore, therapeutic dosages of rivaroxaban are recommended to be taken with meals.[27] Maximum plasma concentrations are reached after 2 to 4 hours, terminal half-life is 5 to 9 hours in young adults and 11 to 13 hours in the elderly.[27] Being practically insoluble in water, rivaroxaban has high plasma protein binding and is expected not to be dialyzable.[26]

Two-thirds of the drug are transformed into inactive metabolites via different CYP450 isoenzyme (CYP3A4/5 or CYP2J2) and via CYP-independent mechanisms.[26] In vitro studies showed that rivaroxaban is also a substrate for P-gp.[29] It is excreted predominantly in the urine (66% of the administered drug, 36% unchanged) and only 28% in the feces.[29] Therefore, rivaroxaban should be avoided in patients with moderate-severe hepatic impairment and severe renal failure (TABLE 2).[27]

Rivaroxaban is susceptible to few drug-drug interactions. Coadministration of combined P-gp and CYP3A4 strong inhibitors (e.g., azole-antimycotics or human immunodeficiency virus protease inhibitors) and inducers (e.g., rifampicin or some antiepileptic drugs) is contraindicated since they may increase or reduce, respectively, plasma concentrations.[27]

Trials The ROCKET-AF trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)[30] enrolled 14,264 patients with nonvalvular AF at moderate-high risk of stroke (history of stroke, TIA or systemic embolism, or ≥2 risk factors among symptomatic heart failure or left ventricular ejection fraction ≤35%, hypertension, age ≥75 years or diabetes mellitus). The proportion of patients with previous stroke was 55%, much higher compared with approximately 20% in the RE-LY[14] and ARISTOTLE[31] trials.

In a double-blind double-dummy fashion, patients in ROCKET-AF were randomized to rivaroxaban 20 mg daily (or 15 mg if creatinine clearance 30–49 ml/min) or adjusted-dose warfarin to a target INR 2.0–3.0. Rivaroxaban was administered once daily, despite the short half-life, since a pharmacokinetic study showed differences only in trough concentrations, not in total exposure expressed by the area under the curve,[32] and moreover this regimen has been effective as a maintenance dose in the treatment of VTE.[33]

In ROCKET-AF, rivaroxaban was noninferior to warfarin in the primary endpoint of stroke and systemic embolism with an annual rate of 2.1% vs. 2.4%, respectively (P <0.001 for noninferiority; P = 0.12 for superiority), in the intention-to-treat analysis. In the as-treated population, rivaroxaban was rather found to be superior (1.7% vs. 2.2% per year, P <0.001).[30] There were no significant differences in major bleeding between rivaroxaban and warfarin (3.6% vs. 3.4% per year, P = 0.58), except for intracranial and fatal hemorrhages, which were significantly reduced in the rivaroxaban group, while major gastrointestinal bleeding was more frequent (TABLE 3).[30]

In a subanalysis of patients with moderate renal impairment (20.7% of the study cohort), population at higher thromboembolic and bleeding risk and treated with reduced dosage of rivaroxaban provided results consistent with the overall trial.[34]

License Rivaroxaban was licensed by the EMEA in 2008 for VTE prevention after hip or knee replacement surgery.[35] At the beginning of November 2011, rivaroxaban was approved by the FDA for the prevention of stroke and systemic embolism in patients with nonvalvular AF, at a dose of 20 mg (or 15 mg if creatinine clearance 15–50 ml/min) taken once daily with the evening meal.[27]

Apixaban **Pharmacodynamics** Apixaban is an oral FXa inhibitor that shares the same mechanism of action with rivaroxaban. Apixaban directly inhibits the activity of free FXa, thrombus-associated FXa and FXa within the prothrombinase complex.[36]

Pharmacokinetics Oral bioavailability of apixaban is approximately 50%, independently from food administration. Peak plasma level is reached within 1 to 4 hours and half-life is 8 to 13 hours. Because of elevated protein binding, large proportion of the drug remains in the blood, resulting in a low distribution volume.[36]

About one-third of the drug is metabolized by hepatic cytochrome P-450 isoenzyme system (mainly CYP3A4/5) and apixaban is also a substrate for P-gp.[37] Its concentration may be increased after coadministration of strong inhibitors of both CYP3A4 and P-gp, which are contraindicated, and decreased by strong inducers of both CYP3A4 and P-gp, for which only caution is recommended.[38] Otherwise, the potential of apixaban to modify the cytochrome activity is minimal.[36]

Approximately 25% of the drug is excreted in the urine and more than 50% in the feces.[37] The multiple elimination pathways suggest that even patients with moderate hepatic or renal impairment may be suitable for this anticoagulant (TABLE 2).

Trials Apixaban has been investigated for stroke prevention in AF in 2 large randomized clinical trials, ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) and AVERROES (Apixaban Versus

Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment).

ARISTOTLE[31] compared apixaban 5 mg bid (dose reduced to 2.5 mg bid in a subset of patients with at least 2 criteria among age ≥80 years, body weight ≤60 kg, and serum creatinine ≥1.5 mg/dl) with warfarin dose-adjusted to target INR 2.0–3.0, using a double-blind double-dummy design. The study enrolled 18,201 patients with nonvalvular AF or flutter and at least 1 risk factor for stroke: age ≥75 years, previous stroke or TIA or systemic embolism, symptomatic heart failure or left ventricular ejection fraction ≤40%, diabetes mellitus, or hypertension (**TABLE 3**).

In ARISTOTLE, apixaban was superior to warfarin in the primary outcome of stroke or systemic embolism, with an annual event rate of 1.27% vs. 1.60% (P <0.001 for noninferiority; P = 0.01 for superiority). This impressive 21% reduction in the primary endpoint was largely driven by a reduction in hemorrhagic stroke, with no significant difference in ischemic stroke rate between apixaban and warfarin. Major bleeding events were lower in the apixaban group (2.13% vs. 3.09% per year, P <0.001), particularly intracranial hemorrhages. Apixaban was also associated with lower total mortality rate (3.52% vs. 3.94% per year, P = 0.047). The benefit of apixaban in the primary efficacy and safety outcomes was consistent across all age groups.[31]

Apixaban was also compared directly with antiplatelet therapy in the AVERROES trial.[39] In a double-blind double-dummy manner, 5599 patients with AF at increased risk for stroke (prior stroke or TIA, age ≥75 years, hypertension, symptomatic heart failure or left ventricular ejection fraction ≤35%, diabetes mellitus, or peripheral artery disease) and unsuitable or unwilling to take VKAs, were randomized to apixaban 5 mg bid (dose reduced to 2.5 mg bid in selected cases) or aspirin 81–324 mg daily. The trial was stopped prematurely, after approximately 1 year, because of clear benefit of apixaban. Apixaban was superior to aspirin in the primary outcome of stroke and systemic embolism (1.6% vs. 3.7% per year, P <0.001) and was associated with the reduction in the rate of death (3.5% vs. 4.4% per year, P = 0.07) without increasing the risk of major bleeding (1.4% vs. 1.2% per year, P = 0.57).

License Apixaban was licensed by the EMEA in May 2011 for VTE prevention after elective hip or knee replacement.[38] This novel oral anticoagulant has not been approved yet for AF patients, but an application to the FDA was expected by the end of 2011.

The challenge of choice The decision to initiate an anticoagulant treatment in AF patients is based on the balance between thromboembolic and bleeding risk factors,[5] well summarized by the CHA2DS2VASc[40] and HASBLED[41] scores. After 60 years of VKAs, the availability of NOACs, which can be easily managed without the need for routine monitoring, certainly opens a new era for anticoagulation. There are no direct comparisons among these new drugs, but differences in pharmacological properties and side effects may support the decision of the most suitable anticoagulant for each individual patient.[42]

VKAs may be considered for patients already on anticoagulant treatment, with optimal control of INR, good tolerance, and preference for periodic monitoring. In severe renal impairment, they are a safer option in view of the almost complete hepatic metabolism. Lastly, VKAs are still the inescapable choice for patients with valvular AF, given the lack of evidence with NOACs.

Intracranial hemorrhages are the most feared complications of anticoagulant therapy, ranging from 0.1% to 2.5% per year with warfarin[43] and potentially being devastating. NOACs are associated with a much lower risk of intracranial bleeding, possibly related to selective inhibition of specific coagulation factors and maintenance of other hemostatic mechanisms.

Dabigatran has the advantage of being available in 2 different dosages, both being noninferior to warfarin. There are also data on dabigatran use as a substitute for warfarin in patients undergoing cardioversion. Nevertheless, dabigatran is associated with an increased risk of major gastrointestinal bleeding.[13] The side effect of dyspepsia might also require swapping to an alternative oral anticoagulant treatment.

Rivaroxaban reached noninferiority in the ROCKET-AF trial and the suboptimal control of INR in the warfarin group (mean TTR only 55%) has provoked some discussion. However, rivaroxaban has been tested in a high-risk AF population (55% being a secondary prevention population), where it revealed to be at least as effective and as safe as warfarin, with the benefit of less intracranial bleeding. This drug, compared with other NOACs, has also the advantage of once-daily administration, which can perhaps promote patients' compliance.

Apixaban seems the most favorable given that it achieved superiority in both efficacy and safety outcomes, as well as a significant reduction of total mortality.

Dabigatran and apixaban arise as alternatives to antiplatelet therapy in real-life AF patients, who receive suboptimal treatment regardless of high stroke risk.[44] These NOACs could replace aspirin in patients unsuitable or unwilling to receive oral anticoagulation with VKAs. The safety of NOACs in AF patient, which require a long-term treatment, is still under evaluation in the ongoing extension of the above mentioned trials.

The trouble of hepatotoxicity with ximelagatran has not been confirmed with the other compounds. Until now, dabigatran, rivaroxaban, and apixaban have not shown any excess of liver enzyme elevations compared with warfarin. Nonetheless, the RE-LY trial raised the problem of acute coronary syndrome. There were numerically,

but not statistically significant, more myocardial infarction events in the dabigatran groups compared with warfarin groups.[14] This finding raises the question whether warfarin might be protective against myocardial infarction, as suggested by a recent analysis.[45] However, the trials with 2 FXa inhibitors, rivaroxaban and apixaban, both had a trend towards a lower rate of myocardial infarction compared with warfarin. The management of anticoagulated patients with AF who present with an acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting remains a complex management issue.[46-48]

Another problem of NOACs is the price. Warfarin itself is relatively inexpensive, but the costs of laboratory monitoring and of complications due to under- or overanticoagulation are considerable. Dabigatran is priced approximately 10-fold higher than warfarin, but in several economic models the lower rate of clinical events increased patients' survival and reduced the cost of long-term disability.[49,50] Thus, dabigatran appeared a highly cost-effective alternative to current care with VKAs, especially where anticoagulation control is suboptimal.

Conclusions New oral anticoagulants, with favorable pharmacokinetics profile and unnecessary routine monitoring, emerged recently as effective and safe alternative to VKAs in the prevention of stroke and systemic embolism triggered by AF. Each compound has its own features that may address the necessity of the individual patient. Some practical issues (e.g., safety of long-term therapy, absence of antidote and standardized laboratory test, cost-effectiveness in real life, etc.) still need to be resolved in the management of AF patients.

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Nowy okres w leczeniu przeciwzakrzepowym chorych z migotaniem przedsionków

Który antykoagulant należy wybrać do przewlekłej prewencji powikłań zakrzepowo-zatorowych u chorych z migotaniem przedsionków?

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SŁOWA KLUCZOWE

apiksaban, dabigatran, doustne antykoagulanty, migotanie przedsionków, rywaroksaban

STRESZCZENIE

Przez ponad 60 lat antagoniści witaminy K byli jedynymi doustnymi antykoagulantami w prewencji udaru mózgu i zatorowości w krążeniu dużym u chorych z migotaniem przedsionków. Ostatnio opracowano kilka nowych cząsteczek o korzystnym profilu farmakokinetycznym, niewymagających rutynowego monitorowania, co rozpoczęło nowy okres w antykoagulacji. Bezpośredni inhibitor trombiny (dabigatran) i inhibitory czynnika Xa (rywaroksaban i apiksaban) są nowymi doustnymi antykoagulantami, które według wyników dużych badaniach klinicznych z randomizacją nie są gorsze od warfaryny w prewencji udaru mózgu i powikłań zakrzepowo-zatorowych migotania przedsionków, a ich zaletą jest, że powodują mniejsze ryzyko udaru krwotocznego i krwawienia wewnątrzczaszkowego. Choć wyniki tych badań są zachęcające, to kilka praktycznych zagadnień (np. brak swoistego antidotum, bezpieczeństwo długoterminowego leczenia i efektywność kosztów w praktyce klinicznej) wciąż wymaga wyjaśnienia.

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