TIMOČKI MEDICINSKI GLASNIK

Vol. 47 (2022) br. 2-3

UDK 616.12-008.313-085
COBISS.SR-ID 78579465

ZNAČAJ ORALNE ANTIKOAGULANTNE TERAPIJE U PREVENCIJI TROMBOEMBOLIJSKIH KOMPLIKACIJA KOD PACIJENTA SA ATRIJALNOM FIBRILACIJOM TOKOM 14-TOGODIŠNJEG PRAĆENJA - PRIKAZ SLUČAJA

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Sažetak: UVOD. Atrijalna fibrilacija (AF) je najčešća dugotrajna aritmija i predstavlja jedan od glavnih problema javnog zdravlja pre svega zbog starenja opšte populacije, kod koje se ova aritmija češće javlja i može da izazove tromboembolijski moždani udar. Kardioembolijski moždani udar udružen sa AF je obično težak, sklon recidivima i često fatalan ili sa trajnom nesposobnošću. Uobičajeni faktori rizika za moždani udar sumirani su u kliničkom skoru baziranom na faktorima rizika koji se naziva **CHA_2DS_2-VASc** Skor. Antikoagulantni efekat se meri internacionalnim normalizovanim odnosom protrombinskih vremena (PT/INR). Loša kontrola antikoagulantnog efekta povećava rizik kako od tromboembolijskih, tako i od hemoragijskih komplikacija. Optimalan balans između koristi i rizika od primene oralnih antagonista vitamina K (VKA) postiže se kada je INR 2,0 do 3,0 i vreme provedeno u tom terapijskom opsegu (TTR) ≥ 70%. **PRIKAZ SLUČAJA**: Prikazujemo slučaj pacijentkinje gde je sprovedena uspešna prevencija ponovnih tromboembolijskih komplikacija tokom 14-togodišnjeg praćenja. Na ovaj način se potvrđuje značaj oralne antikoagulantne terapije, kada je INR u terapijskom opsegu u najvećem broju merenja. Pacijentkinja M.D, starosti 60 godina prvi put dolazi na pregled u Internističku ordinaciju "Dr Bastać" 2008. godine zbog osećaja nestabilnosti i osećaja lupanja srca. Zbog hipertenzije gradus II koja nije dobro regulisana uzima antihipertenzivnu terapiju dve godine unazad. Pacijentkinja leči povišen holesterol statinima. Navodi da je pre dve godine imala prvi moždani udar a pre godinu dana se desio i drugi moždani udar. Oba moždana udara su verifikovana višeslojnim komjuter-tomografskim skenom (MSCT) endokranijuma. Našoj pacijentkinji je izračunat visok **CHA_2DS_2-VASc** skor 4 (hipertenzija, ženski pol i prethodni moždani udar) a procenjeni godišnji rizik za moždani udar iznosi 9,27 %. Njen rizik od krvarenja -HAS BLED Skor je umeren i iznosi 2 (hipertenzija, CVI). Na osnovu **CHA_2DS_2-VASc** rizik od neželjenih tromboembolijskih događaja je visok i zahteva uvođenje oralne antikoagulante terapije. Pacijentkinji je uveden u terapiju acenokumarol po šemi da vrednost PT/INR bude između 2.0 i 3.0. Dobra antikoagulisanost je definisana da 3 do 4 vrednosti PT /INR budu u terapijskom opsegu (analogno TTR 50 do 60% vremena) dok je slaba antikoagulisanost: 0-2 izmerene vrednosti INR u terapijskom opsegu (TTR <50%). U slučaju naše pacijentkinje TTR iznosi oko70 % što predstavlja odličnu antikoagulisanost. Tokom 14 godina praćenja na tri meseca, kao i na skorašnjoj kontroli 2022 godine pacijentkinja se oseća dobro, bez novih tromboembolijskih komplikacija i bez epizoda krvarenja. **ZAKLJUČAK.** Antitrombotskom terapijom sa vitamin K antagonistima postignuta je dobra antikoagulisanost kod naše pacijenkinje i dugorajna uspešna prevencija kardioembolijskih moždanih udara kod AF. Ističemo potrebu visoke motivisanosti pacijenata za redovno praćenje nivoa antikoagulisanosti putem INR i punu angažovanost ordinirajućeg lekara. Povodom ovog slučaja ističemo čest problem kašnjenja sa uvođenjem antokoagulantne terapije kod atrijalne fibrilacije. Prevencija moždanog udara je kamen temeljac u zbrinjavanju pacijenata sa atrijalnom fibrilacijom.

Ključne reči: atrijalna fibrilacija, prevencija moždanog udara, tromboembolijski moždani udar, vitamin K antagonisti, non-vitamin K antikoagulantni lekovi, INR, TTR,

UVOD

Atrijalna fibrilacija (AF) je najčešća dugotrajna aritmija i predstavlja jedan od glavnih problema javnog zdravlja pre svega zbog starenja opšte populacije, kod koje se ova aritmija češće javlja i izaziva tromboembolijski moždani udar [1]. Atrijalnu fibrilaciju (AF) karakteriše dezorganizovana, brza i nepravilna

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Rad primljen: 01.09.2022. Elektronska verzija objavljena: 04.11.2022.

TIMOK MEDICAL GAZETTE

Vol. 47 (2022) No. 2-3 Case report

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 ≥ 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 BLED 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

aktivacija pretkomora, uz nedostatak kontrakcije pretkomora i sa nepravilnom frekvencijom komora. Elektrokardiografski se registruju apsolutno nepravilni RR intervali (zbog čega se naziva i apsolutna aritmija), nedostatak P talasa i pretkomorska frekvenca je veća od 300/min. Faktori rizika za razvoj AF, osim starosti, obuhvataju hipertenziju, dijabetes melitus, oboljenje srca i apneju tokom spavanja/ sleep apnea). AF petostruko povećava rizik od ishemijskog moždanog udara. Kardioembolijski moždani udar udružen sa AF je obično težak, vrlo sklon recidivima i često fatalan ili sa trajnom nesposobnošću [2]. Ishemijski moždani udar kod bolesnika sa AF najčešće je uzrokovan diseminacijom tromba formiranog u aurikuli leve pretkomore [3]. Rizik za moždani udar udružen sa AF nije homogen, zavisi od prisustva specifičnih faktora rizika/modifikatora moždanog udara. Uobičajeni faktori rizika sumirani su u kliničkom skoru baziranom na faktorima rizika koji se naziva **CHA_2DS_2-VASc** Skor. Kongestivna srčana insuficijencija, hipertenzija, starost 65-74 godina, dijabetes, periferna vaskularna bolest i ženski pol donose po 1 poen, dok prethodni ishemijski moždani udar ili tranzitorni ishemijski atak (TIA) kao i starost ≥ 75 godina nose 2 poena u ovom skoru (TABELA 1). Doživotna antikoagulantna terapija preporučuje se uvek kod pacijenata sa atrijalnom fibrilacijom u prevenciji moždanog udara kada je **CHA_2DS_2-VASc** skor > 2 kod muškaraca i > 3 kod žena (klasa preporuka I, nivo dokaza A), a može biti razmotrena kod **CHA_2DS_2-VASc** skora = 1 kod muškaraca ili = 2 kod žena (klasa preporuka IIa, nivo dokaza B) [4].

TABELA 1. **CHA_2DS_2-VASc** skor: Klinički faktori rizika za moždani udar i tranzitorni ishemički atak

CHA_2DS_2-VASc Skor faktori rizika		Skor
C	Kongestivna srčana insuficijencija	1
H	Hipertenzija	1
A2	Starost >75 godina	2
D	Dijabetes	1
S	Šlog/tranzitorni ishemijski atak	2
V	Vaskularna bolest	1
A	Starost 65-74 godina	1
Sc	Ženski pol	1
Maksimalni skor		9

TABELA 2. Jednogodišnja učestalost moždanog udara (%) kod AF prema vednosti **CHA_2DS_2-VASc** skor

CHA_2DS_2-VASc skor	Jednogodišnja učestalost moždanog udara %
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

Pre uvođenja oralne antikoagulantne terapije bi trebalo proceniti rizik od krvarenja i za to se koristi HAS-BLED skor (hipertenzija, abnormalna bubrežna/renalna funkcija, predhodni moždani udar, anamneza o krvarenju ili predispozicija, labilan INR, starost preko 65

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].

godina, upotreba droga/alkohola). Ukoliko je on visok, odnosno preko 3, treba razmotriti korekciju faktora rizika koji se mogu modifikovati i češće pratiti te pacijente. Visok skor nije razlog obustave antikoagulantne terapije već nalaže povećanu opreznost. (klasa preporuka IIa, nivo dokaza B) (TABELA 3) [5].

TABELA 3. HAS-BLED Skor: procena rizika od krvarenja za pacijente sa AF

Faktori rizika		Skor
H	Hipertenzija	1
A	Abnormalna funkcija jetre ili bubrega (1 poen za svaki)	1 ili 2
S	Šlog	1
B	Krvarenje ili predispozicija	1
L	Labilne vrednosti INR	1
E	Stariji od 65 godina	1
D	Lekovi ili alkohol (1 poen za svaki)	1 ili 2
Maksimalni skor		9

Više od 60 godina u prevenciji moždanog udara kod pacijenta sa AF koriste se vitamin K antagonisti (VKA) [6]. Oralni VKA su derivati kumarina koji inhibiraju sintezu vitamin K – zavisnih faktora koagulacije (II, VII, IX i X) u jetri. Predstavnici ove grupe lekova su acenokumarol, varfarin i fenprokumon [7]. Bezbedna i efikasna primena ovih lekova podrazumeva redovne kontrole pokazatelja intenziteta anti-koagulantnog efekta VKA koji je označen kao INR-a (internacionalni normalizovani odnos protrombinskih vremena. pacijenta prema zdravoj kontroli), koji treba da bude u opsegu od 2,0 do 3,0 [8].

Loša kontrola INR-a povećava rizik kako od tromboembolijskih, tako i od hemoragijskih komplikacija, a optimalan balans između koristi i rizika od primene oralnih VKA postiže se kada je TTR odnosno vreme u terapijskom opsegu ≥ 70% [9].

Poslednjih nekoliko godina završeno je više randomizovanih kliničkih studija faze III koje su poredile efekat novih oralnih antikoagulantnih lekova (NOAC ili pravilnije ne-vitamin K antagonista) sa varfarinom u prevenciji trombo-embolizma u AF. Novi lekovi su podeljeni u dve grupe:

- oralni direktni inhibitori trombina (dabigatran) i
- oralni direktni inhibitori faktora Xa (rivaroksaban, apiksaban, edoksaban).

Prednost novih lekova leži u manjem broju klinički značajnih interakcija sa hranom i drugim lekovima i odsustvu potrebe za redovnim laboratorijskim praćenjem antikoagulantnog efekta, uz jednaku efikasnost u prevenciji tromboembolija i manju učestalost značajnih krvarenja u poređenju sa VKA [10,11].

Prikaz slučaja

Prikazujemo slučaj pacijentkinje kojim se ukazuje na značaj oralne antikoagulantne terapije, kada je najveći deo vremena INR u terapijskom opsegu između 2-3, u prevenciji ponovnih tromboembolijskih komplikacija tokom 14-togodišnjeg praćenja. Dokumentacija za izradu ovog rada je elektronski zdravstveni karton pacijenta kao i njegova lična medicinska dokumentacija (nalazi laboratorijskih analiza, izveštaji lekara specijalista i otpustna lista). Primenjen je metod retrospektivne analize medicinske dokumentacije.

Radi se o pacijentkinji M.D, starosti 60 godina koja prvi put dolazi na pregled u Internističku ordinaciju “Dr Bastać” 2008. godine zbog osećaja nestabilnosti i osećaja lupanja srca. Zbog hipertenzije gradus II koja nije dobro regulisana uzima antihipertenzivnu terapiju dve godine unazad, leči povišen holesterol statinom. Lupanje i preskakanje srca traje unazad 2 godine Navodi da je pre dve godine imala prvi moždani udar a pre godinu dana se desio i drugi moždani udar (hemipareza levo). Oba moždana udara su verifikovana višeslojnim komjuter-tomografskim skenom (MSCT) endokranijuma. Pacijentkinja je nepušač, predgojazna BMI 29.0 sa izraženom abdominalnom gojaznošću (obim struka 104cm)

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 ≥ 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

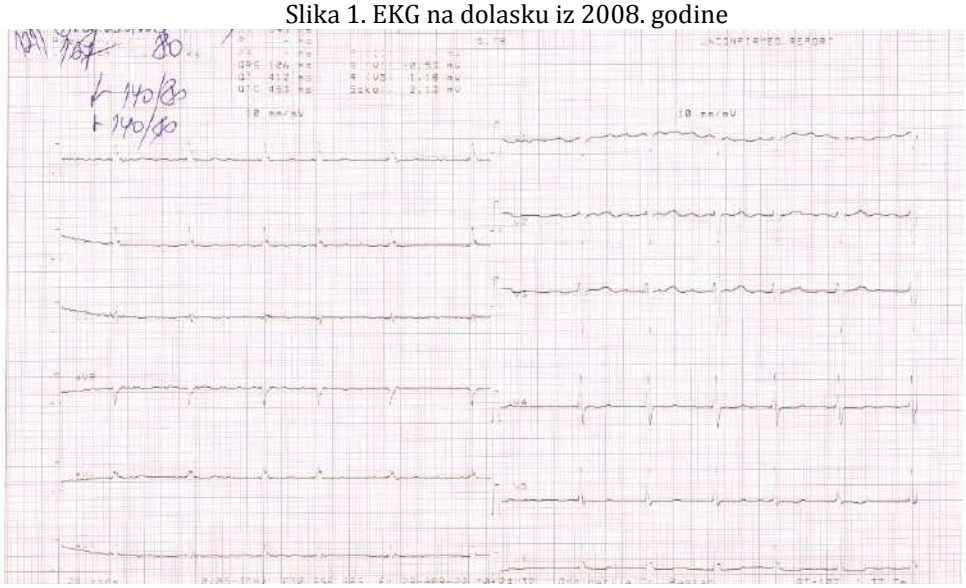
The material used for the preparation of this paper was the patient's electronic health record as well as his personal medical documentation (laboratory analysis findings, specialist doctor's reports and discharge list). The method of retrospective analysis of medical records was applied.

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

i metaboličkim sindromom. Pri fizikalnom pregledu utvrđujemo da je pacijentkinja kardiopulmonalno kompenzovana i hemodinamski stabilna. Srčani ritam je nepravilan, tonovi jasni, šumovi se ne registruju. Krvni pritisak na dolasku izmeren na brahijalnoj arteriji obostrano je 170/100 mmHg. Auskultacijom pluća nalazi se normalan disajni šum. Jetra nije uvećana i nema pretibijanih edema. Hematološke i biohemijske analize su u granicama normale. EKG na dolasku: atrijalna fibrilacija, fr 85/min, normogram, inkompletni blok leve grane, horizontalna depresija ST -0,5 u V5-V6 (Slika 1).

Slika 1. EKG na dolasku iz 2008. godine



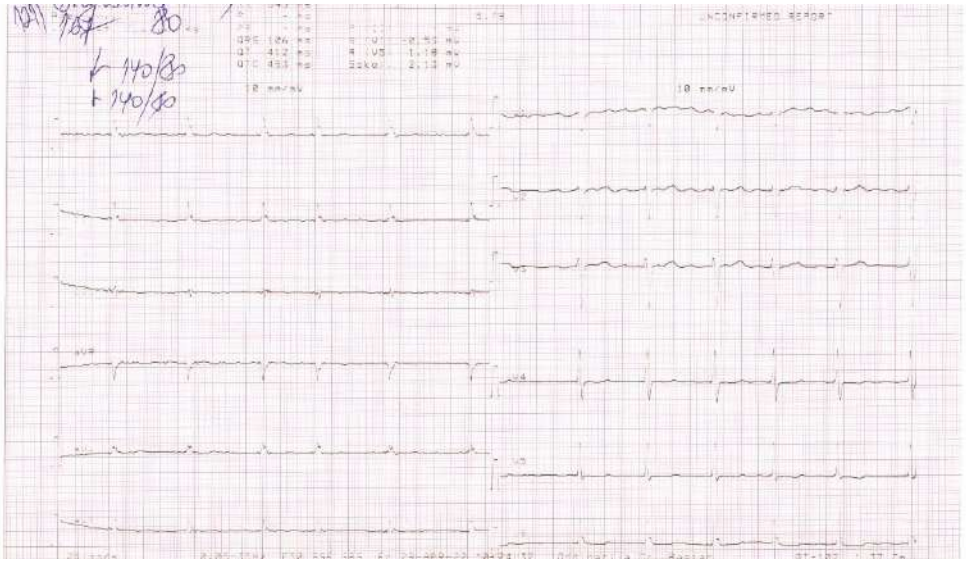
Ehokardiografski nalaz iz 2008. godine ukazuje da je leva komora normalnih dimenzija bez hipertrofije miokarda i sa očuvanom globalnom sistolnom funkcijom i dijastolnom disfunkcijom gradus I. Nema segmentnih ispada u kontraktilnosti zidova leve komore. Mitralni kuspisi su lako voluminozniji sa minornom mitralnom regurgitacijom. Leva prekomora lako dilatirana, 39 mm merena u standardnom parasternalnom preseku. Desna komora normalnih dimenzija.

Nakon završenog fizikalnog pregleda i dodatne dijagnostike izračunat je rizik od možadnog udara **CHA_2DS_2-VASc** Skor kao i **HAS BLED** Skor. Našoj pacijentkinji je izračunat visok rizik od moždanog udara - **CHA_2DS_2-VASc** skor 4 (hipertenzija, ženski pol i prethodni moždani udar) a procenjeni godišnji rizik za moždani udar iznosi 9,27 %. (TABELA 2). Izračunati rizik od krvarenja - HAS BLED Skor iznosi 2 (hipertenzija, CVI). Na osnovu **CHA_2DS_2-VASc** rizik od neželjenih tromoembolijskih događaja je visok i zahteva odmah uvođenje oralne antikoagulante terapije. Pacijentkinji se u terapiju uvodi acenokumarol po šemi da vrednost PT/INR bude između 2.0 i 3.0 uz napomenu da ukoliko dođe do epizode ozbiljnog krvarenja obustavi uzimanje acenokumarola, da proveri vrednost PT/INR-a i da se javi lekaru. Nakon ovog prvog pregleda pacijentkinja je redovno dolazila na kontrolne preglede. PT/INR je rađen u početku na 2 nedelje a kasnije na mesec dana. Kada je postignuta stabilnost u INR, bile su dovoljne kontrole INR na 2 meseca, što je optimalno za ove pacijente.

Vreme u terapijskom opsegu (TTR) nije moglo da se izračuna najčešće korišćenom metodom Rosendaal-a zbog nepostojanja dovoljno velikog broja merenja INR-a u toku godina dana (12 odnosno jednom mesečno). Zato je korišćena metoda koju su u svojoj studiji "Jednogodišnje praćenje kvaliteta oralne antikoagulantne terapije u bolesnika sa atrijalnom fibrilacijom i analiza uticaja na kvalitet antikoagulacije" koristili Dr D. Bastać i saradnici gde je kriterijum za odličnu antikoagulisanost bio da u toku godinu dana 5 do 7 izmerenih vrednosti PT/INR bude ≥ 2 - TTR >60-85% vremena). Dobra antikoagulisanost je definisana da 3 do 4 vrednosti PT/INR budu u terapijskom opsegu (analogno TTR 50-60% vremena) dok je slaba antikoagulisanost: 0-2

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

izmerene vrednosti INR u terapijskom opsegu (TTR <50%) [3]. U slučaju naše pacijentkinje TTR iznosi oko70 % što predstavlja odličnu antikoagulisanost.

Tokom 14 godina redovnog praćenja na tri meseca, kao i telefonskim konsultacijama oko postizanja optimalnog INR, kao i na skorašnjoj kontroli 29.04.2022. godine, pacijentkinja ima dobru antikogulisanost, stabilan INR i subjektino se oseća dobro. Hipertenzija je regulisana, LDL holesterol <1,4mmol. Zahvaljujuči tome pacijentkinja je bez novih tromboembolijskih komplikacija i bez epizoda krvarenja.

DISKUSIJA

Poslednjih nekoliko godina završeno je više randomizovanih kliničkih studija faze III koje su poredile efekat novih oralnih antikoagulantnih lekova sa varfarinom u prevenciji trombo-embolizma u AF. Novi lekovi su podeljeni u dve grupe: oralni direktni inhibitori trombina (dabigatran) i oralni direktni inhibitori faktora Xa (rivaroksaban, apiksaban, edoksaban). Prednost novih lekova leži u manjem broju klinički značajnih interakcija sa hranom i drugim lekovima i odsustvu potrebe za redovnim laboratorijskim praćenjem antikoagulantnog efekta, uz jednaku efikasnost u prevenciji tromboembolija i manju učestalost značajnih krvarenja u poređenju sa VKA [10,11]. Ali, prikazani slučaj pokazuje da se i klasičnom antitrombotskom terapijom sa VK antagonistima može postići dugotrajna uspešna prevencija ponavljanih kardioembolijskih moždanih udara u bolesnika sa permantnom atrijalnom fibrilacijom.

Visok **CHA_2DS_2-VASc** skor 4 (hipertenzija, ženski pol i prethodni moždani udar) sa procenjenim godišnjim rizikom za moždani udar 9,27 % bio je apsolutna indikacija za uvođenje antikoagulantne terapije kod naše pacijentkinje. Njen rizik od krvarenja - HAS BLED Skor je umeren i iznosi 2 (hipertenzija, CVI). Na osnovu **CHA_2DS_2-VASc** rizik od neželjenih tromoembolijskih događaja je visok i uvedena je odmah oralna antikoagulantna terapija acenokumarolom po šemi da vrednost PT/INR bude između 2.0 i 3.0 Nažalost, zbog kašnjenja u terapijskom smislu, propušteno je 2 godine od strane ordinirajućih lekara i tek posle 2 moždana udara mi uvodimo antikoagulantnu terapiju. Problem kašnjenja sa uvođenjem antokoagulantne terapije kod posebno asimptomaske AF je veliki u praktičnom radu. Potreban je napor u medicinskoj praksi da se rano uvede oralna antikoagulantna terapija kod AF i izbegnu dobro preventabilni događaji kao što je kardioembolijske komplikacije, posebno moždani udar.

Osobe koje nemaju finansijsku mogućnost za uzimanje NOAK-a, mogu biti adekvatno lečene kvalitetnom antikoagulacijom dikumarolskim preparatima (VKA) uz angažovanje ordinirajućeg lekara i motivisanost pacijenta. Ipak, jasne indikacije za prelazak sa antagonista vitamina K na NOAK bez obzira na finansijsko opterećenje pacijenta jesu: labilan INR, česta krvarenja, tromboembolijski ataci uprkos relativno dobrom vremenu provedenom u terapijskom opsegu (TTR).

Sa druge strane antagonista vitamina K imaju prednost kod AF u prevenciji moždanog udara kada su novi antikoagulantni lekovi (NOAC, non-VK antagonisti) kontraindikovani kod AF u sklopu mitralne stenoze i kod mehaničkih veštačkih valvula. Takođe, kod teže bubrežne insuficijencije, kada je brzina glomerularne filtracije manja od 30 ml/min i kod svih bolesnika na hemodijalizi mora se sa NOAK-a preći na dikumarolske preparate.

ZAKLJUČAK

Prikazani slučaj potvrđuje stav da se i u eri novih antikoagulantnih lekova NON-VK antagonista (NOAK-a) klasičnom antitrombotskom terapijom sa Vitamin K antagonistima može postići dobra antikoagulisanost i dugorajna uspešna prevencija ponavljanih kardioembolijskih moždanih udara u bolesnika sa permantnom ali i paroksizimalnom atrijalnom fibrilacijom na osnovu **CHA_2DS_2-VASc** skora. Takodje se može postići odsustvo značanih hemoragijskih komplikacija, čiji rizik procenjujemo HAS BLED Skorom.

Tokom 14 godina praćenja na tri meseca, kao i na skorašnjoj kontroli, 2022. godine naša pacijentkinja je bez novih tromboembolijskih komplikacija i bez epizoda krvarenja. To dokazuje da bolesnici sa atrijalnom fibrilacijom mogu biti adekvatno lečeni kvalitetnom antikoagulacijom dikumarolskim preparatima uz veliko angažovanje ordinirajućeg lekara i dobru motivisanost pacijenta i kada nemaju finansijske mogućnosti za prelazak na NON VITAMIN K antikoagulantne lekove.

(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

Povodom ovog slučaja ističemo čest problem kašnjenja sa uvođenjem antokoagulantne terapije kod atrijalne fibrilacije. Potreban je napor u medicinskoj praksi da se rano uvede oralna antikoagulantna terapija kod AF i izbegnu dobro preventabilni događaji kao što su kardioembolijske komplikacije posebno moždani udar. Prevencija moždanog udara je kamen temeljac u zbrinjavanju pacijenata sa atrijalnom fibrilacijom.

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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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