Journal of Health Study and Medicine

2022, No. 1
pp. 57–73
DOI 10.36145/JHSM2022.04

Safety and Efficacy of Using NOAC as Prevention of Ischemic Stroke in the Geriatric Population with Atrial Fibrillation – Review Article

Submitted: 19 January 2022 Accepted: 14 February 2022 Published: 25 May 2022

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Abstract

Introduction: *Atrial fibrillation is a common arrhythmia in the elderly population, which may lead to thromboembolic events complicated by ischemic stroke. The frequency increases with age along with other chronic diseases such as diabetes or hypertension. Non-vitamin K antagonist oral anticoagulants (NOACs) are the main drugs used in the prevention of stroke, taking the place of vitamin K antagonists (VKAs).*

Materials and Methods: *The article reviews the literature using the Pubmed and Google Scholar databases. Articles were analyzed using keywords: atrial fibrillation, elderly, NOAC, VKA, ischemic stroke.*

Results: *Many studies have shown that NOACs are a groundbreaking achievement in treating thromboembolic events such as ischemic stroke, even in the elderly. Their efficiency and safety surpasses VKAs as they have better pharmacokinetics and pharmacodynamics along with a wider therapeutic index, no need for monitoring, less risk of interactions and fatal bleeding, but with higher risk of gastrointestinal bleeding.*

Conclusion: *NOACs are efficient and safe in the elderly with atrial fibrillation for ischemic stroke prevention. Caution should be kept in patients with renal failure or a prosthetic valve. Interactions are not serious but possible when taking NOACs with drugs such as carbamazepine. Investigation is still indicated for reviewing this issue further.*

Key words: *atrial fibrillation, elderly, NOAC, VKA, ischemic stroke*

Introduction

Atrial fibrillation (AF) is the most common arrhythmia. Estimated data indicate that in 2016 it affected 46.3 million people worldwide. Age is the main risk factor, which is confirmed by the increasing trends in the elderly.

Morbidity is increasing because appropriate treatment of chronic diseases in the elderly population extends their lives, which however, results in an increased incidence of atrial fibrillation. In addition to age, risk factors include high BMI, hypertension, heart attack, heart failure, smoking and genetic predisposition [1, 2].

Atrial fibrillation results from atrial fibrosis and enlargement, which lead to the wrong conduction of electrical impulses and the chaotic work of the heart. This arrhythmia is one of the major risk factors for stroke. This is due to the disturbed mechanical work of the atria and blood stagnation, which serves to form a blood clot in the left atrium. The embolic material is a cause of ischemic stroke, the probability of which is increased 4–5 times in patients with AF [1, 3]. Therefore, appropriate treatment should be implemented to prevent stroke. The main therapy is oral anticoagulation (OAC). Among the drugs, vitamin K antagonists (VKAs) have dominated for many years but there is an increasing trend of using non-vitamin K antagonist oral anticoagulants (NOACs), which have quickly become first choice drugs.

OAC, especially the use of NOACs, reduces mortality, the occurrence of ischemic stroke and hospitalizations. In connection with all these expected results OACs are indicated to prevent stroke especially in the elderly. However, during the therapy, people are in danger of major bleeding, mainly intracranial hemorrhage (ICH). Despite that, the benefits outweigh the risks, which show the need to use them even in the geriatric population [4].

Results

NOAC – characteristics

Oral anticoagulants are used to prevent ischemic stroke in patients with atrial fibrillation. It is especially important to use them in the elderly. However, this raises many concerns, mainly due to multiple diseases, multi-drug use or the presence of geriatric syndromes. The main concern is the risk of major bleeding, and special attention is given to intracranial bleeding (ICH), especially because of the risk of falls in this age group. As a result, some elderly patients are excluded from anticoagulation therapy or are treated less effectively, e.g. by administering acetylsalicylic acid (ASA) [5, 6].

Many European and American societies (AHA, ESC, EHRA) indicate the need for anticoagulant treatment of patients with AF, especially the elderly. Despite the fact that, in the studies, people over 75 years of age do not constitute the majority, the obtained results allow for drawing conclusions and recommendations as to the safety and efficacy of OAC in this age group. Treatment discontinuation is recommended only when there is a low risk of stroke. The CHA2DS2-VASc scale, which takes into account e.g. cardiovascular diseases, age, sex and thromboembolic events is crucial in assessing the necessity of stroke prevention. According to the gender scoring, OAC should be used in men with ≥ 2 points and in women with ≥ 3 points [7, 8].

In addition to the CHA2DSc-VASC classification, the acronym ABC (A – avoid stroke / anticoagulation, B – better symptom control, C – cardiovascular risk and comorbidity optimization) highlights the role of anticoagulation in the treatment of AF. It is equally important to assess the risk of bleeding using the HAS-BLED scale (Hypertension, Abnormal liver / renal, Stroke, Bleeding, Labile INR, Elderly, Drugs and alcohol). Obtaining ≥ 3 points means a high risk of bleeding and is the basis for considering the withdrawal from OAC [9, 10].

For several decades, the main drugs have been VKAs, mainly warfarin. Drugs in this group are characterized by several mechanisms of action, primarily blocking the production of vitamin K-dependent coagulation factors. However, their use is associated with many problems, such as slow onset

of action, a narrow therapeutic index, drug and food interactions, and the need to monitor coagulation parameters. To avoid this, NOACs were created, which are distinguished primarily by the fact that they block only one coagulation factor. Apixaban, rivaroxaban and edoxaban block factor Xa, while dabigatran blocks thrombin (factor II). These drugs have the advantage of a quick onset of action, favorable pharmacodynamics and pharmacokinetics, no food interactions, and little drug interaction. In addition, they are characterized by a wide therapeutic window and no need to monitor coagulation parameters. Their use is limited by liver diseases and kidney failure. Many studies show their greater effectiveness and safety, mainly compared to VKAs. So far, based on research, they have been recognized as the drugs of choice for the treatment of non-valvular atrial fibrillation, deep vein thrombosis and pulmonary embolism and for the prevention of thromboembolic complications after hip and knee arthroplasty [5, 11, 12].

The RE-LY, ARISTOTLE, ROCKET-AF, ENGAGE-AF studies showed at least the same or even higher efficacy of each drug when separately compared to VKAs. A better therapeutic effect was demonstrated for apixaban and dabigatran. A statistically significant reduction in the risk of major bleeding was demonstrated primarily for apixaban, but also for edoxaban. However, most importantly, when using NOACs, there is a lower risk of ICH compared to VKAs, also in people over 75 years of age. Apart from ICH, an important issue is the occurrence of gastrointestinal bleeding – among NOACs, apixaban shows the greatest reduction of this risk. Additionally, this effect can be achieved by not using ASA and NOACs together and by including PPIs – mainly pantoprazole [4, 13].

Renal failure and the related creatinine clearance are an important issue with the use of NOACs. With age, kidney function deteriorates, which limits the use of certain medications. This also applies to NOACs, the dosage of which depends on the creatinine clearance. In this case, the dose should be reduced (usually by half), which, however, reduces the anticoagulant efficacy and increases the frequency of thromboembolic events. In contrast, the risk of major bleeding does not decrease with dose reduction. In the absence of concomitant renal failure in people over 80 years of age, the dose of the

NOAC should not be reduced, except for dabigatran. Even with dose reduction, a higher efficacy of NOACs over VKAs was demonstrated, except for rivaroxaban [4, 7]. Table 1. shows the standard and reduced doses as well as the indications for dose reduction [3, 13].

There are also important contraindications to anticoagulant therapy, including hemorrhagic diathesis, subarachnoid hemorrhage, gastrointestinal bleeding and liver failure (Child-Pugh C). Moderate/severe mitral stenosis and the presence of a mechanical heart valve are also contraindications to NOAC therapy. In this case, a VKA is recommended for therapy [9, 14]. Moreover, the manifestation of even major bleeding is not a contraindication to return to NOAC therapy later [13]. Absolute contraindications to OAC may be an indication for the closure of the left atrial appendage [15].

Until recently, there was concern about the lack of an antidote to the treatment of NOACs in the event of bleeding, which was particularly severe and life-threatening. Currently there are antidotes. For dabigatran it is idarocizumab and for factor Xa inhibitors it is andexanet alpha. This is another premise for their use instead of VKAs [5].

NOACs compared to VKAs

NOACs (new oral anticoagulants) are drugs used increasingly in the prevention of thromboembolic events in atrial fibrillation as a relatively safe and convenient option; however, VKAs (vitamin K antagonists) are still a popular choice – primarily due to their lower cost, which is an important determining factor, especially in the elderly population. Warfarin, introduced in the 1950s, was the basic anticoagulant drug; it effectively protected against venous thrombosis and pulmonary embolism, and for many years it had no suitable alternative. Due to the fact that NOACs were introduced only in 2009, VKAs have been used for a considerable period of time, and their therapy is often still continued in patients who have been taking them for so long and do not want to switch to NOAC therapy, which mainly concerns the geriatric population [16].

VKAs work by inhibiting the Y-carboxylation of factors II, VII, IX, X (dependent on vitamin K) by blocking vitamin K epoxide reductase, which leads

to the formation of the so-called PIVKA (protein induced by vitamin K absence) with reduced activity. The main representatives are warfarin and acenocoumarol. They are administered orally, once a day, and the dose must be adjusted to the INR value [17]. Due to the fact that the anticoagulant action is delayed – therefore, when the effect must be obtained immediately, bridge therapy is used, i.e. together with low-molecular-weight heparin for at least 5 days, until the INR is 2–3 for 2 consecutive days. INR should be measured regularly (usually every 4–6 weeks), because VKAs have a narrow therapeutic index, and elevated INR may lead to bleeding [17, 18].

The convenience of using NOACs is not having to determine any laboratory values and carry out such strict controls. This limits the number of necessary medical visits and examinations. It is worth emphasizing that patients often do not follow the rules defined in the case of VKAs, which may pose a risk of bleeding. Studies have shown that it is more common in people taking VKAs, especially in the elderly population with atrial fibrillation [19]. Major NOAC bleeding was also less frequent in patients aged 85 and over and in those with a low BMI [20]. According to the meta-analysis published in the European Heart Journal, Cardiovascular Pharmacotherapy, which included 22 studies and over 440,000 patients, in elderly patients with AF, the use of NOACs is associated with a lower risk of events such as intracranial bleeding, cerebral hemorrhagic stroke and fatal bleeding than VKAs, but the risk of gastrointestinal bleeding increases [21, 22]. NOACs cannot be used in patients with end-stage renal failure and those on dialysis [23, 24].

VKAs are metabolized by cytochrome P-450, which is associated with another problem, namely numerous interactions with other drugs and chemicals (more than 200 of them have been described for warfarin) – much more intense than in the case of NOACs [17]. It is a huge obstacle for the elderly, who are most often affected by polypragmasy. Drugs such as amiodarone, statins, paracetamol and antibiotics like ciprofloxacin or metronidazole, enhance the anticoagulant effect of VKAs. Diet also has a great influence, because the consumption of green, leafy vegetables, such as cabbage or lettuce, which are after all a rich source of vitamin K, will lead to a reduction in the activity of vitamin K antagonists [25]. This can be a problem for seniors,

for whom vegetables should be an important part of the diet, especially if they suffer from atherosclerosis, diabetes or arterial hypertension, often co-occurring with atrial fibrillation. NOACs do not have clinically significant interactions with food, and drug interactions are less frequent. It should be remembered that in people with a prosthetic heart valve, VKAs are the first choice. In addition, they are safer in the case of renal failure [23, 26]. Table 2. shows VKAs and NOACs compared to each other [27, 28].

NOAC – interactions

Knowledge about NOAC interactions with other drugs is constantly evolving and requires the construction of new, wider clinical trials. NOACs do not show numerous interactions, and if they do, they are not as significant as in the case of VKAs. One Turkish study by Ersoy and others obtained information on NOAC interactions with other drugs and the impact of these interactions on adverse events and deaths. 704 patients with atrial fibrillation participated in the study. All drugs used were tested for drug interactions using the Lexicomp software. Each drug interaction was described according to a risk assessment. A total of 9,883 drugs were analyzed for interactions. Most drug interactions were negligible; therefore they were assigned to group A (80.7%). The clinically significant drug interaction groups were as follows: 256 C class (2.7%), 1168 class D (11.8%) and 23 class X (0.2%). The majority (66%) of group X are antiepileptic drugs (carbamazepine, phenytoin) [29].

After a stroke, seizures occur frequently, so medications to prevent seizures are indicated. There have been reports of interactions suggesting a reduction in the effect of NOACs by antiepileptic drugs, resulting in further strokes or pulmonary embolism. Carbamazepine, levetiracetam, phenobarbital, phenytoin and valproic acid may reduce the effect of NOACs by inducing P-glycoprotein (P-gp) activity. Carbamazepine, oxcarbazepine, phenytoin, phenobarbital and topiramate may reduce the effect of NOACs by induction of CYP3A4. As a result, the anticoagulant effect is weakened [30].

The antiepileptic drugs recommended by the European Heart Rhythm Association for people using NOACs are lamotrigine, zonisamide, pregabalin

and gabapentin. It should be noted that almost all the evidence to date on the risk of recurrent thromboembolic events comes from individual cases. Therefore, it makes sense to create more complex studies to solve a given problem and provide solid evidence. Until then, caution should be exercised when combining antiepileptic drugs and NOAC, especially levothyracetam, carbamazepine, phenobarbital, phenytoin, topiramate and valproic acid [31].

A common group of drugs used among the elderly are SSRIs (serotonin reuptake inhibitors), i.e. drugs with an antidepressant effect. These drugs when combined with the NOAC group increase the risk of bleeding due to their effect on platelets. Therefore, caution should be exercised when combining these groups of drugs [32, 33].

Another group of drugs that may hinder anticoagulant treatment are azole antifungal drugs. In one Danish study, apixaban users had a significantly increased risk of bleeding following exposure to systemic fluconazole. However, there was no increased risk in people taking rivaroxaban and dabigatran. Topical application of azoles did not increase the risk of bleeding [34, 35].

Theoretically there are inhibitors/inducers of CYP3A4 or P-glycoprotein in foods or herbs, but no direct evidence of such interactions has been shown. St. John's wort is a strong inducer, so caution should be exercised when combining this herb with NOAC medications. It is expected that this interaction would lower the concentration of the new oral anticoagulants and would not produce a satisfactory effect. Rivaroxaban shows increased bioavailability when taken with food, so it is best to do so. It has been postulated that citrus, especially grapefruit, affects the bioavailability of rivaroxaban, but this has not been confirmed by clinical studies [36]. Further investigation is needed regarding this important issue due to elderly people taking many medications because of their co-occurrent chronic diseases. Therefore, their safety is also affected by interactions problems.

Discussion

In recent years, there have been some groundbreaking events for NOACs, resulting from large and numerous studies. In 2020 NOACs were added to the

WHO's Essential Medicines List thanks to the work of a team of international experts in various fields, such as cardiology, neurology and public health, who issued an appeal to the WHO, emphasizing the noticeable improvement in safety and efficiency in the prevention of stroke in the treatment of non-valvular atrial fibrillation, with a significant reduction in the number of hemorrhagic strokes, intracranial hemorrhages and, above all, a decrease in mortality with this group of drugs. These conclusions are based on the results of large, randomized studies, primarily published in the NEJM in the years 2009–2013 [37].

A previous attempt to add NOAC to the EML was unsuccessful. The application was rejected on the grounds that evidence based solely on study populations would not be representative of patients who would actually receive such treatment. In addition, attention was then paid to the lack of specific antidotes and the costly nature of such therapy. As we know today, substances are available that are able to reverse the effects of NOACs. Adding NOACs to the List of Essential Medicines increased their therapeutic significance and initiated the course of activities increasing their worldwide availability. Perhaps this significant change will allow the treatment costs to be reduced over time, which will contribute to more frequent conversion of VKAs to NOACs also in the geriatric population [37]. In 2021, NOACs are still on the list [38].

In 2021, Anna Plit, Thomas Zelniker and colleagues conducted a large meta-analysis published in the European Heart Journal – Cardiovascular Pharmacotherapy covering approximately 60 thousand patients with atrial fibrillation coexisting with type 2 diabetes, which is a common problem in the elderly group. The effects of NOACs and warfarin were compared, as well as the benefit-risk balance of their use. It was questioned whether diabetes could be a significant variable, with the result that the outcome would indicate an older class of drugs as the preferred one. However, it turned out as expected – NOACs are safer and more effective, also in diabetics [35, 39, 40].

Summary

The use of NOACs in the prevention of ischemic stroke in the geriatric group is very important and should be the preferred choice. A large part of the

article has been devoted to determining the benefits of this type of anticoagulant treatment. The reason for expanding and delving into this topic is the fact that nearly 50 million people suffer from AF and need effective and safe anticoagulant treatment. Such therapy should also involve minimal or no drug interactions, and this is the pattern shown by NOACs. Still, a large group of elderly people use VKA drugs and we should strive to withdraw them in most cases and replace them with NOACs. This is a debatable topic and when choosing a specific drug, we should take into account the medical and economic aspects together with the patient. There are many advantages to using NOACs, but the most important is the lack of routine monitoring of blood clotting parameters and a relatively low risk of fetal bleeding.

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Table 1. Standard and reduced doses of NOACs in appropriate indications

Drug	Standard dose	Reduced dose + indications
Apixaban	2 x 5 mg/day	2 x 2,5 mg/day (≥ 2 criteria: > 80 yrs, GFR 15–30, body mass < 60 kg, creatinine clearance < 1,5 mg/dL)
Dabigatran	2 x 150 mg/day	2 x 110 mg/day (> 80 yrs, GFR 30–50)
Edoxaban	1 x 60 mg/day	1 x 30 mg/day (GFR 15–49, body mass < 60 kg, concomitant use of verapamil / dronedarone / quinidine)
Rivaroxaban	1 x 20 mg/day	1 x 15 mg/day (GFR 30–49)

GFR – glomerular filtration rate (ml/min per m^2)

Source: [3, 13].

Table 2. Comparison of VKAs and NOACs

Anticoagulants	VKAs	NOACs
Representatives	Acenocoumarol, warfarin	Rivaroxaban, apixaban, edoxaban, dabigatran
Year of introduction	1954	2009
Effect	Inhibition of the reduction of vitamin K and thus the activity of coagulation factors II, VII, IX and X, proteins C and S Factor	Xa factor inhibitors Direct inhibition of thrombin-dabigatran
The way of taking	For the first 2 days – acenocoumarol 6 and 4 mg, warfarin 10 and 5 mg (the elderly can start with 4 mg and 5 mg respectively), then depending on the INR. Therapeutic action after 3–5 days	A tablet up to twice a day depending on the specimen. In patients > 80 years of age < 60 kg or when GFR < 15 ml/min, do not use, < 30 reduce the dose
Monitoring	INR approximately every 4 weeks (target 2.0–3.0, with prosthetic heart valves 2.5–3.5)	Unnecessary
Interactions	Many with drugs (e.g. antibiotics, painkillers, antiarrhythmics) and food (green vegetables)	Few with drugs (e.g. antibiotics, carbamazepine)
Bleeding risk	Increased risk of intracranial bleeding, cerebral hemorrhagic stroke, and fatal bleeding	Increased risk of gastrointestinal bleeding
Cost of therapy	Low cost – PLN 10–20 / package	High – PLN 60–150 / package

Source: [27, 28].