

THE SIGNIFICANCE OF ORAL ANTICOAGULANT THERAPY IN THE PREVENTION OF THROMBOEMBOLIC COMPLICATIONS IN PATIENTS WITH ATRIAL FIBRILLATION DURING A 14-YEAR FOLLOW-UP - CASE REPORT

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Summary: INTRODUCTION. Atrial fibrillation (AF) is the most common long-term arrhythmia and represents one of the main public health problems primarily due to the aging of the general population, in which this arrhythmia occurs more often and causes thromboembolic stroke. Cardioembolic stroke associated with AF is usually severe, highly recurrent, and often fatal or with permanent disability of specific stroke risk factors/modifiers. Common risk factors are summarized in a risk factor-based clinical score called the CHA2DS2-VASc Score. Poor INR control increases the risk of both thromboembolic and hemorrhagic complications, and the optimal balance between the benefits and risks of using oral VKAs is achieved when the TTR, or time in the therapeutic range, is $\geq 70\%$ [9]. We present the case of a female patient that confirms the importance of oral anticoagulant therapy when the INR is in the therapeutic range between 2-3, in the largest number of measurements in the successful prevention of recurrent thromboembolic complications during a 14-year follow-up. CASE REPORT: We present a 60-year-old MD patient who first came to the Office of Internal Medicine "Dr. Bastać" in 2008 due to a feeling of instability and heart palpitations. Due to grade II hypertension, which is not well regulated, she has been taking antihypertensive therapy for the past two years, treats elevated cholesterol with statins, and states that in two years and a year before her first examination at the Office of Internal Medicine "Dr. Bastać", she had two minor strokes verified by MSCT of the endocranium. In our patient, a high CHA2DS2-VASc score of 4 was calculated (hypertension, female gender and previous stroke) and the estimated annual risk for stroke is 9.27% (TABLE 2). Her bleeding risk - HAS BLEED Score is moderate and is 2 (hypertension, CVI). Based on CHA2DS2-VASc, the risk of adverse thromboembolic events is high and requires the introduction of oral anticoagulant therapy. The patient in therapy receives acenocoumarol according to the scheme so that the value of PT/INR is between 2.0 and 3.0. Good anticoagulation is defined as having 3 to 4 PT/INR values in the therapeutic range (similar to TTR 50 to 60% of the time), while poor anticoagulation is: 0-2 measured INR values in the therapeutic range (TTR <50%) [3]. In our patient, the TTR is about 70%, which represents excellent anticoagulation. During 14 years of monitoring for three months, as well as at the recent control on 04/29/2022. the patient feels well, with no new thromboembolic complications and no bleeding episodes. CONCLUSION. Antithrombotic therapy with vitamin K antagonists can achieve good anticoagulation and long-term successful prevention of repeated cardioembolic strokes in patients with atrial fibrillation. We emphasize the need for highly motivated patients to regularly monitor the level of anticoagulation via INR and the full engagement of the prescribing physician. In this case, we emphasize the frequent problem of delays in the introduction of anticoagulation therapy in atrial fibrillation. Stroke prevention is the cornerstone of care for patients with atrial fibrillation.

Key words: atrial fibrillation, stroke prevention, thromboembolic stroke, vitamin K antagonists, non-vitamin K anticoagulant drugs, INR, TTR,.

INTRODUCTION

AF is the most common long-term arrhythmia and represents a major public health problem. It is estimated that the number of patients will progressively increase in the next few decades, primarily due to the aging of the

general population, in which this arrhythmia occurs more often [1]. Atrial fibrillation (AF) is characterized by disorganized, rapid, and irregular activation of the atria, with a lack of atrial contraction and irregular ventricular rate. Absolutely irregular RR intervals (which is why it

is also called absolute arrhythmia), lack of P waves, and atrial frequency higher than 300/min, are registered electrocardiographically. Risk factors for developing AF, in addition to age, include hypertension, diabetes mellitus, heart disease, and sleep apnea. AF increases the risk of ischemic stroke fivefold. Cardioembolic stroke associated with AF is usually severe, highly recurrent, and often fatal or with permanent disability [2]. Ischemic stroke in patients with AF is most often caused by the dissemination of a thrombus formed in the auricle of the left atrium [3]. The risk for stroke associated with AF is not homogeneous, considering that it depends on the presence of specific stroke risk factors/modifiers. Common risk factors are

summarized in a risk factor-based clinical score called the CHA2DS2-VASc Score, in which congestive heart failure, hypertension, age 65-74 years, diabetes, peripheral vascular disease, and female gender contribute 1 point each, while previous ischemic stroke or transient ischemic attack (TIA) as well as age ≥ 75 years carry 2 points (TABLE 1). Lifelong anticoagulant therapy is always recommended in patients with atrial fibrillation for stroke prevention when the CHA2DS2-VASc score is > 2 in men and > 3 in women (recommendation class I, level of evidence A), and may be considered in CHA2DS2-VASc score = 1 in men or = 2 in women (recommendation class IIa, level of evidence B) [4].

TABLE 1 CHA2DS2-VASc Score: Clinical Risk Factors for Stroke, Transient Ischemic Attack

CHA2DS2-VASc Risk Factor Score		Score
C	Congestive heart failure	1
H	Hypertension	1
A2	Age >75 years	2
D	Diabetes	1
S	Stroke/transient ischemic attack	2
V	Vascular disease	1
A	Age 65-74 years	1
Sc	Females	1
Maximum score		9

TABLE 2 One-year frequency of stroke (%) in AF according to CHA2DS2-VASc score

CHA2DS2-VASc score	One-year incidence of stroke %
0	0.78
1	2.01
2	3.71
3	5.92
4	9.27
5	15.26
6	19.74
7	21.50
8	22.38
9	23.64

Before initiating oral anticoagulant therapy, the risk of bleeding should be assessed using the HAS-BLED score (hypertension, abnormal kidney/renal function, stroke, bleeding history or predisposition, labile INR, age over 65 years, drug/alcohol use) and if it is high, i.e. over 3, the

correction of modifiable risk factors should be considered and those patients should be monitored more often, but certainly a high score is not a reason to stop anticoagulant therapy (recommendation class IIa, level of evidence B) (TABLE 3) [5].

TABLE 3. HAS-BLED Score: assessment of bleeding risk for patients with AF

Risk factors		Score
H	Hypertension	1
A	Abnormal liver or kidney function (1 point for each)	1 or 2
S	A punchline	1
B	Bleeding	1
L	Labile INR values	1
E	Older than 65 years	1
D	Drugs or alcohol (1 point for each)	1 or 2
Maximum score 9		

For more than 60 years, vitamin K antagonists (VKA) have been used to prevent stroke in patients with AF [6]. Oral VKAs are coumarin derivatives that inhibit the synthesis of vitamin K-dependent coagulation factors (II, VII, IX and X) in the liver. Representatives of this group of drugs are acenocoumarol, warfarin, and rarely phenprocoumon [7]. The safe and effective use of these drugs implies regular control of indicators of the intensity of the anticoagulant effect of vitamin K antagonists, the INR (international normalized ratio of prothrombin times), which should be in the range of 2.0 to 3.0 [8] .

Poor INR control increases the risk of both thromboembolic and hemorrhagic complications, and the optimal balance between the benefits and risks of using oral VKAs is achieved when the TTR or time in the therapeutic range is $\geq 70\%$ [9] .

In the last few years, several phase III randomized clinical trials comparing the effect of new oral anticoagulant drugs with warfarin in the prevention of thromboembolism in AF have been completed. The new drugs are divided into two groups: oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (rivaroxaban and apixaban). The advantage of the new drugs lies in the smaller number of clinically significant interactions with food and other drugs and the absence of the need for regular laboratory monitoring of the anticoagulant effect, with equal effectiveness in the prevention of thromboembolism and a lower frequency of significant bleeding compared to VKA (10,11).

We present the case of a female patient, which confirms the importance of oral anticoagulant therapy when the INR is in the therapeutic range between 2-3 for most of the time in the prevention of recurrent thromboembolic complications during the 14-year follow-up.

Material and methods

The material used for the preparation of this paper was the patient's electronic health record as well as his personal medical documentation (laboratory analysis findings, specialist doctor's reports and discharge list). The method of retrospective analysis of medical records was applied.

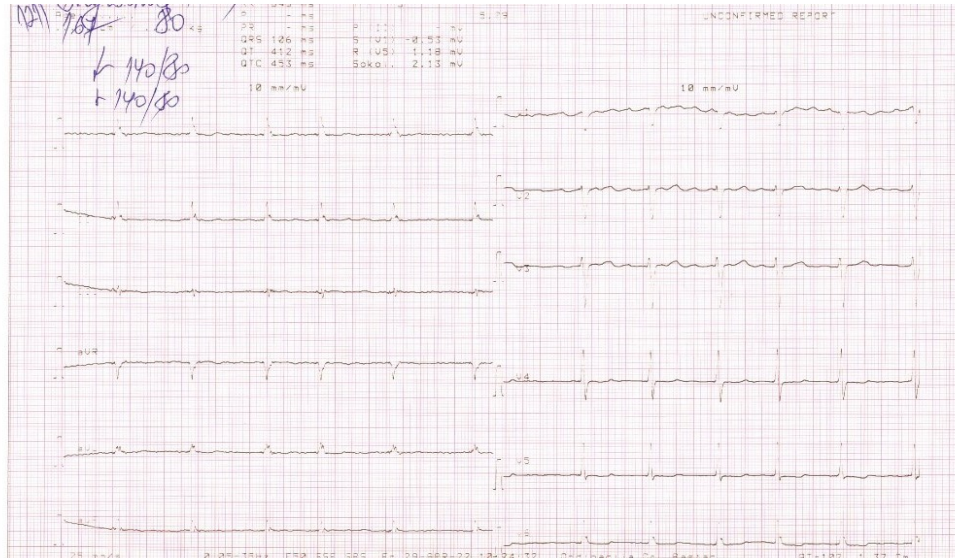
Case presentation

The case is about a 60-year-old MD patient who came to the Office of Internal Medicine "Dr. Bastać" for the first time in 2008 due to a feeling of instability and heart palpitations. Due to grade II hypertension, which is not well regulated, she has been taking antihypertensive therapy for the past two years, treating elevated cholesterol with a statin. She has had palpitations and arrhythmia for the last 2 years, two years ago and a year before her first examination at the Office of Internal Medicine "Dr. Bastać" office, she had two minor strokes verified by MSCT of the endocranium. The patient is a non-smoker, pre-obese BMI 29.0 with pronounced abdominal obesity (waist circumference 104 cm). During the physical examination, we determined that the patient was cardiopulmonarily compensated and hemodynamically stable. Heart rhythm was irregular, tones were clear, murmurs were not registered. Blood pressure on arrival, measured

brachially bilaterally, was 170/100 mmHg. Auscultation of the lungs revealed a normal respiratory murmur. The liver was not enlarged and there was no pretibial edema. Hematological and biochemical analyzes were within normal

limits. ECG on arrival: atrial fibrillation, fr 85/min, normogram, incomplete left bundle branch block, horizontal depression ST -0.5 in V5-V6 (Figure 1).

Figure 1. ECG on arrival from 2008



Echocardiographic findings from 2008 indicate that the left ventricle was of normal dimensions without myocardial hypertrophy and with preserved global systolic function. There were no segmental outbursts in the contractility of the left ventricular walls. Mitral cusps were slightly more voluminous with minor mitral regurgitation. Left sternum dilated, 39 mm measured in a standard parasternal section. Right ventricle of normal dimensions.

After the completed physical examination and additional diagnostics, the CHA2DS2-VASc Score and the HAS BLED Score were calculated. In this patient, CHA2DS2-VASc was 4 (hypertension, female gender and previous stroke) and the estimated annual risk for stroke is 9.27% (TABLE 2). The calculated HAS BLED Score is 2 (hypertension, CVI). Based on CHA2DS2-VASc, the risk of adverse thromboembolic events is high and requires the introduction of oral anticoagulant therapy. The patient in therapy receives acenocoumarol according to the scheme that the value of PT/INR should be between 2.0 and 3.0 with the note that if a serious bleeding episode occurs, she should stop taking acenocoumarol, check the value of

PT/INR and contact the doctor. After this first examination, the patient regularly came for follow-up examinations. PT/INR was done initially for 2 weeks and later for a month. When INR stability was achieved, INR control for 2 months was sufficient, which is optimal for these patients.

The time in the therapeutic range (TTR) could not be calculated by the most commonly used Rosendaal method due to the lack of a sufficiently large number of INR measurements over the years (12, ie once a month). That is why the method used in their study "One -year monitoring of the quality of oral anticoagulant therapy in patients with atrial fibrillation and analysis of the impact on the quality of anticoagulation" was used by Dr. D. Bastać and colleagues, where the criterion for excellent anticoagulation was that within a year 5 to 7 measured values of PT/INR will be ≥ 2 (TTR >60-85% of the time). Good anticoagulation is defined as having 3 to 4 PT/INR values in the therapeutic range (analogous to TTR 50 to 60% of the time), while poor anticoagulation is: 0-2 measured INR values in the therapeutic range

(TTR <50%) [3]. In this patient, TTR is about 70%, which represents excellent anticoagulation.

During 14 years of regular follow-up every three months, as well as telephone consultations to achieve optimal INR, as well as at the recent check-up on 04/29/2022., the patient felt well, with no new thromboembolic complications and no bleeding episodes.

DISCUSSION

In the last few years, several phase III randomized clinical trials comparing the effect of new oral anticoagulant drugs with warfarin in the prevention of thromboembolism in AF have been completed. The new drugs are divided into two groups: oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (rivaroxaban and apixaban). The advantage of the new drugs lies in the smaller number of clinically significant interactions with food and other drugs and the absence of the need for regular laboratory monitoring of the anticoagulant effect, with equal effectiveness in the prevention of thromboembolism and a lower frequency of significant bleeding compared to VKA (10,11). But the presented case shows that long-term successful prevention of repeated cardioembolic strokes in patients with permanent atrial fibrillation can also be achieved with classic antithrombotic therapy with VK antagonists.

A high CHA2DS2-VASc score of 4 (hypertension, female gender and previous stroke) with an estimated annual risk for stroke of 9.27% was an absolute indication for the introduction of anticoagulant therapy. Her bleeding risk - HAS BLED Score is moderate and is 2 (hypertension, CVI). Based on CHA2DS2-VASc, the risk of adverse thromboembolic events is high, and oral anticoagulant therapy was immediately introduced, with acenocoumarol according to the scheme that the value of PT/INR should be between 2.0 and 3.0 Unfortunately, due to the delay in the therapeutic sense, 2 years were missed by the prescribing doctors and only after 2 strokes we introduced anticoagulant therapy

A high CHA2DS2-VASc score of 4 (hypertension, female sex, and previous stroke) with an estimated annual risk for stroke of 9.27% was an absolute indication for the initiation of anticoagulant therapy before strokes occurred. The problem of delay in the introduction of anticoagulant therapy in

particularly asymptomatic AF is great in practical work. An effort is needed in medical practice to introduce early oral anticoagulant therapy in AF and avoid well-preventable events such as cardioembolic complications, especially stroke.

People who do not have the financial ability to take NOAKA can be adequately treated with high-quality anticoagulation with dicoumar preparations with the involvement of the prescribing physician and the patient's motivation. However, clear indications for switching from vitamin K antagonists to NOAC regardless of the patient's financial burden are: labile INR, frequent bleeding, thromboembolic attacks despite a relatively good time spent in the therapeutic range (TTR).

On the other hand, vitamin K antagonists have an advantage in AF in the prevention of stroke when new anticoagulant drugs, non-VK antagonists are contraindicated in AF as part of mitral stenosis and mechanical artificial valves. Also, in severe renal insufficiency, when the glomerular filtration rate is less than 30 ml/min, and in all hemodialysis patients, NOAKA must be switched to dicoumarol preparations.

CONCLUSION

The presented case confirms the view that, even in the era of new anticoagulant drugs NON-VK antagonists (NOACs), classic antithrombotic therapy with Vitamin K antagonists can achieve good anticoagulation and long-term successful prevention of repeated cardioembolic strokes in patients with permanent as well as paroxysmal atrial fibrillation based on CHA2DS2-VASc score without significant hemorrhagic complications, the risk of which we assess HAS BLED Score During 14 years of monitoring for three months, as well as at the recent control on 04/29/2022., our patient has had no new thromboembolic complications and no bleeding episodes. This proves that patients with atrial fibrillation can be adequately treated with high-quality anticoagulation with dicoumarol preparations with great involvement of the prescribing physician and good motivation of the patient even when they do not have the financial means to switch to non-vitamin k anticoagulant drugs.

In connection with this case, we highlight the frequent problem of delay in the introduction of anticoagulant therapy in atrial fibrillation. An effort is needed in medical practice to introduce early oral anticoagulant

therapy in AF and avoid well-preventable events such as cardioembolic complications, especially

stroke. Stroke prevention is the cornerstone of care for patients with atrial fibrillation.

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