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Use of VKAs and NOACs as stroke prophylaxis in patients with atrial fibrillation - a review of the literature

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Abstract

Introduction and Purpose: Stroke is a common complication of one of the most common cardiac arrhythmias, atrial fibrillation. The aim of this study is to provide key information about these diseases and to compare the drugs used to prevent stroke.

Materials and methods: A literature search was conducted using the medical databases PubMed and Google Scholar. Articles were retrieved in English, employing the key words: "VKA", „NOAC", „atrial fibrillation", „anticoagulants" and „stroke" appropriate configurations.

Conclusions: According to the recommendations and available medical literature, the use of NOACs is usually the most appropriate choice for stroke prevention in patients with atrial fibrillation. However there are also clinical situations, in which the use of VKAs would be more appropriate.

Keywords: VKA, NOAC, atrial fibrillation, stroke, anticoagulants.

Introduction

Atrial fibrillation is one of the most common cardiovascular diseases and one of its complications is stroke. To prevent this complication, vitamin K antagonists (VKAs) (e.g. warfarin, acenocoumarol) or, increasingly, oral anticoagulants (NOACs) such as rivaroxaban, dabigatran, apixaban or edoxaban are used. Although the use of vitamin K has resulted in a significant reduction in thromboembolic incidents, the number of side-effects and the need for constant monitoring of patients taking these drugs has led to the need to find alternatives. Examples of such drugs are the thrombin or factor Xa inhibitors just mentioned [1,2].

1. Atrial fibrillation.

For about 100 years, atrial fibrillation has been recognised as one of the most commonly studied types of arrhythmia [3]. The prevalence of this condition ranges from about 2% to about 10-12% among the elderly population (age 80 years and older) [3]. According to the Global Burden of disease, AF affects 33.5 million people worldwide and in some countries up to 3.5 per cent of their population [4]. AF is thought to lead to up to a twofold increase in premature mortality and to various complications, including cardiovascular events such as heart failure, severe stroke or myocardial infarction [5]. Atrial fibrillation is a heart rhythm disorder characterised by rapid atrial action and irregular electrical activity, which often leads to ventricular arrhythmias. Atrial fibrillation can manifest with a wide variety of symptoms that cause a significant reduction in comfort and quality of life. The most common include palpitations, breathlessness, chest discomfort, fatigue and dizziness. The pathomechanism for the development of fibrillation is now thought to be complex, consisting mainly of stretch-induced fibrosis, excessive epicardial fat volume, inflammation, disorders in the autonomic nervous system with an indication of vagus nerve overactivity and genetic factors. High blood pressure or increased blood volume leads to the transformation of fibroblasts into myofibroblasts, which in turn secrete significant amounts of extracellular matrix proteins causing fibrosis. Fibrosis in turn interferes with the spread of signals and electrical impulses in the heart causing arrhythmias.

Excess adipose tissue also acts in a very similar way - infiltration of adipose tissue causes electro-structural remodelling of the myocardium and thus conduction disturbances. Controlling inflammation is an important protective factor against the occurrence of AF [6]. Oxidative stress and cytokines also affect muscle remodelling. In addition, calcium ion disturbances induced by certain inflammatory mediators have been proven to cause mitochondrial dysfunction and consequently additional production of oxygen free radicals, which, as mentioned above, is a risk factor for AF [7,8]. Abnormalities in vagus nerve conduction cause changes in ion channel function secondary to activation of muscarinic receptors for acetylcholine, resulting in slower heart rate, shorter action potential duration, reduced atrial contraction force and ultimately reduced conduction velocity in the atrioventricular node. Acetylcholine can inhibit gap junction communication and thus reduce conduction velocity in the atrium causing re-entry atrial fibrillation. To confirm the condition, an ECG should be performed and an episode of fibrillation lasting at least 30 seconds should be recorded [6]. The use of smartwatches in the prevention of atrial fibrillation is becoming increasingly popular. Studies such as the Apple Heart Study and Fitbit Heart Study have shown high predictive values for AF diagnosis.

2. Stroke.

Stroke has become a major problem in the United States, as more than 795 000 US citizens suffer a stroke each year. Approximately 610,000 patients have a first-time stroke, while 185,000 occur in people who have already had a stroke. Stroke is also responsible for approximately 140,000 deaths in the United States each year, accounting for about one in twenty deaths in the country. This also makes it the 5th most common cause of death in America. It is also the most common cause of disability in this country. There are two most common causes of stroke. Ischaemic stroke, caused by a blockage in the arteries of the brain, and haemorrhagic stroke, caused by extravasation of blood inside the brain. Both types of stroke cause hypoxia, which damages brain tissue causing death or disability. Prompt intervention makes it possible to prevent death and also to limit the negative effects of a stroke. Common disabilities resulting from stroke include motor impairments such as hemiparesis (weakness of the left or right side of the body), hemiplegia (paralysis of the left or right side of the body) and central facial paresis. Language and speech disorders such as global or mixed aphasia (impairment of language comprehension) and dysarthria (speech impairment) are also common. Other disabilities include impaired consciousness, impaired vision and reduced blood flow to parts of the brain. Currently, the most effective treatment for stroke is thrombolytic therapy using tissue plasminogen activator. However, this type of therapy has its downsides. Treatment must be started no more than 4.5 hours after the onset of stroke symptoms, otherwise there may be an increased risk of haemorrhage, including cerebral haemorrhage. Thrombolytic drugs can lead to severe bleeding, especially when tissues are already damaged and further damage to the brain. The second treatment for stroke is thrombectomy - mechanical removal of the thrombus. This therapy is used when thrombolytic treatment is impossible or ineffective [9].

3. The CHA2DS2-VASc score.

The CHA2DS2-VASc scale is the recommended scale for assessing the risk of stroke in patients with atrial fibrillation and helps identify those for whom anticoagulant treatment is necessary [11]. Atrial fibrillation alone increases the risk of stroke by approximately fivefold. The CHA2DS2-VASc risk scale brings together the most common risk factors for stroke. These include congestive heart failure, hypertension, age, diabetes, stroke, vascular disease and gender. Characteristically, according to this scale, female gender alone represents an increased risk of stroke. Studies have shown that women with atrial fibrillation with at least one risk factor have a significantly higher risk of stroke than men [10]. The study 'CHA2DS2-VASc score in acute ischemic stroke with atrial fibrillation: results from the Clinical Research Collaboration for Stroke in Korea' showed that the CHA2DS2-VASc score enabled risk stratification of vascular events in patients with atrial fibrillation treated with anticoagulation. The results of this study showed that with each score on the scale, the chance of a subsequent vascular event increased. There was an estimated relative risk increase of 31% for primary events, 25% for recurrent stroke and 36% for mortality from any cause [11].

4. The ABC scheme.

In the prevention of stroke in the course of atrial fibrillation, the so-called ABC (Atrial fibrillation Better Care) scheme can be used. Letter A in the scheme corresponds to the recognition of the patient's risk of a thromboembolic incident and the introduction of appropriate anticoagulant treatment. Letter B stands for the patient's normal heart rhythm control, while component C refers to lifestyle optimisation and appropriate management of comorbidities [12]. The ABC pathway has been tested in many types of clinical trials, which have confirmed its usefulness in improving clinical outcomes, including stroke reduction [13,14]. According to the study, the use of the ABC regimen resulted in a reduced chance of stroke. The risk of stroke (OR: 0.55; 95% CI: 0.37-0.82;) [14]. In this work, we will mainly focus on letter A of the ABC- avoid strok regimen, comparing the use of vitamin K and NOACs in stroke prevention.

4.1 A-Avoid Stroke.

In the Avoid strike step, it is primarily a matter of identifying the patient's risk of stroke, for example using the CHA2DS2-VASc scale and administering appropriate anticoagulant treatment - vitamin K antagonists and NOACs are used for this purpose. According to 'Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials', both NOACs and VKAs significantly reduce not only the risk of ischaemic stroke, but also the overall risk of death [15]. There is now an increasing use of NOACs over VKAs, especially in western countries, as they not only reduce the risk of thromboembolic incidents, but are also associated with a lower risk of major bleeding and intracranial haemorrhage. The use of NOACs is also associated with patient convenience, as the patient, unlike a VKA user, does not need to perform cyclical blood INR tests. An important step in stroke prevention is also to assess the risk of bleeding. The use of anticoagulants may be associated with an increased risk of bleeding.

For this reason, every patient should be assessed for risk factors such as unstable INR values, blood pressure, renal function or alcohol consumption before starting an anticoagulant. The HAS BLED scale may be useful for this purpose [16].

5. The HAS-BLED scale.

As mentioned in the previous chapter, before starting a patient on anticoagulants, the patient should first be assessed for bleeding risk. There are many factors that contribute to an increased risk of bleeding and can be divided into modifiable, partially modifiable and non-modifiable factors. Modifiable bleeding risk factors include hypertension/high SBP, concomitant use of antiplatelet/NSAIDs, excessive alcohol consumption, non-adherence to OACs, dangerous hobbies/occupation, heparin bypass therapy, INR control (target 2.0-3.0), target TTR >70%c, appropriate choice of OACs and their correct dosing. Non-modifiable factors, on the other hand, include: age >65 years, history of major bleeding, severe renal impairment (dialysis or kidney transplant), severe liver impairment (cirrhosis), malignancy, genetic factors (e.g. CYP 2C9 polymorphisms), history of stroke, small vessel disease. diabetes, cognitive impairment, dementia. In contrast, potentially modifiable risk factors include: very severe frailty ± excessive risk of falls, anaemia, reduced platelet count or function, renal impairment with CrCl <60, VKA treatment strategy. By collecting modifiable and non-modifiable risk factors and segregating them, it was possible to create scales to assess bleeding risk. According to the guidelines, the use of the HAS-BLED scale has the best results when it comes to the long-term identification of patients with a low risk of bleeding (HAS BLED score 0-2). The HAS-BLED scale is particularly useful in patients using VKAs (oHAS BLED); however, a modified scale (rHAS BLED) is necessary in patients using NOACs. This is because the risk of bleeding in patients using NOACs is not INR-dependent. Determining renal insufficiency can also be a problem, as Kidney Disease: Improving Global Outcomes (KDIGO) classifies renal insufficiency based on GFR values and albuminuria, whereas oHAS BLED uses creatinine to assess renal insufficiency, which may not reflect the severity of the impairment. The modified scale, unlike the original one, assesses instability of anticoagulant control based on the SAMe-TT2R2score (scoring 3 on the SAMe-TT2R2score gives 1 point on the rHAS BLED score) instead of an unstable INR. Studies show that eGFR below 60 ml/min/1.73 m2 predicts bleeding risk more accurately than creatinine levels in patients with AF [17]. The guidelines indicate that a high risk of bleeding occurs when a patient's score on this scale is 3 or higher. Nonetheless, a high score on the HAS-BLED scale should not result in abandoning the use of NOACs, but should induce increased vigilance on the part of the physician and a focus on changing modifiable bleeding risk factors and reassessing them. With this scale, high-risk patients with non-modifiable bleeding risk factors can be identified. In this way, they can be assessed more frequently - once a month (instead of every 4-6 months). The scale also allows the selection of appropriate treatment for AF patients with comorbidities [18].

Table 1: Stroke and bleeding risk stratification with the CHA_2DS_2-VASc and HAS-BLED schemas

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension i.e. uncontrolled BP	1
Hypertension	1	Abnormal renal/liver function	1 or 2
Aged ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INR	1
Vascular disease [prior MI, PAD, or aortic plaque]	1	Age (e.g. >65)	1
Aged 65-74 years	1	Drugs (e.g. concomitant aspirin or NSAIDSs) or alcohol	1
Sex category [i.e. female gender]	1		
Maximum score	**9**		**9**

Fig. 1- Camm, AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation. *Eur Heart J* 2012. [Epub ahead ofprint] PubMed PMID: 22922413 [19].

6. NOAC VS VKA.

Atrial fibrillation is one of the most common reasons for the use of oral anticoagulants. The most commonly used drugs to date have been VKAs (vitamin K antagonists), the most common of which is warfarin. Despite their many advantages, including high efficacy in stroke prevention, these drugs also have disadvantages, which include a narrow therapeutic window, slow onset and cessation of action, and variable dose response. VKAs also have numerous interactions with other drugs and certain foods, which may enhance or impair the drug's effect. According to recent recommendations, the use of NOACs (formerly an abbreviation for new anticoagulants - nowadays these drugs are not so new, so the term used is oral anticoagulants that are not vitamin K antagonists) has been shown to be better or equally good at preventing haemorrhagic strokes in patients with atrial fibrillation. Nevertheless, the use of NOACs has its limitations. These limitations are mainly related to medical reasons, but also to economic reasons - NOACs are relatively expensive drugs and, in countries where the drugs are reimbursed by the state, they are a heavy burden on the healthcare budget, so their prescription must be regulated accordingly. According to the Choice of New Oral Anticoagulant Agents Versus Vitamin K Antagonists in Atrial Fibrillation: FANTASIIA Study: 'NOACs are recommended in specific clinical scenarios: (1) in patients with contraindications to VKA, hypersensitivity or allergy; (2) in patients with a history of intracranial haemorrhage; (3) in patients with a history of stroke and high risk of bleeding (HAS-BLED >3 and leukoaraiosis grade III/IV or multiple cortical microbleeds); (4) embolic events in VKA patients despite good INR control; (5) VKA-treated patients with poor INR control (time in therapeutic range <65% according to the Rosendaal method or <60% as a direct calculation, in the previous 6 months); and (6) patients with no access to INR control' [20].

Oral anticoagulants other than vitamin K were associated with a lower risk of intracranial bleeding (HR 0.46; 95% CI 0.38-0.58) and haemorrhagic stroke (HR 0.61; 95% CI 0.48-0.79) than VKAs. In contrast, the risk of gastrointestinal bleeding is significantly lower in the VKA group (HR 1.46; 95% CI 1.30-1.65) [21]. The greatest clinical benefit of oral anticoagulants other than vitamin K can be seen in the elderly, where thromboembolic incidents and the risk of haemorrhagic stroke were significantly reduced. The risk of major bleeding in the NOAC group assessed by adjusted indirect comparison was significantly lower for apixaban compared with rivaroxaban and dabigatran and for edoxaban compared with rivaroxaban [21]. Also according to the study 'Efficacy and safety of NOAC versus warfarin in AF patients with left atrial enlargement', in patients with enlarged left atrium, the use of NOAC was associated with a lower risk of ischaemic stroke (IS) and systemic embolism compared to the use of warfarin, while the amount of major bleeding remained the same [22]. A post hoc analysis of the ROCKET AF trial, which included 214 patients with atrial fibrillation and aortic stenosis, showed that patients with atrial fibrillation and aortic stenosis taking 20 mg of rivaroxaban daily had similar rates of stroke or systemic embolism compared with patients taking warfarin (HR not stated), but higher rates of major bleeding (HR, 1.73; 95% CI, 0.73-4.12) and major bleeding/clinically significant bleeding (HR, 1.18; 95% CI, 0.70-1.97) [23]. In a post hoc analysis of the ARISTOTLE trial, which included 1150 patients with AF and aortic valve disease, 384 of whom had aortic stenosis, patients with AF and aortic valve disease taking 5 mg apixaban twice daily had a lower risk of stroke or systemic embolism (HR, 0.55; 95% CI, 0.30-1.01) and major bleeding (HR, 0.72; 95% CI, 0.44-1.18) compared with patients taking warfarin [24]. In these 2 post hoc studies, the finding of a lower or similar risk of thrombosis in the NOAC group compared with the warfarin group differs from the findings in the 'Effectiveness and Safety of NOAC Versus Warfarin in Patients With Atrial Fibrillation and Aortic Stenosis' study, in which a significantly higher risk of thrombosis was observed in the NOAC group compared with the warfarin group (HR, 1.62; 95% CI, 1.08-2.45 in the ITT analysis; HR, 1.92; 95% CI, 1.011-3.30 in the PP analysis). The results regarding major bleeding in the 'Effectiveness and Safety of NOAC Versus Warfarin in Patients With Atrial Fibrillation and Aortic Stenosis' study are consistent with the results of the post hoc analysis in the ARISTOTLE study, as a lower risk of major bleeding was also observed in the NOAC group compared with the warfarin group (HR, 0.73; 95% CI, 0.59-0.91 in the ITT analysis; HR, 0.78; 95% CI, 0.60-0.99 in the PP analysis) [22]. The study 'Long-term stroke and major bleeding risk in patients with non-valvular atrial fibrillation: A comparative analysis between non-vitamin K antagonist oral anticoagulants and warfarin using a clinical data warehouse', which followed patients from 2009 to 2020, results indicated that NOACs were more effective than warfarin in preventing ischaemic stroke and reducing haemorrhagic side effects in patients with atrial fibrillation at long-term follow-up. "In the combined dataset, 858 patients were treated with warfarin, 2343 patients were treated with NOACs. After diagnosis of AF, the incidence of ischaemic stroke during follow-up was 199 (23.2%) in the warfarin group, 209 (8.9%) in the NOAC group. Intracranial haemorrhage occurred in 70 patients (8.2%) in the warfarin group, 61 (2.6%) in the NOAC group. Gastrointestinal bleeding occurred in 69 patients (8.0%) in the warfarin group, 78 patients (3.3%) in the NOAC group.

The risk ratio (HR) of ischaemic stroke by NOAC was 0.479 (95% CI 0.39-0.589, $p < 0.0001$), the HR of intracranial haemorrhage was 0.453 (95% CI 0.31-0.664, $p < 0.0001$) and the HR of gastrointestinal bleeding was 0.579 (95% CI 0.406-0.824, $p = 0.0024$)." [25]. This study suggests that patients with atrial fibrillation should be treated with NOACs to reduce the incidence of ischaemic stroke [25]. However, NOACs are not always superior to VKAs. The INVICTUS and PROACT Xa trials proved that in specific cases such as patients with AF and rheumatic heart disease, comorbidities such as advanced liver disease and renal disease or drugs interacting with NOACs, or patients with AF and mechanical heart valves or phospholipid syndrome, vitamin K antagonists perform better in terms of patient survival compared to NOACs. Death occurred in 8.0% of patients per year in the rivaroxaban group compared to 6.4% of patients per year in the VKA group. The lower mortality outcome is not exactly dependent on fewer vascular events, as according to the IVICTUS trial, the number of strokes and systemic embolisms for VKA and rivaroxaban were 1.1% and 1.4%, respectively. The reason for this may be twofold - firstly, VKA users need to make more frequent visits to the doctor to control INR so patient compliance may be better, and medical control of comorbidities and heart failure may also be more effective. The second hypothesis is that VKAs have a protective effect on the heart by inhibiting the synthesis of vitamin K-dependent proteins such as, for example, Growth arrest - specific 6 (GAS6), which, together with its ligand AXL-receptor tyrosine kinase, causes activation of the signalling pathway that causes heart failure. The PROACT Xa and RE-ALIGN study showed that warfarin performed better in stroke prevention compared to rivaroxaban and apixaban in patients with artificial heart valves. The likely reason for this was that the maximum NOAC dose was not sufficient to compensate for the amount of thrombin generated by the artificial valves (Artificial heart valves cause clotting by binding and activating factor XII, which in turn activates factor Xa and thrombin via the common and intrinsic clotting pathway- NOACs such as dabigatran inhibit this process) [26].

Conclusions

Atrial fibrillation is one of the most common cardiac arrhythmias and can lead to many different complications. One of the most dangerous of these is stroke, which can take various forms, but always leads to severe complications or death. In line with the idea that prevention is better than cure, appropriate thromboprophylaxis selected specifically for the individual patient should be used. Currently, NOACs are most commonly recommended, especially in atrial fibrillation patients with a high risk of central nervous system bleeding and in elderly patients. Vitamin K antagonists, on the other hand, are more useful for treating heavily multi-disease patients with artificial heart valves and rheumatic heart disease.

Summary
Stroke is one of the most common and dangerous complications of atrial fibrillation, affecting more and more people worldwide every year. Various scales such as the CHA2DS2-VASc and HAS BLED exist to assess the risk of stroke and bleeding, making it relatively easy to identify those at risk and introduce appropriate preventive treatment. New anticoagulants for stroke prevention according to recommendations and available literature are in the vast majority of cases a better choice over VKAs.
However, the use of VKAs cannot be completely abandoned, as they reduce the risk of death, especially in people with multimorbidity or in patients with implanted artificial heart valves.

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