REVIEW ARTICLE

Practical aspects of new oral anticoagulant use in atrial fibrillation

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KEY WORDS

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ABSTRACT

Dabigatran, a direct thrombin inhibitor and 2 factor Xa inhibitors, rivaroxaban and apixaban, are target-specific oral anticoagulants (TSOACs) approved for prevention of stroke or systemic embolism in patients with nonvalvular atrial fibrillation (AF). Published data suggest that all 3 agents are at least as efficacious as dose-adjusted warfarin in stroke prevention. Because of their greater specificity, rapid onset of action, and predictable pharmacokinetics, TSOACs have some advantages over vitamin K antagonists, which facilitates their use in clinical practice. The current review addresses the practical questions relating to the use of TSOACs in AF patients based on the available data and personal experience. We discuss topics such as patient selection, renal impairment, drug interactions, switching between anticoagulants, laboratory monitoring, and the risk of bleeding along with its management. We will focus on the aspects of the optimization of treatment with TSOACs in stroke prevention. The understanding of these practical issues by clinicians and patients is of key importance for the safe and effective use of TSOACs in everyday practice.

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Introduction Atrial fibrillation (AF) has a prevalence of about 1% in the general population, ranging from 0.5% in individuals aged between 50 and 59 years to 18% in those older than 85 years. AF is the leading preventable cause of ischemic stroke, and for this reason, stroke prevention represents a key management strategy for AF patients, beside rate and rhythm control. The annual risk of stroke in individual AF patients not receiving prophylaxis with anticoagulants varies substantially from 1% to about 23% at the age of 80 to 89 years, with an average overall risk reaching 4.5%.[1-3]

Strokes due to AF represent from 15% to 20% of all strokes and are associated with higher mortality and morbidity. It is estimated that up to 70% of AF-associated strokes are fatal (mortality of 20% to 25% within the first 30 days since the event) or associated with persistent and severe neurological deficits.[1] The risk of AF-associated ischemic stroke is reduced by 65% by oral vitamin K antagonist (VKA) therapy and by about 20% by antiplatelet agents. About 50% of AF patients do not receive anticoagulation and, among the anticoagulated subjects with AF, every second individual on VKAs is undertreated, which is of particular importance in countries such as Poland where there are no specialized anticoagulation clinics.

New (novel) oral anticoagulants or target-specific oral anticoagulants (TSOACs) including 1 thrombin inhibitor, dabigatran, and 2 activated factor X (FXa) inhibitors, rivaroxaban and apixaban, are increasingly used worldwide in patients with nonvalvular AF for the prevention of ischemic stroke and peripheral embolism. All TSOACs have common features that distinguish them from VKAs, such as warfarin, including rapid onset of action, shorter half-life, few drug–drug interactions, a predictable anticoagulant response, no need for routine coagulation monitoring, and no need for titration or routine dose adjustments (TABLE 1).

Current evidence indicates that TSOACs have at least equivalent efficacy to VKAs with similar severe bleeding risk and reduced intracranial bleeding risk in AF patients (see previous reviews

TABLE 1 Characteristics of target-specific oral anticoagulants

Variable	Warfarin	Dabigatran etexilate[a]	Rivaroxaban	Apixaban
mode of action	↓ synthesis vitamin K-dependent coagulation factors	direct selective and reversible thrombin inhibitor	direct selective and reversible activated factor X inhibitor	direct selective and reversible activated factor X inhibitor
time to peak plasma concentration	90 min (peak action after 4–5 d)	0.5–2 h	2–4 h	1–4 h
half-life	36–42 h	12–14 h	5–9 h (young) 11–13 h (age >65 y)	8–13 h
substrate of P-glycoprotein transporter	no	yes	yes	yes
substrate of CYP enzymes	yes (CYP3A4, CYP2C9)	no	yes (CYP3A4/5, CYP2J2)	yes (CYP3A4, CYP2C9)
route of elimination	various[c]	80% renal	66% renal (33% unchanged)	25% renal
protein binding	99%	35%	90%	90%
basic daily dose in AF	~5 mg (1–18 mg) target INR, 2–3	2 × 150 mg	1 × 20 mg	2 × 5 mg
reduced daily dose	not applicable	2 × 110 mg[b]	1 × 15 mg	2 × 2.5 mg
indications for reduced dosage	not applicable	– CrCl, 30–49 ml/min – HAS-BLED ≥3 points – age ≥80 y – coadministration of verapamil	– CrCl, 30–49 ml/min – HAS-BLED ≥3 points	– creatinine ≥133 µM – age ≥80 y – body weight ≤60 kg (2 or 3 criteria met)

a a prodrug that undergoes biotransformation to the active molecule, dabigatran, by esterases
b in the United States: 2 × 75 mg daily (2 × 110 mg not approved)
c the anticoagulant effect of warfarin is eliminated through synthesis of functionally active coagulation factors rather than through elimination of warfarin; coagulation factor synthesis is hastened by exogenous vitamin K

Abbreviations: INR – international normalized ratio

published in the *Pol Arch Med Wewn*).[1-3] The results of 3 key clinical trials with TSOACs have been summarized in TABLE 2.[1] Briefly, all 3 TSOACs were noninferior to VKAs in reducing stroke or systemic embolism in patients with nonvalvular AF, and dabigatran 150 mg twice daily and apixaban 5 mg twice daily were superior to warfarin in terms of efficacy.[4-6]

Reimbursement of TSOACs in AF is currently pending in Poland, and partial reimbursement of rivaroxaban for patients with venous thromboembolism was introduced in September 2013. Since an increasing number of patients with AF buy TSOACs out of their own pockets in Poland, about 10% of AF patients are treated with TSOACs (most commonly with rivaroxaban), and this number is rising slowly but steadily. To effectively treat AF patients with this new class of anticoagulants, several practical aspects of this therapy should be considered.

In this review, we focus on the key issues related to the efficacy and safety of TSOACs administered in patients with AF, based on clinical evidence and our own experience.

Efficacy and patient-selection concerns The benefits of TSOACs in nonvalvular AF were established on the basis of large phase III clinical trials that were conducted, at least in part, in Poland (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY], Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET-AF], Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE]).[4-6] Both dabigatran and apixaban were tested in low-to-moderate-risk patients (mean $CHADS_2$ [Congestive heart failure, Hypertension, Age, Diabetes, Stroke] score, about 2), whereas rivaroxaban was tested in high-risk patients (mean $CHADS_2$ score, 3.48). The studies, therefore, provide relatively little data on the efficacy of these drugs in patients at very high risk of stroke or systemic embolization.

The recent European Society of Cardiology (ESC) Guidelines on the Management of AF recommend long-term anticoagulation in all patients with nonvalvular AF with at least moderate thromboembolic risk (1 point in the CHA_2DS_2VASc score, level of evidence A).[7] Scores are presented in TABLE 3.

In CHA_2DS_2-VASc, the score recommended by the ESC, in contrast to the $CHADS_2$ score, a relatively younger age (>65 years), female sex, and vascular disease are recognized as additional stroke risk factors in AF patients.[7] A CHA_2DS_2-VASc score of 0 identifies a "truly low risk" group of subjects. Such patients constitute as few as 7% of the population of AF patients.[7] In conclusion, the current guidelines state that a vast majority of patients with paroxysmal or permanent AF not associated with reversible causes will benefit and should receive life-long oral anticoagulation.

TABLE 2 Summary of the landmark randomized clinical trials evaluating target-specific oral anticoagulants vs. vitamin K antagonists in atrial fibrillation[1]

Trial	Patients, N	Characteristics	Intervention	Duration of follow-up	Primary outcome: stroke or systemic embolism, %/y (n/N)	Rate ratio (95% CI) [*P* value]	Major bleeding,%/y (n/N)	Rate ratio (95% CI) [*P* value]
RE-LY	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 dabigatran, 110 mg bid dabigatran, 150 mg bid blinded dosage of dabigatran, unblinded warfarin assignment	2.0 y (median)	1.71%/y (202/6022) 1.54%/y (183/6015) 1.11%/y (134/6076)	 0.90 (0.74–1.10) [0.30][b] 0.65 (0.52–0.81) [<0.001][b]	3.57%/y (421/6022) 2.87%/y (342/6015) 3.32%/y (399/6076)	 0.80 (0.70–0.93) [0.003][b] 0.93 (0.81–1.07) [0.32][b]
ROCKET-AF	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 rivaroxaban, 15–20 mg od double blind, double dummy	1.9 y (median)	2.4%/y (306/7090) 2.1%/y (269/7081)	 0.88 (0.75–1.03) [0.12][c]	3.4%/y (386/7125) 3.6%/y (395/7111)	 1.04 (0.90–1.20) [0.58][c]
ARISTOTLE	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 apixaban, 2.5–5 mg bid double blind, double dummy	1.8 y (median)	1.60%/y (265/9081) 1.27%/y (212/9120)	 0.79 (0.66–0.95) [0.01][c]	3.09%y (462/9052) 2.13%/y (327/9088)	 0.69 (0.60–0.80) [<0.001][c]

a the definition of TTR differed in the trials: RE-LY excluded INRs during the 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

Abbreviations: AF – atrial fibrillation, CAD – coronary artery disease, $CHADS_2$ score – cardiac heart failure, hypertension, age ≥75 years, diabetes mellitus (1 point each), previous stroke or transient ischemic attack or systemic embolism (2 points), CI – 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**

This conclusion is based on the data demonstrating that the risk of death or severe sequelae of stroke are much higher than the risk of death for bleeding.[7]

According to the 2012 ESC guidelines, TSOACs represent a preferred prophylactic option over VKAs in nonvalvular AF patients.[7] The authors of those guidelines recommend these drugs be considered first in VKA-naive AF patients and in certain subsets of patients already receiving anticoagulation, including patients: 1) who despite well-controlled treatment with VKAs suffer from ischemic stroke or systemic embolism; 2) who have unstable anticoagulation (time in therapeutic range of international normalized ratio [INR] below 60%–65%) despite regular VKA administration and following dietary recommendations aiming at stabilizing vitamin K intake over time. It is crucial to highlight that if unstable INRs are due to noncompliance, VKAs still remain the anticoagulant of choice in the majority of AF patients, since the ability to monitor them will allow ongoing compliance assessment; 3) who report intolerance to VKAs, including allergic reactions, or who cannot monitor INRs for logistic reasons.

Not all patients with nonvalvular AF should be treated with TSOACs; AF patients on stable VKA anticoagulation without adverse events and with high time in the therapeutic range (TTR) values should continue VKAs.[1-3]

Comparison of target-specific oral anticoagulants A cumulative analysis including data for 14,527 patients on TSOACs showed that these drugs were associated with a significant reduction of stroke/systemic embolism (odds ratio [OR], 0.85; 95% CI, 0.74–0.99) compared with warfarin.[8] From a practical point of view, the key question for many physicians is: Which of TSOACs should be the preferred option in a given patient? As much as all TSOACs are similar, they do differ as shown in TABLES 1 and 2.

Given lack of "head-to-head" direct comparisons of TSOACs, several analyses of the relative effect of different treatment interventions have been published based on indirect comparisons, using a common comparator such as warfarin in the 3 landmark trials with TSOACs.[4-6] However, it is obvious that any intertrial comparison has several limitations. First of all, the 3 cohorts differed significantly in terms of the $CHADS_2$ score and the number of individuals with a past history of stroke, transient ischemic attack (TIA), or systemic embolism (TABLE 2). Further, warfarin control, measured by TTR, varied substantially between the studies.[4-6]

These indirect comparisons suggest that AF patients with a $CHADS_2$ score of 3 or higher treated with dabigatran (150 mg), apixaban (5 mg), and rivaroxaban (20 mg) had similar relative risks of stroke and systemic embolism, although stroke rates in patients allocated to apixaban and dabigatran were numerically better than warfarin, whereas rivaroxaban was only noninferior to warfarin.[9] Another indirect analysis of all the participants of the trials with TSOACs[4-6] found a significantly lower risk of stroke and systemic embolism (by 26%) for dabigatran (150 mg twice daily) compared with rivaroxaban, without any differences for apixaban vs. dabigatran (both doses) or rivaroxaban; or rivaroxaban vs. dabigatran (110 mg twice daily).[10] For ischemic stroke alone, there were no significant differences between the TSOACs.[10] Apixaban, in this indirect and thus less reliable analysis, might be seen to be the preferred agent given its better efficacy and safety outcomes as well as a significant reduction of total mortality by 11% compared with warfarin.[1,4-6] However, apart from the results of this indirect and thus questionable comparative analysis, other considerations when deciding on the appropriateness and timing of the introduction of TSOACs are relevant in a particular patient and include, among others, frequency of administration (once vs. twice daily), bleeding risk, and costs. We conclude that there is insufficient evidence to recommend a particular TSOAC in preference to the others.

Valvular defects and the use of target-specific oral anticoagulants The definition and prevalence of valvular AF have changed over the last 30 years, from severe symptomatic mitral stenosis (now reduced in frequency owing to reduced rheumatic fever and increased valve replacements) to mild valvular regurgitations frequently detected by echocardiography in asymptomatic patients. There were substantial differences in the exclusion criteria related to valvular defects applied in the 3 landmark trials with TSOACs.[4-6] Moderate-to-severe mitral stenosis excluded AF patients from RE-LY and ARISTOTLE,[4,6] while in ROCKET-AF, subjects with hemodynamically significant mitral valve stenosis were ineligible.[5] Most experts agree with the statement that, in patients with AF and concomitant inconsequential valvular disease, either TSOACs or VKAs can be used.[11] Based on the current evidence (and extrapolated from the experience with mechanical heart valves), novel oral anticoagulants (NOACs) should not be used in AF patients with moderate-to-severe mitral stenosis and other severe valvular defects requiring surgery. Most AF patients with mild or moderate mitral regurgitation may be considered as candidates for anticoagulation with TSOACs. Patients following annuloplasty with or without prosthetic ring, commissurotomy, and/or valvuloplasty who were not excluded from the trials[4-6] could also receive TSOACs.

A strong contraindication to TSOACs, at least in the doses used by investigators, is AF concomitant with mechanical heart valves, as convincingly evidenced by the results of the RE-ALIGN study.[12] This study was terminated prematurely because of a significant excess of thromboembolic events (including fatal mitral valve thrombosis) and bleeding, especially pericardial bleeding, in patients allocated to dabigatran at doses of 150 to 300 mg twice daily.[12] Patients with bioprosthetic

heart valves who have received an initial 3 month course of VKAs may subsequently safely receive a TSOAC for long-term prevention of stroke or systemic embolism in the setting of paroxysmal or permanent AF.

Safety concerns Phase III clinical trials (RE-LY, ROCKET-AF, ARISTOTLE) were conducted in large multiethnic populations that might be, however, not fully representative of real-world European AF patients.[4-6] Caution should thus be exercised when prescribing a TSOAC for a patient who would have likely has been excluded from the randomized controlled trials.

Most important considerations are advanced age, impaired renal function, low body weight, presence of multiple comorbidities, and the need for concomitant therapies. Such conditions commonly coexist, particularly in very elderly patients.

Advanced age The mean/median age of AF patients enrolled into large trials with TSOACs were 70 years in the ARISTOTLE trial with apixaban, 71 years in the RE-LY trial with dabigatran, and 73 years in the ROCKET-AF trial with rivaroxaban (TABLE 2).[4-6] It is estimated that about 40% of AF patients treated with TSOACs in Western Europe are 75 years of age and older.

Prespecified subgroup analyses of patients older than 75 years performed in these trials reported benefits and harms that were not different to those observed in the general study populations.[4-6] It seems that older age by itself should not to be considered a contraindication to the use of TSOACs but some age-related comorbidities should be taken into account while prescribing these agents.[13] A major issue regarding the use of TSOACs in the elderly is high prevalence of renal insufficiency.[13]

Based on the results of the EPICA study, demonstrating the efficacy and safety of anticoagulation with VKAs in patients aged 80 years and older,[14] one might suspect that the similar risk factors for stroke on warfarin could pose threat in TSOAC-treated subjects, i.e., previous stroke or TIA, clinically overt ischemic heart disease or peripheral artery disease, and arterial hypertension. Since history of bleeding, active cancer, and history of falls have been shown to be independently associated with bleeding risk at the age of 80 years and older,[14] it is likely that the same factors may contribute to bleeds in very elderly patients on TSOACs. These subsets of anticoagulated AF patients at advanced age should be carefully monitored in outpatient clinics with renal function assessment and blood cell count every 6 to 8 weeks in subjects with the results below the reference ranges at the time of the first dose of TSOACs.

Impaired renal function Because all the currently available TSOACs are excreted, at least partially, via the kidneys (TABLE 1), renal impairment might result in drug accumulation. This is particularly important for dabigatran as renal excretion accounts for 80% of dabigatran clearance. Creatinine clearance (CrCl) lower than 30 ml/min is thus an absolute contraindication to the use of dabigatran.[7] A dose reduction to 110 mg twice daily is recommended for patients with CrCl between 30 and 49 ml/min in Europe.[8] Despite the fact that the kidneys clear only about one-third of rivaroxaban, and rivaroxaban is approved for clinical use in patients with CrCl between 15 and 29 ml/min, the ESC guidelines recommend against using it in such patients.[7] Importantly, severe renal insufficiency was an exclusion criterion both in the ROCKET-AF (rivaroxaban) and RE-LY (dabigatran) studies.[4,5] Dose reduction from 20 mg of rivaroxaban once daily to 15 mg once daily is recommended for patients with CrCl between 30 to 49 ml/min, which results in the need for monitoring renal function at least 2 to 3 times a year. A substudy of the ROCKET-AF trial showed this lower dose of 15 mg daily to be safe and effective in AF patients with CrCl between 30 and 49 ml/min, who represented 20.7% of the study population.[5] None of the TSOACs should be used in patients with CrCl below 30 ml/min, including those on dialysis, based on the ESC guidelines.[7]

In the RE-LY and ROCKET-AF trials,[4,5] drug eligibility and dosing were determined using CrCl calculated with the Cockcroft–Gault formula. It has been shown that among AF patients aged 80 years and older, 15% were ineligible for dabigatran based on CrCl below 30 ml/min but would have been judged eligible applying the estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease method, while for those younger than 80 years, 5% would have received too high a dose of dabigatran.[15] For rivaroxaban, the trend was similar though the proportions were slightly lower.[15] We recommend the calculation of CrCl in AF patients aged 75 years and older.

Liver injury Patients with active liver disease were excluded from enrollment in the landmark studies with TSOACs.[4-6] Child Pugh B and C liver cirrhosis currently represents a contraindication to the use of TSOACs, and, in general, patients with elevated serum transaminases exceeding twice the upper limit of normal should not be started on TSOACs, especially in the presence of laboratory signs of hepatic coagulopathy.[4-6] AF patients with slightly elevated transaminases or bilirubin levels or both are eligible for treatment with TSOACs; however, they require monitoring of abnormal liver transaminases, starting within 3 months since the initiation of anticoagulation. Of note, abnormal liver function or chronic liver disease is a bleeding risk factor (1 point in the HAS-BLED score, TABLE 3) which occurs in about 3% of the AF patients.[4-6] TSOACs can also cause a transient elevation of hepatic transaminases in about 2% of the treated patients,[4-6] and such complication requires drug

TABLE 3 Scores used to assess thromboembolic and bleeding risks (adapted from Douketis[39])

$CHADS_2$	
congestive heart failure	1
hypertension	1
age ≥75 y	1
diabetes	1
prior stroke or transient ischemic attack	2
CHA_2DS_2-VASc	
congestive heart failure/left ventricular dysfunction	1
hypertension	1
age ≥75 y	2
diabetes	1
prior stroke or transient ischemic attack or systemic embolism	2
vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
age 64–74 y	1
female sex	1
HAS-BLED	
hypertension (systolic pressure >160 mmHg)	1
abnormal renal function	1
abnormal liver function	1
age ≥65 y	1
prior stroke	1
prior bleeding	1
labile INRs (e.g., TTR <60%)	1
taking other drugs at the same time (e.g., ASA, NSAIDs)	1
alcohol intake at the same time	1

Abbreviations: ASA – acetylsalicylic acid, NSAIDs – nonsteroidal anti-inflammatory drugs, others – see TABLES 1 and 2

withdrawal. Normalization of liver enzymes is usually observed within 2 weeks.

Thrombocytopenia A platelet count of 100,000/μl or less is considered a bleeding risk factor in AF patients (1 point in the HAS-BLED score).[7] A platelet count between 50,000/μl and 100,000/ μl does not contraindicate administration of TSOACs or VKAs, although, for example, in the RE-LY and ROCKET-AF trials, patients with platelet count below 100,000/μl and 90,000/μl, respectively, were excluded.[4,5] Within the first weeks of such therapy, the patient should be carefully monitored and the platelet count serially monitored. From our experience, AF patients with mild persistent thrombocytopenia of about 60,000 to 90,000/μl and a HAS-BLED score of 3 or less can be safely treated with NOACs (TABLE 3). Subjects with a persistent platelet count of 50,000/μl or less should not be treated with TSOACs. Irrespective of the platelet count in all patients with thrombocytopenia, it is appropriate to explore causes of thrombocytopenia as they may elevate bleeding risk and require special management.[16,17]

Concomitant drugs Dabigatran etexilate is a prodrug that is a substrate for transporter P-glycoprotein (P-gp), and changes in the bioavailability of the active drug, dabigatran, can be expected with the concomitant use of strong P-gp inhibitors (e.g., amiodarone, verapamil, ketoconazole, clarithromycin, and quinidine) or inducers (e.g., rifampicin and St John's wort). Concomitant use of dabigatran and cyclosporin, itraconazole, ketoconazole, and tacrolimus is currently contraindicated given an increase in drug's concentration of up to 160%.[16] A reduction of the dose of dabigatran with concomitant use of amiodarone or verapamil is recommended by the 2012 ESC guidelines.[7] It is recommended to take verapamil 2 h prior to administration of dabigatran. Dabigatran is further metabolized by cytochrome P450, but isoform CYP3A4 has a negligible role in its metabolism. However, CYP3A4 plays an important role in the oxidative metabolism of rivaroxaban and apixaban. The interactions with cytochrome CYP3A4 inducers such as rifampin, carbamazepine, St John's wort, or inhibitors that include azole antimycotics and human immunodeficiency virus protease inhibitors can be expected. Drugs potently disturbing anticoagulation with NOACs, for example azole antimycotics, should be stopped at least 4 days before starting such treatment.[17]

Low-dose aspirin was allowed in clinical trials on TSOACs; the proportion of AF patients on aspirin was from 30% to 40%.[4-6] Concomitant use of antiplatelet agents and TSOACs is associated with an increase in bleeding risk (in particular gastrointestinal bleeding risk) similar to that observed with concomitant aspirin and warfarin.[5,6] Dual therapy should be continued for the shortest possible period of time and be restricted to patients with low bleeding risk combined with high thrombotic risk. Dual therapy increases the bleeding risk by about 60%; therefore, it is reasonable to discontinue aspirin in AF patients with stable angina, with no history of recent coronary event (within the previous year) if bleeding risk is increased.[16] However, given the data on a slightly increased risk of myocardial infarction in patients on dabigatran in the RE-LY trial,[4] some experts recommend that dabigatran, but not rivaroxaban or apixaban, should be used in combination with aspirin in patients with stable angina who had AF with elevated thromboembolic risk. Little is known about the combination of TSOACs with clopidogrel, prasugrel, or ticagrelor.[4-6] Such therapy should be avoided, where possible, because of the likely increased risk of bleeding seen with coincident therapy.[16]

In contrast to dabigatran and apixaban, low-dose rivaroxaban (2.5 mg twice daily) reduces cardiovascular death, myocardial infarction, stroke, and stent thrombosis in patients with acute coronary syndromes.[18] Whether such therapy is safe in patients with AF is unknown; the dose of rivaroxaban used in such study is well below that used for prevention of stroke or systemic embolism in patients with AF.[3] Triple

TABLE 4 How to switch a patient from vitamin K antagonists to new oral anticoagulants

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)
INR values suggested by the manufacturers	≤2	≤3	≤2
acceptable INR values	≤2.3–2.5	≤2.3–2.5	≤2.3–2.5
number of days without VKA if the initial INR is >3.5	2	2	2

Abbreviations: VKA – vitamin K antagonist, others – see **TABLE 1**

antithrombotic therapy (i.e., a TSOAC with 2 antiplatelet agents) with TSOACs is not recommended.[16,19] In our opinion, following acute coronary syndrome or percutaneous coronary intervention in AF patients with low bleeding risk, a TSOAC combined with aspirin may be prescribed after 6 months of triple therapy using a VKA as the anticoagulant of choice.

Conversion from vitamin K antagonist to a target-specific oral anticoagulants and vice versa Surprisingly, manufacturers of TSOACs recommend different cut-off INR values that are perceived as safe while starting TSOACs in patients treated with VKAs (**TABLE 4**). It has been suggested to start dabigatran or rivaroxaban when warfarin has been discontinued and the INR has decreased below 2.3.[17] This value has been adopted from the RE-LY trial where patients might have been receiving warfarin before starting dabigatran; transition at an INR value of 2.3 or less was not associated with an increased bleeding risk.[4] In our opinion, INR values of up to 2.3–2.5 seem acceptable on the day when the first dose of NOACs is administered, which is particularly relevant in outpatients at high thrombotic risk, with limited access to anticoagulation clinics and INR measurements.

For patients who are unable to continue on TSOACs and who are transitioning to warfarin, it has been suggested that the first INR should be obtained on day 3 of warfarin medication in combination with the TSOAC, similarly to the strategy used during introduction of VKAs in subjects receiving heparins. The INR should be obtained when the TSOAC level is at trough to reduce the potential for the TSOAC to increment the INR beyond the effect of warfarin alone. It is reasonable to measure the first INR on day 2 in patients starting acenocoumarol, which has a rapid onset of action compared with warfarin. From our personal experience, this strategy appears to be safe.

Point-of-care INR monitors should not be used to assess the INR during transition from rivaroxaban or apixaban to VKAs owing to the potential for artifactual prolongation of clotting times.[17]

Laboratory monitoring The fact that laboratory monitoring is not required is a considerable advantage of TSOACs; however, there are some clinical situations when laboratory monitoring of anticoagulant effect is desirable.

The measurement of TSOAC levels may be considered in the following situations: a) "clinically important bleeding; b) before surgery or invasive procedure when patient has taken drug in previous 24 hours, or longer if CrCl is <50 ml/min; c) identification of sub- or supra-therapeutic levels in patients taking other drugs that are known to significantly affect pharmacokinetics; d) identification of sub- or supra-therapeutic levels in patients at extremes of body weight; e) patients with deteriorating renal function; f) peri-operative management; g) reversal of anticoagulation; h) suspicion of overdose; i) assessment of compliance in patients suffering thrombotic events whilst on treatment.[20-23]

Traditional coagulation tests can be used to provide guidance with respect to the presence of novel agents. Within the first 2 to 8 h after intake of dabigatran, depending on renal function and the machine and reagent used to perform the test, the activated partial thromboplastin time (aPTT) may be prolonged to between 40 and 60 s, with a linear relationship with dabigatran concentrations up to 200 ng/ml.[22] Patients may have significant amounts of dabigatran in their circulation with a normal PTT; therefore, a normal PTT is not a reassurance that clinically important levels of drug are absent. In patients treated with dabigatran, thrombin time (TT) is prolonged at low concentrations and becomes rapidly unclottable as plasma levels rise. A normal TT excludes significant plasma concentrations of dabigatran. Rivaroxaban or apixaban does not have any effect on the TT; therefore, a normal TT does not exclude the presence of significant concentrations of these drugs. PT and INR values may also be elevated by dabigatran. Substantial differences are noted, depending on the thromboplastin reagent used to perform the test.[20,22]

In patients receiving rivaroxaban, PT values are often elevated by 20% to 30% above the upper limit of the reference range, leading to increased INR calculated by most automatic analyzers. Prolongation is seen within 2 to 4 h since the drug's intake.[20-22] There is a marked variability in responsiveness to rivaroxaban between PT reagents.[22] Apixaban produces a weaker effect of PT; therefore, INR values on this agent are mostly below 1.2. These observations confirm that the INR cannot be used to monitor TSOACs.[19-22] Inhibition of FXa activity by rivaroxaban as well as apixaban prolongs the PT in a dose-dependent manner.[20]

TABLE 5 How to stop new oral anticoagulants prior to invasive procedure depending on bleeding risk (modified from Heidbuchel H, et al.[10])

Creatinine clearance, ml/min	Dabigatran should be stopped before the procedure, h		Rivaroxaban/apixaban should be stopped before the procedure, h	
	low bleeding risk	high bleeding risk	low bleeding risk	high bleeding risk
≥80	≥24	≥48	≥24	≥48
50–79	≥36	≥72	≥24	≥48
30–49	≥48	≥96	≥24	≥48
15–29	dabigatran not indicated		≥36	≥48
<15	dabigatran contraindicated		rivaroxaban/apixaban contraindicated	

TSOACs may interfere with other clot-based tests such as clotting factor levels, antithrombin (false normal results in deficient patients on dabigatran in a thrombin-based assay), protein C (false normal results in deficient patients on dabigatran), lupus anticoagulant (false positive results in some patients at peak plasma concentrations of drug), thrombin generation, and others.[22] Genetic thrombophilia tests, chromogenic assays, and measurements of plasma D-dimer concentrations are, however, unaffected by TSOACs.[20-22]

The HEMOCLOT assay to measure dabigatran concentration has been approved for clinical use in Europe.[21-23] Rivaroxaban and apixaban can be quantified in clinical practice with calibrated chromogenic FXa assays, given their calibration with appropriate calibrants, not low-molecular-weight heparin (LMWH) standards.[22,23] Unlike a VKA-treated patient, to interpret the results of the tests, it is important to know the exact time when the blood sample was drawn relative to the intake of the last dose of TSOACs because the drugs have short half lives—this is quite different from warfarin where the slow rate of change of the INR does not require "timing" of sample acquisition.

Follow-up strategies and adherence issues Compliance is a significant concern with TSOACs owing to the lack of need for routine monitoring, their cost, and ease of use, which may lead patients to underestimate the risks of stopping them. Available evidence suggests that once-daily administration is associated with similar compliance as twice-daily administration (79% ±14% and 69% ±15%, respectively).[24] Dabigatran causes dyspepsia as a result of the tartaric acid included in its capsule; in the RE-LY study, 2% of withdrawals from anticoagulation were related to dyspepsia, while this adverse event was reported in almost 12% of the patients on dabigatran.[4] The intake of food with dabigatran is recommended and a proton-pump inhibitor can be prescribed to alleviate such symptoms. Persistent symptoms may be a reason to switch to an alternate TSOAC.[16]

Perioperative management To decide whether and how discontinue oral anticoagulation with TSOACs, the following 2 aspects should be considered:

1 risk of bleeding associated with a given procedure that could be low (some plastic surgery, minor orthopedic, endoscopic, ear, nose and throat surgery, eye anterior chamber surgery, dental procedures), intermediate, or high (major abdominal surgery, cardiovascular, major orthopedic, ear, nose and throat, urology, reconstructive, and neurosurgery)

2 the level of renal function impairment, if any.[25]

The ESC experts issued the following recommendations based largely on TSOAC manufacturers' recommendations (TABLE 5).[16] Briefly, in patients undergoing procedures with a low risk of bleeding, rivaroxaban and apixaban should be stopped 24 h in advance, regardless of CrCl, whereas it is advised to stop dabigatran 24 h in subjects with CrCL exceeding 60 ml/min. Given the lack of antidote, many experts have proposed that if CrCl is below 50 ml/min, dabigatran treatment should be stopped 7 days prior to a high-risk procedure, while in patients treated with rivaroxaban, anticoagulation should be stopped 5 days prior to such intervention.[26,27]

Patients undergoing surgery with a high risk of life-threatening complications from bleeding, (e.g., spinal anesthesia, intracranial neurosurgery, intervention in the spinal cord, eye posterior chamber surgery) can have a TT performed preoperatively. Normal results indicate insignificant dabigatran levels. These results are unhelpful in patients receiving apixaban or rivaroxaban.[17]

Bridging therapy is generally not needed with TSOACs as the short half-life of the products allows discontinuation much closer to the procedure than can be safely undertaken with warfarin.[17] However, alternative preoperative management based on bridging therapy with LMWH has been proposed by French and Spanish experts.[28] In patients with high or moderate thrombotic and/or hemorrhagic risk, one could consider stopping the TSOAC 5 days prior to the intervention and bridging therapy with LMWH.[28]

Two concepts of heparin initiation following preoperative discontinuation of TSOACs have been suggested.[28,29] In the first strategy consistent with the manufacturers' recommendations for dabigatran and rivaroxaban, heparin should be initiated 12 h after the last dose of dabigatran or apixaban given twice a day or 24 h after

the last dose of rivaroxaban administered once daily.[29] The other approach has suggested that the first dose of LMWH should be given 24 h after the last dose of the TSOAC to limit the risk of bleeding and one might recommend this option in particular in subjects with lower CrCl values who were taking dabigatran. It is advisable to administer the last therapeutic dose of LMWH 24 h before surgery, and this should be half dose if was given once daily, like during bridging therapy in patients on VKAs.[28] In patients receiving TSOACs who undergo surgery, the highest risk of bleeding is observed postoperatively because TSOACs produce an immediate anticoagulant effect, and thus, early reintroduction of full-dose therapy may be associated with bleeding that would not be seen with warfarin, whose anticoagulant effect takes days to develop. To reduce the risk of bleeding in an early postoperative period, it might be reasonable to resume TSOAC administration with a half dose (75 mg for dabigatran and 10 mg for rivaroxaban)[17] or use prophylactic doses of an LMWH with reintroduction of the TSOAC on the third or fourth postoperative day 24 h after the last dose of LMWH.[30] If, for any reason, reinstitution of oral anticoagulation is not considered following the procedure, stroke prophylaxis with heparins should be used.[28]

Post-stroke management Owing to limited evidence, several approaches have been suggested in stroke survivors with documented AF episodes. There is consensus that following ischemic stroke in AF patients, the onset of treatment with TSOACs largely depends on the infarct size.[31] The 2013 European Heart Rhythm Association practical guide recommends reinstitution of anticoagulation in patients with an acute transient ischemic attack (TIA) after 1 day, with small, nondisabling infarct after 3 days, with a moderate stroke after 6 days, while large infarcts involving large parts of the arterial territory will not be treated for 2 to 3 weeks,[16] although this strategy has been disputed.[32] Observational studies suggest that although hemorrhagic transformation of ischemic stroke can be observed on magnetic resonance imaging in up to 30% of infarcts if TSOACs are started within the first 14 days (median, 2 days) after the event, this process is largely asymptomatic indicating that TSOACs may be safe in patients with acute stroke or TIA.[32] In patients who suffered from ischemic stroke despite adequate anticoagulation with VKAs or TSOACs, other causes of ischemic stroke should be investigated. Given the quick offset of anticoagulant effects of TSOACs compared with VKAs, inadequate compliance should be considered. However, it is important to recognize that stroke does occur even in well-anticoagulated patients.[4-6]

The AVERROES trial supports the hypothesis that AF patients considered ineligible for VKAs could be treated with apixaban in preference to aspirin for stroke prevention.[31]

Bleeding The annual incidence of major bleeding in AF patients treated with a a therapeutic dose of oral anticoagulants ranges from 1.3% to 7.2% depending on multiple risk factors including the intensity of anticoagulation and patient characteristics.[33] Intracranial hemorrhage (ICH) is the most feared complication of anticoagulant therapy, ranging in frequency from 0.1% to 2.5% per year with warfarin. ICH is fatal in 50% of the patients.[1] The key advantage of TSOACs in terms of bleeding risk is a 2- to 3-fold lower risk of intracranial bleeding estimated at 0.2% to 0.4% per year.[4-6]

The ESC guidelines have recommended the HAS-BLED score of bleeding risk in AF patients as a valuable additional method to help guide decisions about anticoagulant treatment[7]; a score of 3 and higher suggests a high bleeding risk that merits some caution or regular clinical review of the patient, but it is not an absolute contraindication to anticoagulation.[7]

It is unclear which of the TSOACs is safer in terms of bleeding risk in AF patients. Based on an indirect intertrial comparison, it has been concluded that the risk of major bleeding was lower with apixaban at a dose of 5 mg twice daily compared with dabigatran at a dose of 150 mg twice daily (by 26%) and rivaroxaban (by 34%), but not significantly different from that observed on dabigatran at a dose of 110 mg twice daily.[10] When compared (indirectly) with rivaroxaban, dabigatran (110 mg twice daily) was associated with less major bleeding (by 23%) and intracranial bleeding (by 54%).[10] There was a significantly lower risk of hemorrhagic stroke for dabigatran given at a dose of 150 mg twice daily compared with rivaroxaban.[10] This information could be useful if, after bleeding on a TSOAC, the physician would like to prescribe another drug from this class, but it is all based on indirect (and thus methodologically uncertain) comparisons.

Many concerns have been raised regarding the safety of TSOACs in patients with a history of non-stroke-related cerebral bleeding. The exclusion criteria in the trials on TSOACs were previous cerebral hemorrhage as well as known intracranial neoplasm, arteriovenous malformation, or aneurysm.[4-6] The highest risk of cerebral bleeding, reaching 20% during 1 year, has been reported in patients with severe uncontrolled hypertension, amyloid angiopathy, and lobar intracerebral hemorrhage.[34] The 2010 American Heart Association guidelines discourage chronic anticoagulation after spontaneous intracerebral lobar hemorrhage in AF patients because this type of hemorrhage is generally associated with cerebral amyloid angiopathy, and a 1-year risk of recurrence of intracerebral hemorrhage reaches 15%.[34] It is reasonable to consider TSOACs for restarting anticoagulation in patients who suffered from nonlobar intracerebral hemorrhage during warfarin therapy. Italian experts have recently suggested that patients with previous deep hemispheric

intracerebral hemorrhage and a $CHADS_2$ score of 4 and higher or CHA_2DS_2-VASc score of 5 and higher (baseline risk of ischemic stroke exceeding 6.5% per year) benefit from restarting anticoagulation preferably after 10 weeks since the index bleeding event.[34] Most experts advise against antiplatelet therapy as an alternative to warfarin in AF patients following intracerebral hemorrhage on treatment; however, a left atrial appendage occlusion should be considered.[16] When the risk of bleeding and stroke are both high, TSOACs appear to have a greater net clinical benefit than warfarin.[34]

In the licensing studies, dabigatran and rivaroxaban were both associated with an increased risk of major gastrointestinal bleeding compared with warfarin. In these studies, apixaban produced a similar risk of bleeding risk as warfarin.[4-6] In clinical use, dabigatran (110 mg twice daily) is associated with a significantly decreased risk of gastrointestinal bleeding compared with warfarin.[35] It is reasonable to use TSOACs even in patients with a history of severe gastrointestinal bleeding, particularly if the gastrointestinal lesion has been successfully treated. Reduced doses of TSOACs might be considered. Recurrent bleeding despite the use of a proton-pomp inhibitor and withdrawal of cyclooxygenase inhibitors is a contraindication to TSOACs on a long-term basis, especially if a given patient has the HAS-BLED score above 3. Similar concerns refer to patients who experienced lower gastrointestinal bleeding. Patients with intestinal angiodysplasia, inflammatory bowel disease, in particular active ulcerative colitis, or those with prior gastrointestinal bleeding, for example associated with diverticulosis, may experience bleeding during treatment with TSOACs.[17] TSOACs should be used in these AF patients with extreme caution.[17]

A recent analysis of 5 phase III trials has indicated that patients treated with dabigatran who had major bleeding have a trend to lower mortality compared with those who had major bleeding on warfarin.[36] These data might suggest that major bleedings associated with the treatment with TSOACs, in particular dabigatran, have a more favorable outcome than bleeding on warfarin, even if a specific antidote is not available yet.

Management of bleeding in patients taking TSOACs requires risk stratification based on the following factors: hemodynamic stability, location of bleeding, magnitude of blood loss, the time elapsed since the last dose, creatinine clearance, concomitant medication associated with increased bleeding risk (in particular, antiplatelet agents).[16,17,37,38]

In bleeding patients, TSOACs should be discontinued. Standard supportive management including surgical hemostasis and fluid replacement are highly effective in most minor or moderate bleeding because, in contrast to subjects on VKAs, normal hemostasis will be restored within 12 to 24 h in the vast majority of patients on TSOACs with normal or slightly impaired renal function.[16,17] There are no clinical studies demonstrating the efficacy and safety of fresh frozen plasma in the setting of TSOAC-associated bleeding, but it should be used in patients with coagulopathy, for example, dilutional coagulopathy.[38] Vitamin K is also ineffective in bleeding patients treated with TSOACs.[17]

In patients with severe bleeding on TSOACs, prothrombin complex concentrates (i.e., vitamin-K-dependent coagulation FII, IX, X [3-factor prothrombin complex concentrate (PCC)] or II, VII, IX, X [4-factor PCC] and agents that are used to treat bleeding in hemophilia complicated by FVIII or IX inhibitory antibodies or acquired hemophilia (activated PCC [aPCC] and recombinant FVIIa [rFVIIa]) should be considered.[16,17,37,38]

It has been suggested that aPCC (factor eight inhibitor bypassing activity [FEIBA], 80 U/kg) is slightly more effective than PCC in patients with severe bleeding on dabigatran.[16,38] Four-factor PCC (80 U/kg) might be preferred over aPCC in patients bleeding on rivaroxaban.[38] Recombinant FVIIa is rarely used in patients with life-threatening bleeding on NOACs.[16] However, the use of PCC agents to control bleeding in patients receiving TSOACs is supported by limited evidence and is associated with an increased risk of thromboembolic events.[17] Hemodialysis removes dabigatran (but not rivaroxaban or apixaban) and should be considered in patients with life-threatening bleeding.[16,17,38] Platelet transfusion is recommended and used in bleeding patients on TSOACs who also have thrombocytopenia or impaired platelet function for example due to the use of antiplatelet agents.[16,17] Also, antifibrinolytics such as tranexamic acid and ε-aminocaproic acid might be useful in severe bleeding on TSOACs, particularly, in the perioperative period, although their hemostatic efficacy is unknown in this setting.[17,38]

For emergency surgery, prophylactic administration of FFP, PCC (activated or not), or rFVIIa is not routinely recommended.[37] Instead, they have been proposed in patients with moderate or severe hemorrhage directly or indirectly related to TSOACs, such as spontaneous or traumatic cerebral bleeding.[20] PCC at a dose of 25 U/kg may be repeated once or twice, while aPCC (50 IE/kg; up to 200 IE/kg/day) has been advised and it can be considered before PCC if available.[16]

Antidotes to TSOACs, including a humanized monoclonal antibody fragment against dabigatran and recombinant FXa derivatives lacking catalytic and membrane-binding activity (andexanet alpha), are being tested in clinical studies.[38]

Conclusions TSOACs represent a major and much awaited advance in stroke prevention in AF patients. Because there is little clinical experience with these anticoagulants outside randomized controlled trials, it is not yet quite clear whether TSOACs show increased real-world benefits and safety profile in a wide spectrum of nonvalvular AF patients compared with well-controlled warfarin.

The prescription of a TSOAC must be preceded by a thorough evaluation of patient characteristics including age, body weight, history of renal or liver disease, history of bleeding, other comorbidities, and use of concomitant drugs. The results of laboratory tests, including full blood count, PT and aPTT, serum creatinine, transaminases, and bilirubin, should be available and carefully evaluated. CrCl should always be calculated using a commonly available formula. This information will not only guide correct prescription but will also identify patients requiring dose adjustments, which are recommended in fragile patients such as elderly patients defined at increased risk of bleeding and patients with moderate-to-severe renal impairment.

A widespread and increasing use of TSOACs in various patient populations requires careful education of family doctors as well as specialists in different areas of medicine on how to use these agents safely and effectively. Further prospective and observational studies are needed to optimally prescribe TSOACs in a number of complex clinical settings encountered quite frequently among patients with AF and almost unseen in published large clinical trials.

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ARTYKUŁ POGLĄDOWY

Praktyczne aspekty stosowania nowych doustnych antykoagulantów w migotaniu przedsionków

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SŁOWA KLUCZOWE

apiksaban, dabigatran, migotanie przedsionków, rywaroksaban, udar mózgu

STRESZCZENIE

Dabigatran (inhibitor trombiny) oraz rywaroksaban i apiksaban (inhibitory aktywnego czynnika X) to bezpośrednie, swoiste pod względem miejsca aktywnego doustne antykoagulanty (*target-specific oral anticoagulants* – TSOACs) zatwierdzone do stosowania w prewencji udaru mózgu lub zatorowości obwodowej u pacjentów z niezastawkowym migotaniem przedsionków (*atrial fibrillation* – AF). Opublikowane dane sugerują, że wszystkie te 3 leki są przynajmniej tak skuteczne jak warfaryna w dawce dostosowanej w prewencji udaru mózgu. Dzięki większej swoistości, szybkiemu początkowi działania i przewidywalnej farmakokinetyce, TSOACs mają pewne zalety w porównaniu z antagonistami witaminy K, co ułatwia ich stosowanie w praktyce klinicznej. Ten artykuł poglądowy zajmuje się praktycznymi zagadnieniami związanymi ze stosowaniem TSOACs u pacjentów z AF na podstawie dostępnych danych i własnego doświadczenia. Omówimy takie tematy, jak dobór pacjentów, upośledzenie czynności nerek, interakcje lekowe, zmianę antykoagulantów, monitorowanie laboratoryjne i ryzyko krwawienia wraz z postępowaniem przy takim powikłaniu. Skupimy się na kwestiach dotyczących optymalizacji leczenia za pomocą TSOACs w prewencji udaru mózgu. Rozumienie tych praktycznych kwestii przez klinicystów i pacjentów ma kluczowe znaczenie dla bezpiecznego i skutecznego stosowania TSOACs w codziennej praktyce.

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