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The use of novel oral anticoagulants in non-valvular atrial fibrillation

Nowe doustne antykoagulanty w leczeniu niezastawkowego migotania przedsionków

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Słowa kluczowe
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Summary

Atrial fibrillation (AF), the most common cardiac arrhythmia, is associated with high risk of thromboembolic events, especially ischemic stroke. Most AF patients require chronic anticoagulation. Novel oral anticoagulants (NOACs) represent a new therapeutic option in stroke prevention in AF. They are gaining popularity on account of their high efficacy, safety and predictable pharmacokinetics. In this article we provide a short characteristic of NOACs currently available on the Polish market: dabigatran, rivaroxaban and apixaban. Several issues concerning NOACs have been covered: mechanisms of action, pharmacokinetics, efficacy and safety in clinical trials, bleeding complications, dosing regimens, food and drug interactions. Also practical aspects such as: preparation for elective electrical cardioversion, interrupting NOACs before surgery and invasive procedures, switching between different types of anticoagulants or treatment of bleeding complications, have been discussed. In our review NOACs have been compared to standard antithrombotic therapy with vitamin K antagonists. It was the authors' intention to stress the potential advantages and disadvantages of NOACs.

Streszczenie

Migotanie przedsionków (AF), najczęstsza arytmia serca u człowieka, wiąże się z istotnie podwyższonym ryzykiem powikłań zakrzepowo-zatorowych, a w szczególności udaru niedokrwiennego mózgu. Większość pacjentów z AF wymaga przewlekłego leczenia przeciwkrzepliwego. Od kilku lat nowe doustne antykoagulanty (NOACs) stanowią alternatywę dla antagonistów witaminy K (VKA) w prewencji powikłań zatorowych, w tym udaru mózgu w AF. Ze względu na wysoką skuteczność, bezpieczeństwo i przewidywalną farmakokinetykę są one coraz powszechniej stosowane. W pracy przedstawiono krótką charakterystykę NOACs aktualnie dostępnych na polskim rynku: dabigatranu, riwaroksabanu i apiksabanu. Omówiono szereg zagadnień związanych z NOACs: mechanizmy działania, właściwości farmakokinetyczne, skuteczność i bezpieczeństwo w badaniach klinicznych, powikłania krwotoczne, sposoby dawkowania, interakcje. Szczególny nacisk położono na aspekty praktyczne stosowania NOACs: przygotowanie do kardiowersji elektrycznej, przerywanie terapii przed zabiegami inwazyjnymi, sposoby zamiany leczenia przeciwkrzepliwego, postępowanie w przypadku powikłań krwotocznych. NOACs porównano do standardowego leczenia z użyciem VKA. Intencją autorów było zaakcentowanie potencjalnych wad i zalet stosowania NOACs.

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in humans. It is diagnosed in 1-2% of the population and its prevalence increases with age, reaching 5-15% in those above 80 years of age (1). AF regardless of its type (paroxysmal, persistent, permanent) is associated with a high risk of thromboembolic events, especially ischemic stroke. It has been demonstrated that AF increases the risk of stroke 5-fold in comparison to sinus rhythm. 15-20% of all strokes are believed to be associated with AF (2, 3).

ANTITHROMBOTIC TREATMENT IN AF PATIENTS

Antithrombotic treatment is one of the major treatment strategies in AF. According to the current guidelines of the European Society of Cardiology (ESC), the type of treatment introduced should depend on CHA_2DS_2-VASC stroke risk evaluation scheme (tab. 1).

Table 1. CHA_2DS_2-VASC score (4).

Risc factor	Score
Congestive heart failure/left ventricular dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease	1
Age 65-74	1
Female sex	1

In patients with a CHA_2DS_2-VASC score ≥ 1 chronic anticoagulation is recommended. On the other hand, in patients with no risk factors (and in female patients who are aged below 65 years of age) no such therapy should be considered.

Until recently the only possible antithrombotic treatment option in AF was the chronic use of vitamin K antagonists (VKAs). Indeed, meta-analysis data have confirmed that warfarin reduces the occurrence of stroke by 64% in comparison to controls (5).

However, VKA therapy is associated with several limitations, including slow onset of action, prolonged activity after drug withdrawal and multiple interactions with other therapeutics or food (6). Last but not least, VKA therapy requires frequent dose adjustments and regular monitoring of its anticoagulant effect by the use of the International Normalized Ratio (INR). Only the therapeutic range of the INR (2-3) guarantees the efficacy and safety of VKA anticoagulation. It has been demonstrated that up to 30% of patients with indications for chronic anticoagulation, refuse VKA treatment (1).

Novel oral anticoagulants (NOACs) have recently emerged as an alternative to VKAs and they are currently becoming more and more popular. According to the ESC guidelines, NOACs are preferred to VKAs in most FA patients (class IIa recommendations) (4). Currently 3 different NOACs are available on the Polish market: dabigatran (Pradaxa, Boehringer Ingelheim), rivaroxaban (Xarelto, Bayer HealthCare/Janssen Pharmaceuticals) and apixaban (Eliquis, Bristol-Meyers Squibb/Phizer).

It should be stressed that all NOACs have been registered only in the treatment of non-valvular AF. In the case of AF associated with rheumatic valvular disease (predominantly mitral stenosis) or the presence of prosthetic heart valve, VKAs still remain the only therapeutic option (4).

MECHANISMS OF ACTION AND PHARMACOKINETIC PROPERTIES OF NOACS

Unlike VKAs, all NOACs inhibit only a single activated factor in the coagulation cascade. Dabigatran is a strong, selective and reversible inhibitor of thrombine (factor II), both free and conjugated to fibrin. Additionally it interferes with platelet activation induced by thrombine (7). Dabigatran is administered as a prodrug (dabigatran etexilate) and is then converted into its active metabolite (dabigatran) in the liver. Rivaroxaban and apixaban do not require prodrugs due to high oral bioavailability. Both rivaroxaban and apixaban are selective inhibitors of factor Xa (7, 8). The main characteristics of NOACs are listed in table 2.

Table 2. Characteristics of NOACs (9-11).

	Dabigatran	Rivaroxaban	Apixaban
Chemical structure	$C_{25}H_{25}N_7O_3$	$C_{19}H_{18}ClN_3O_5S$	$C_{25}H_{25}N_5O_4$
Prodrug	Yes	No	No
Target	IIa	Xa	Xa
Bioavailability (%)	6-7	80-100	50
Time to peak concentration (h)	0,5-2	2-4	3-4
Halftime (h)	12-14	5-13	~ 12
Serum protein binding (%)	35	92-95	87
Renal excretion (%)	85	66	27

EFFICACY OF NOACS IN AF – CLINICAL EVIDENCE

Antithrombotic efficacy of NOACs in non-valvular AF has been proved in several phase III randomised clinical trials (12). In RE-LY trial, dabigatran 150 mg b.i.d. was superior to warfarin in stroke and systemic embolism prevention. Dabigatran 110 mg b.i.d. was noninferior to warfarin (13). In a similar trial – ROCKET AF, rivaroxaban proved to be as good as warfarin (14). On the other hand, in ARISTOTLE trial, a higher efficacy of apixaban was demonstrated as regards stroke and embolic prevention, in comparison to warfarin (15).

The rates of major bleedings were similar (rivaroxaban, dabigatran 150 mg b.i.d.) or significantly lower (apixaban, dabigatran 110 mg b.i.d.) when compared to VKAs. Interestingly, apixaban therapy was demonstrated to result in a significant reduction of all-cause mortality (15).

NOACS AND ELECTRICAL CARDIOVERSION

Post hoc analysis of ROCKET AF, RE-LY and ARISTOTLE trials indicate that dabigatran, rivaroxaban and apixaban can be safely used in preparation for elective cardioversion in persistent AF (16). Like VKAs, NOACs should be administered for at least 3 weeks prior to and at least 4 weeks post cardioversion.

Only recently, the results have been published of X-VeRT, which is the first prospective clinical trial comparing the efficacy and safety of NOAC (rivaroxaban) in comparison to VKA (warfarin) in the setting of electrical cardioversion (17). The study showed no significant differences in either thromboembolic complications or bleedings between warfarin and apixaban, both in the case of early (1-5 days of thromboprophylaxis) and delayed (21-25 days of thromboprophylaxis) electrical cardioversion. Rivaroxaban significantly reduced the time to cardioversion in those undergoing delayed cardioversion.

NOACS – DOSING REGIMENS

The standard dose of dabigatran in non-valvular AF is 150 mg b.i.d. Dose reduction (110 mg b.i.d.) is required in the elderly (above 80 years of age), in moderate renal failure (creatinine clearance; CrCl = 30-49 ml/min), in patients with a high risk of bleeding (HAS-BLED score ≥ 3) (tab. 3) and in the case of concomitant use of interacting drugs (e.g. verapamil). Rivaroxaban is usually administered 20 mg q.d. Reduced dosing (15 mg q.d.) is recommended in moderate renal impairment (CrCl = 30-49 ml/min) and in individuals with a high bleeding risk (HAS-BLED score ≥ 3). The standard apixaban dose is 5 mg b.i.d. Dose reduction (2.5 mg b.i.d.) is required in patients with at least 2 risk factors from the following: age ≥ 80, body weight ≤ 60 kg, serum creatinine level ≤ 1.5 mg/dl (12, 18).

Table 3. HAS-BLED score (4).

Clinical characteristics	Score
Hypertension	1
Abnormal renal and/or liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Age > 65 years	1
Antiplatelet or anti-inflammatory drugs/alcohol (1 point each)	1 or 2

NOAC therapy requires regular renal function assessment. CrCl should be captured annually or more frequently (2-3 times per year) in patients with moderate renal impairment. Severe renal failure (CrCl < 30 ml/min) is a contraindication for NOACs. NOACs are also contraindicated in pregnancy and lactation.

No NOAC requires routine laboratory coagulation screening or dose adjustments, which means that NOACs are easy to use. On the other hand, all NOACs have very short half-lives and their anticoagulation effect drops rapidly 12-24 h after the last dose intake. This is why strict therapy compliance by the patient is crucial for adequate protection (12).

If a single dose of any NOAC is missed, no double dose is recommended. The forgotten dose should be taken as soon as possible and then the standard dosing regimen should be restored (18).

NOAC – FOOD AND DRUG INTERACTIONS

Rivaroxaban is recommended to be taken together with food, which improves its absorption and bioavailability. There are no special requirements for dabigatran and apixaban in this respect (18).

The number of interactions between NOACs and other drugs is limited. However, one must remember that every NOAC is a potential substrate of P-glycoprotein and may interact with its inhibitors. Concomitant use of NOAC together with amiodarone, verapamil, clarithromycin or ketoconazole may result in elevation of NOAC serum level. On the other hand, rifampicin and phenytoin may decrease NOAC activity (1). Clinically relevant interactions are also known for rivaroxaban or apixaban (but not dabigatran) and drugs interacting with cytochrome P450 3A4 (CYP3A4). CYP3A4 inducers (carbamazepine, phenytoin, rifampicin) decrease, while CYP3A4 inhibitors (protease inhibitors, azole antifungals) increase NOACs serum level (1).

Also co-administration of NOACs and antiplatelets or nonsteroidal anti-infalmmatory drugs requires caution because of increased risk of potential bleeding (18).

INTERRUPTING NOAC THERAPY BEFORE INVASIVE PROCEDURES

Surgical and other invasive procedures associated with a high bleeding risk may require temporary NOAC interruption. Due to short half-lifes of all NOACs, a bridging therapy with heparin is rarely necessary (4). The time of dabigatran discontinuation strictly depends on renal function. Dabigatran should be stopped for 24 h (CrCl > 80 ml/min), 1-2 days (CrCl = 50-80 ml/min) or 2-3 days (CrCl < 50 ml/min) before the procedure (9). In emergency situations, surgery should be delayed for at least 12 h after the last dose. For rivaroxaban, dosing should be stopped for at least 24 h before intervention (10). Apixaban is recommended to be withdrawn for 48 h before moderate/high and 24 h before low bleeding risk procedures (11). NOAC therapy can be restarted shortly after hemostasis has been reached (4).

SWITCHING BETWEEN ORAL ANTICOAGULANTS

When switching from VKA to NOAC, strict INR control after VKA withdrawal is recommended. NOAC can be introduced only when the INR falls below 2.0 (for dabigatran and apixaban) or below 3.0 (for rivaroxaban) (12).

When switching from NOAC to VKA, temporary concomitant treatment with both agents is necessary to ensure adequate anticoagulation with VKA. In the case of dabigatran, the length of such treatment depends of renal function and amounts to 3, 2 or 1 day for CrCl > 50 ml/min, CrCl = 30-50 ml/min and CrCl < 30 ml/min, respectively (9). When switching from rivaroxaban or apixaban to VKA, VKA should be administered until the INR reaches 2.0 (10, 11).

It is worth noting that the INR level can be influenced by rivaroxaban itself. That is why INR testing is recommended directly before rivaroxaban intake, i.e. 24 h after the previous dose.

BLEEDING COMPLICATIONS DURING NOAC THERAPY

In contrast to VKAs, NOACs are characterized by predictable pharmacokinetics and pharmacodynamics and therefore do not require routine coagulation screening. However, in emergency situations such as bleeding or overdose, the measurement of NOAC anticoagulation effect may be needed.

In the case of dabigatran, both the ecarin clotting time (ECT) and the thrombin time (TT) provide an adequate assessment. The activated partial thromboplastin time (aPTT) may also be used. Recently, a specific quantitative anti-IIa assay (diluted thrombin time) has been developed but it still is not routinely available (18, 19). The prothrombin time (PT) seems to be a natural choice for qualitative assessment of the presence of rivaroxaban and apixaban. However, quantitative anti-Xa chromogenic assays do exist (2, 19).

So far there is no specific, commercially available antidote for any NOAC. In the case of severe bleeding or overdose the drug should be promptly discontinued and symptomatic treatment should be introduced (e.g. mechanical compression, surgical hemostasis, fluid replacement). In specific cases desmopressin and tranexamic acid may be considered (12). As dabigatran is mostly excreted renally (80%), in the case of bleeding during dabigatran therapy, forced diuresis and haemodialysis or charcoal haemoperfusion may be recommended. Oral charcoal may be useful shortly after overdose of any NOAC (up to 1-2 h) (1). Life-threatening bleedings in the course of any NOAC therapy can be treated with activated factor VII (rFVIIa), prothrombin complex concentrate (PCC) and activated prothrombin complex concentrate (aPCC) (18). Data on the efficacy of such treatment are still limited.

CONCLUSIONS

NOACs undoubtedly represent a very promising alternative to VKAs for stroke prevention in AF patients. Due to their greater specificity, predictable pharmacokinetics as well as documented efficacy and safety, they address a number of limitations of VKAs. However, the lack of specific antidotes or coagulation assays may still be problematic. Another important issue that is currently a limiting factor in more widespread usage of NOACs, is their price. Nonetheless, the decline of VKAs in non-valvular AF seems to be only a matter of time.

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