Prevalencija i načini detekcije fibrilacije atrija u bolesnika hospitaliziranih zbog ishemijskoga moždanog udara i njezin utjecaj na kliničke ishode

Prevalence and Detection Methods for Atrial Fibrillation in Patients Hospitalized due to Ischemic Stroke and Its Impact on Clinical Patient Outcomes

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SAŽETAK:

Uvod: Fibrilacija atrija (FA) jedan je od čimbenika rizika za ishemijski moždani udar (MU) koji je moguće prevenirati. Visoka prevalencija te mogućnost prevencije upućuju na potrebu za učinkovitim načinom detekcije FA-a. Cilj ovog istraživanja bio je procijeniti prevalenciju i način dijagnoze FA-a u bolesnika s ishemijskim MU te usporediti njihova klinička obilježja i ishode u skupini s FA i bez nje. **Metode:** Ovo je bila retrospektivno opservacijsko istraživanje. Prikupljene su i analizirane povijesti bolesti ispitanika s ishemijskim MU u 2019. godini. **Rezultati:** Među svim ispitanicima njih 39 % imalo je FA, dok je 50,3 % ispitanika s FA-om otkriveno tek nakon ishemijskoga MU-a. Gotovo tri četvrtine (73 %) bolesnika s anamnestičkim podatkom o FA-u nije bilo adekvatno antikoagulirano. Većina novo-otkrivenih FA (87 %) bila je detektirana standardnim 12-kanalnim EKG-om, dok je ostatak detektiran 24-satnim snimanjem EKG-a (12,5 %). FA je bila statistički značajno povezana sa smrtnim ishodom, kao i s višim vrijednostima na CHA_2DS_2-VASc bodovnom sustavu. **Zaključak:** Čak polovica ispitanika s FA-om dijagnosticirana je tek nakon ishemijskoga MU-a. Većina ispitanika s već poznatom FA nije bila adekvatno antikoagulirana. Ishodi su lošiji u bolesnika s pratećom FA, posebice u onih s višim rezulta-tima na CHA_2DS_2-VASc bodovnom sustavu. Stoga treba poticati češći probir bolesnika s kontinuiranim monitoriranjem kao idealnom opcijom.

SUMMARY:

Background: Atrial fibrillation (AF) is one of the preventable risk factors for embolic ischemic stroke. The high prevalence and the possibility of stroke prevention suggest the need for effective screening for AF. The aim of this study was to assess the prevalence of and methods for diagnosing AF in patients with ischemic stroke, compare their clinical characteristics, and subsequently outcomes in the AF and non-AF group. **Patients and Methods**: This was a retrospective observational study. Medical history of patients with ischemic stroke in 2019 was collected and analyzed. **Results:** Out of the total number of the patients with ischemic stroke, 39% had AF, which was newly discovered in 50.3% of all patients with AF. Almost three-quarters (73%) of patients with known AF in their medical history were not receiving adequate anticoagulation therapy. Most of the patients with newly discovered AF (87%) were diagnosed using a standard 12-lead ECG, while the rest was diagnosed using 24-hour Holter monitoring (12.5%). AF was associated with mortality as well as with a higher CHA_2DS_2-VASc score. **Conclusion**: As many as half of patients with AF in our cohort were diagnosed with AF only after suffering a stroke. In addition, most of the previously diagnosed patients with AF were not receiving adequate anticoagulation therapy. Outcomes were worse in patients with stroke who had concomitant AF, especially those with higher CHA_2DS_2-VASc scores. Therefore, more frequent screening of patients is encouraged, with continuous monitoring as an ideal solution.

KLJUČNE RIJEČI: fibrilacija atrija, ishemijski moždani udar, elektrokardiografija.

KEYWORDS: atrial fibrillation, ischemic stroke, electrocardiography.

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Uvod

Fibrilacija atrija (FA) najčešća je postojana aritmija u kliničkoj praksi te je povezana s povećanim mortalitetom i morbiditetom globalno sve starije populacije[1]. Prevalencija FA je u porastu, ponajprije zahvaljujući boljim dijagnostičkim metodama te duljemu životnom vijeku[2]. FA se dijeli na kliničku i supkliničku. Dijagnoza FA-a, koja može biti simptomatska ili asimptomatska, postavlja se ili standardnim 12-kanalnim EKG-om ili jednokanalnim EKG zapisom na kojemu je zabilježena epizoda FA-a dulja od 30 sekundi[3]. Supklinička FA odnosi se na asimptomatske pojedince u kojih su detektirane epizode brzoga atrijskog ritma frekvencije >175 otkucaja u minuti u intrakardijalnim elektrogramima za koje se potvrdilo da su epizode FA-a, undulacije atrija ili atrijske tahikardije[4-6].

FA je jedan od čimbenika rizika za ishemijski moždani udar (MU) koji je moguće prevenirati[7]. Rastuća prevalencija, visok udio asimptomatskih FA-a te mogućnost prevencije MU-a upućuju na potrebu za implementiranjem efektivnog probira za ovu aritmiju[8,9]. Trenutačna preporuka Europskoga kardiološkog društva (ESC) jest oportunistički probir populacije starije od 65 godina palpiranjem frekvencije srca ili snimanjem standardnog 12-kanalnog EKG-a[4].

Najveći problem probira, osim onoga kontinuiranim monitoriranjem, jesu poteškoće dijagnosticiranja zbog često paroksizmalne naravi FA-a, pa stoga postoji mogućnost da neke epizode ostanu neprepoznate kada nadziremo hospitalizirane bolesnike neposredno nakon doživljenoga ishemijskog MU-a[10,11].

Često primjenjivana pretraga, 24-satno snimanje EKG-a, u nizu istraživanja o detekciji FA-a nakon ishemijskog MU-a, pokazala je postotak detekcije FA između 1,2 % i 45 %. Unatoč visokoj stopi detekcije u pojedinačnim istraživanjima, većina istraživanja pokazala je učestalost detekcije između 2 % i 9 %. Za usporedbu, 6,3 % standardnih 12-kanalnih EKG-a snimljenih u prva 72 sata nakon ishemijskog MU-a detektiralo je FA u istraživanju Douena i sur. Također, u istraživanju Kamela i sur. 6,9 % serijski snimanih 12-kanalnih EKG-a u prvih 90 dana nakon ishemijskog MU-a detektiralo je FA[12-14].

Cilj je ovog istraživanja bio istražiti klinička obilježja bolesnika hospitaliziranih zbog ishemijskog MU-a, posebno onih s FA-om, te odrediti učestalost i metode dijagnosticiranja FA-a u ovoj skupini ispitanika. Promatrali smo demografska obilježja ispitanika, adekvatnost antikoagulantne terapije u ispitanika s FA-om, komorbiditete te njihov utjecaj na prevalenciju FA-a.

Bolesnici i metode

Ovo retrospektivno opservacijsko istraživanje provedeno je u Klinici za neurologiju Kliničkoga bolničkog centra Split. Iz protokola i povijesti bolesti prikupljeni su podatci o bolesnicima s vodećom dijagnozom ishemijskog MU-a (MKB-10 dijagnoze I63.0-I63.9) u 2019. godini. Podatci su za svakog ispitanika uključivali: dob, spol, anamnestičke podatke o FA, antikoagulantnoj i antiagregacijskoj terapiji, nalaz MSCT-a mozga i anamnestičke podatke o već preboljelom ishemijskom MU-u, nalaz 12-kanalnog EKG-a, nalaz 24-satnog snimanja EKG-a te podatke o komorbiditetima (arterijskoj hipertenziji, dijabetesu, zatajivanju srca i kardiovaskularnim bolestima). Fibrilacija atrija dijagnosticirana je u prethodnoj medicin-

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is associated with increased morbidity and mortality in the globally aging population[1]. The prevalence of AF is increasing, primarily due to better diagnostic methods and longer life expectancy[2].

AF is usually classified as clinical or subclinical. The diagnosis of clinical AF, which may be symptomatic or asymptomatic, is established by either a standard 12-lead ECG or a single-lead ECG detecting an episode of AF longer than 30 seconds[3]. Subclinical AF refers to asymptomatic individuals with observed episodes of fast atrial rhythm with a frequency greater than >175 beats per minute in an intracardiac electrograms, which have been confirmed as episodes of AF, atrial undulation, or atrial tachycardia[4-6].

AF is one of the preventable risk factors for embolic ischemic stroke[7]. The growing prevalence, the high proportion of asymptomatic fibrillation, and the possibility of stroke prevention suggest the need to introduce effective screening for this arrhythmia[8,9]. The current recommendation of the European Society of Cardiology (ESC) is to employ opportunistic screening of the population over the age of 65 by palpating the pulse or recording a 12-lead ECG[4].

The most significant issue related to screening, apart from the need for continuous monitoring, is the difficulty of diagnosing AF due to its often paroxysmal nature, which is why we may miss some AF episodes when monitoring in-hospital patients immediately after a stroke[10,11].

Frequently used 24-hour Holter monitoring, in a series of studies on the detection of AF after stroke or transient ischemic attack, showed an AF detection rate between 1.2% and 45%. Despite the high detection rates in some studies, most studies showed a detection rate between 2% and 9%. For comparison, 6.3% of serial 12-lead ECGs recordings in patients with stroke in the first 72 hours after admission detected AF, in a study by Douen et al. Similarly, in a study by Kamel et al., 6.9% of serial 12-lead ECGs in the first 90 days after ischemic stroke detected AF[12-14].

This study aimed to examine the clinical aspects of patients hospitalized for ischemic stroke, especially those with AF, and to determine the frequency and method of detection of AF in these patients. We examined the demographic characteristics of patients, the frequency and adequacy of oral anticoagulant therapy in patients with AF, the comorbidities, and their impact on the frequency of AF.

Patients and Methods

This was a retrospective observational study conducted at the University Hospital Center Split, Department of Neurology. Data on all patients with the leading diagnosis of ischemic stroke (MKB-10 diagnosis I63.0-I63.9) in 2019 were collected from the protocol and medical history. Data for each subject included: age, sex, AF history, history of anticoagulant and antiplatelet therapy, MSCT brain scan and history on pre-existing ischemic stroke, 12-lead ECG, 24-hour Holter monitoring results, and comorbidities (hypertension, diabetes, heart failure (HF), and cardiovascular disease). AF was diagnosed from previous medical records, a 12-lead ECG or Holter monitoring record, and records from implantable cardiac devices. HF was defined according

skoj dokumentaciji zapisom 12-kanalnog EKG-a ili 24-satnim snimanjem EKG-a te zapisima s implantabilnih srčanih uređaja. Zatajivanje srca (ZS) definirano je prema postojećim Smjernicama ESC-a, dok su kardiovaskularne bolesti definirane definicijom prema CHA_2DS_2-VASc bodovnom sustavu[4,15]. Dobne skupine bolesnika također su određene po skupinama CHA_2DS_2-VASc (≤65, 65-74, ≥75 godina)[4]. Svim je bolesnicima izračunat rezultat prema CHA_2DS_2-VASc bodovnom sustavu. Istraživanje je odobrilo Etičko povjerenstvo KBC-a Split.

Svi su podatci obrađeni u statističkom programu SPSS 20. Kontinuirane varijable prikazane su kao medijan i interkvartilni raspon, dok su kategorijske varijable prikazane kao cijeli brojevi i postotci. Procjena normalnosti distribucije provedena je Kolmogorov-Smirnovljevim testom. U obradi podataka koristili smo se x^2-testom, Mann-Whitneyjevim testom i logističkom regresijom. Rezultati su interpretirani na razini značajnosti p<0,05. Dobiveni su podatci prikazani tablično i grafički.

Rezultati

Tijekom 2019. hospitalizirano je 887 ispitanika s dijagnozom ishemijskog MU-a. Osam je ispitanika isključeno iz statističke analize: četvero zbog nepotpune dokumentacije, a četvero zato što je otpusna dijagnoza bila epileptički napadaj, a ne ishemijski MU.

Medijan životne dobi ispitanika iznosio je 78 godina (Q1 – Q3: 69 – 84 godine; min. –maks.: 20 – 99 godina). Od ukupnoga broja ispitanika 424 (48 %) su bile žene, medijana životne dobi 81 godine (Q1 – Q3: 72 – 86 godina; min. – maks. 42 – 99 godina), dok je 455 (52%) muškaraca bilo medijana životne dobi 73 godine (Q1 – Q3; 65 – 81 godina; min. – maks. 20 – 94). Medijan životne dobi žena bio je mnogo veći nego muškaraca (z = 8,2; p <0,001).

Od ukupnoga broja ispitanika FA je imalo njih 346 (39 %). Od toga su 172 (49,7 %) bolesnika već imala ranije dokumentiranu FA, dok je u 174 (50,3 %) bolesnika bolest bila novootkrivena.

Tablica 1 prikazuje povezanost čimbenika rizika za razvoj FA-a (ujedno i komponenti CHA_2DS_2-VASc bodovnog sustava), kao i povezanost pojavnosti ponovljenoga ishemijskog MU-a s pojavnošću FA.

Izgled za nastanak FA-a u skupini ispitanika sa ZS-om bio je veći od izgleda za razvoj FA-a u skupini ispitanika bez ZS-a. U ovom istraživanju izgled za FA bio je dvostruko veći u žena nego u muškaraca. Postojala je statistički značajna povezanost dobnih skupina i FA među ispitanicima (**Tablica 1**).

Medijan vrijednosti na CHA_2DS_2-VASc bodovnom sustavu u skupini s FA-om bio je viši nego u skupini ispitanika bez FA-a (z = 9,1) (**Tablica 2**).

Mogućnost smrtnog ishoda bila je veća u skupini bolesnika s FA-om nego u skupini ispitanika bez FA-a. Svakim pak porastom vrijednosti na CHA_2DS_2-VASc za 1 mogućnosti su se smrtnog ishoda povećavale.

Nadalje, provedena je multivarijatna logistička regresija, pri čemu je smrtnost bila zavisna varijabla, a vrijednost na CHA_2DS_2-VASc bodovnom sustavu i FA nezavisne varijable. Potvrdili smo povezanost FA i CHA_2DS_2-VASc sa smrtnim ishodom (**Tablica 3**). Nakon provođenja logističke regresije izgled za smrtni ishod bio je 3,1 puta veći u skupini ispitanika s FA-om (95 % CI = 2 – 4,7; p <0,001), dok je rastao 1,5 puta pri svakom porastu vrijednosti na bodovnom sustavu za 1 (95 % CI = 1,3 – 1,8).

to the current ESC Guidelines, while cardiovascular diseases were defined using the CHA_2DS_2-VASc score definition[4,15]. Age groups of patients were also determined by the CHA_2DS_2-VASc score groups (≤65, 65-74, ≥75)[4]. The CHA_2DS_2-VASc score was calculated for all patients. The study was approved by the Ethics Committee of the University Hospital Center Split.

All data were analyzed in SPSS 20. Continuous variables were presented as a median and interquartile range, while categorical variables were presented as absolute numbers and percentages. Assessment of the normality of the distribution was performed using the Kolmogorov-Smirnov test. For data processing, we used the x^2 test, the Mann-Whitney test, and logistic regression. The results were interpreted at a significance level of p <0.05. The obtained data are presented in tables and graphs.

Results

In 2019, 887 subjects were hospitalized with a diagnosis of ischemic stroke. Eight were excluded from the statistical analysis; four because of incomplete documentation, and four because the discharge diagnosis was an epileptic seizure, not an ischemic stroke.

The median age of participants was 78 years (Q1-Q3: 69-84 years; min-max: 20-99 years). Of the total number of patients, 424 (48%) were women, with a median age of 81 years (Q1-Q3: 72-86 years; min-max 42-99 years) while 455 (52%) were men, with a median age of 73 years (Q1-Q3; 65-81 years; min-max 20-94). The median age of women was significantly higher than that of men (z = 8.2; p <0.001).

Of all participants, 346 (39%) had AF. Of these, 172 (49.7%) had previously documented AF, while 174 (50.3%) had newly diagnosed AF.

Table 1 shows the relationship between risk factors for the development of AF (and also the components of the CHA_2DS_2-VASc score) as well as the relationship between the incidence of recurrent ischemic stroke and the incidence of AF.

The probability of developing AF in the group of subjects with HF was higher than in the group of subjects without HF. In this study, the probability of having AF was twice as high in women than in men. There was also a statistically significant association between age groups and AF (**Table 1**).

The median CHA_2DS_2-VASc score in the AF group was higher than in the group without AF (z = 9.1) (**Table 2**).

The probability of a fatal outcome was higher in the group of subjects with AF than in the group of subjects without it. The probability of a fatal outcome increased with each increase in the CHA_2DS_2-VASc score by 1 (**Table 3**).

Furthermore, we conducted multivariate logistic regression for mortality in which mortality was the dependent variable, while the CHA_2DS_2-VASc score and AF were independent variables. We confirmed the association of both AF and CHA_2DS_2-VASc score with fatal outcome (**Table 3**). After conducting logistic regression, the probability of a fatal outcome was 3.1 times higher in the group of subjects with AF (95% CI = 2-4.7; p <0.001), while the probability of fatal outcomes increased 1.5 times with each increase in score by 1 (95% CI = 1.3-1.8).

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TABLE 1. Correlation of atrial fibrillation with components of the CHA_2DS_2-VASc score.

		Atrial fibrillation				
	Total (n=879) n (%)	No (n=533) n (%)	Yes (n=346) n (%)	P^a	OR (95% CI)	P^b
Heart failure	220 (25)	95 (18)	125 (36)	<0.001	2.6 (1.9-3.6)	<0.001
Hypertension	650 (74)	363 (72)	267 (77)	0.094		
Diabetes	255 (29)	164 (31)	91 (26)	0.177		
Cardiovascular diseases	84 (10)	51 (10)	33 (10)	0.988		
Sex: M	455 (52)	312 (58)	143 (41)	<0.001	2 (1.5-2.6)	<0.001
F	424 (48)	221 (41)	203 (59)			
Age groups				<0.001	3 (2.4-3.8)	<0.001
<65	143 (16)	131 (25)	12 (4)			
65-74	231 (26)	161 (30)	70 (20)			
≥75	505 (58	241 (45)	264 (76)			
Ischemic stroke				0.658		
First	424 (48)	261 (49)	163 (47)			
Repeated	451 (52)	270 (51)	181 (53)			

M – male, F – female, OR – odds ratio, CI – confidence interval

[a] χ^2

[b] binary logistic regression

TABLE 2. Value of the CHA_2DS_2-VASc score in correlation with atrial fibrillation.

		CHA_2DS_2-VASc score MED (Q1-Q3; min-max)	P^a
Atrial fibrillation	No	5 (4-6; 2-9)	<0.001
	Yes	6 (5-7; 2-8)	
Total		5 (4-6;2-9)	

[a]Mann-Whitney test

TABLE 3. Correlation of AF and CHA_2DS_2-VASc score with fatal outcomes in the whole cohort.

		Fatal outcome				
		No (n=755)	Yes (n=124)	P	OR (95% CI)	P^c
Atrial fibrillation	n (%)	261 (35)	85 (68)	<0.001[a]	4.1 (2.7-6.2)	<0.001
CHA_2DS_2-VASc score	MED (Q1-Q3; min-max)	5 (4-6; 2-9)	6 (5-7; 2-8)	<0.001[b]	1.7 (1.4-2)	<0.001

OR – odds ratio

[a] χ^2 test

[b]Mann Whitney

[c]logistic regression

ANTIKOAGULACIJSKI STATUS BOLESNIKA S VEĆ POZNATOM FIBRILACIJOM ATRIJA

U skupini bolesnika s već poznatom FA (49,7 % svih ispitanika s FA-om) analizirali smo i redovitost uzimanja antikoagulantne terapije. Od 172 ispitanika koji su znali za FA, analizirani su podatci njih 170. Prema podatcima, 125 ispitanika (73 %) nije uopće uzimalo antikoagulantnu terapiju ili je nije uzimalo redovito (neadekvatan INR i anamnestički podatci o prekidu terapije). Od ukupno 172 bolesnika s već poznatom FA, njih 25 % (43 bolesnika) uzimalo je antagoniste vitamina K. U 42 bolesnika analizirane su INR vrijednosti, pri čemu njih 83 % nije imalo INR u terapijskom rasponu. Četrdeset pet ispitanika imalo je NOAK u terapiji (26,2 %), međutim, njih 10 (22 %) nije ga redovito uzimalo. Antiagregacijsku terapiju uzimalo je čak 19,8 % ispitanika. Konačno, 46 bolesnika (26,7 %) nije uzimalo ni antikoagulantnu ni antiagregacijsku terapiju. U jednog bolesnika nije bio poznat terapijski status (0,6 %), a 3 bolesnika bila su na enoksaparinu (1,7 %).

DIJAGNOZA FIBRILACIJE ATRIJA U CIJELOJ POPULACIJI BOLESNIKA S ISHEMIJSKIM MOŽDANIM UDAROM

U skupini ispitanika s novodijagnosticiranom FA (174 ispitanika) ona je većinom detektirana 12-kanalnim EKG-om, dok je 24-satni EKG ustanovio FA u 22 bolesnika (12,5 %), a interogacijom srčanoga elektroničkog uređaja (ICD-DR) FA je detektirana u jednog bolesnika.

Dvadesetčetverosatni EKG snimljen je u 400 bolesnika. Od svih zapisa, 15 (4 %) snimljeno je u bolesnika kojima nedostaje 12-kanalni EKG. Od tih 15 bolesnika, 13 ih je bilo u sinusnom ritmu (87 %), a 2 (13 %) bolesnika već su u anamnezi imala FA.

Dvadesetčetverosatni EKG snimljen je i u 96 bolesnika (24 %) u kojih je FA već dijagnosticirana 12-kanalnim EKG-om. U njih 78 (81%) osnovni je ritam bila FA, dok je 18 ispitanika (19 %) bilo u sinusnom ritmu.

Konačno, 24-satni EKG snimljen je u 289 bolesnika sa sinusnim ritmom prema 12-kanalnom EKG-u pri prijemu. U njih 22 (8 %) detektirana nova FA, što je 5,5 % od ukupnoga broja ispitanika (n = 400) sa snimljenim 24-satnim EKG-om (**Slika 1**).

DIJAGNOZA FIBRILACIJE ATRIJA U SKUPINI ISPITANIKA S PRVIM ISHEMIJSKIM MOŽDANIM UDAROM

U skupini ispitanika s prvim ishemijskim MU-om (424 ispitanika), 163 ispitanika (38,4 %) imala su FA, od kojih njih 93 (57 %) novootkrivenu. Novodijagnosticirana FA većinom je detektirana 12-kanalnim EKG-om (82,7 %), dok je 24-satni EKG detektirao FA u 15 bolesnika (16 %), a interogacijom ICD-DR-a FA je detektirana u jednog bolesnika (1,3 %).

Dvadesetčetverosatni EKG snimljen je u 217 bolesnika s prvim ishemijskim MU-om (n = 424). Od svih zapisa 5 (2,3 %) je snimljeno u bolesnika kojima nedostaje 12-kanalni EKG, a od tih 5 bolesnika svi su bili u sinusnom ritmu (100 %).

Dvadesetčetverosatni EKG snimljen je u 51 bolesnika (23,5 %) u kojeg je FA već dijagnosticirana 12-kanalnim EKG-om. U njih 40 (78 %) osnovni je ritam bila FA, dok je 11 ispitanika (22 %) bilo u sinusnom ritmu.

Konačno, 24-satni EKG snimljen je u 161 bolesnika (74,2 %) sa sinusnim ritmom prema 12-kanalnom EKG-u pri prijemu.

ANTICOAGULATION THERAPY STATUS OF PATIENTS WITH PREVIOUSLY DIAGNOSED ATRIAL FIBRILLATION

In the group of patients with previously diagnosed AF (49.7% of subjects with AF), we also analyzed the regularity of anticoagulant therapy. Out of the 172 patients who were aware they had AF, 170 were analyzed. According to the data, 125 subjects (73%) did not take anticoagulation therapy at all or did not take it regularly (inadequate INR and medical history on discontinuation of therapy).

Of the total of 172 patients with known AF, 25% (43 patients) were taking vitamin K antagonists. INR values were analyzed in 42 patients, and 83% had INR outside the therapeutic range. 45 patients (26.2%) were receiving NOAC in their therapy, however, 10 of them (22.0%) did not take therapy regularly. As many as 19.8% of respondents were on antiplatelet therapy. Finally, 46 patients (26.7%) were not receiving anticoagulant nor antiplatelet therapy. Therapeutic status was unknown in one patient (0.6%), and 3 patients were on enoxaparin (1.7%).

DIAGNOSIS OF ATRIAL FIBRILLATION IN ALL PATIENTS WITH ISCHEMIC STROKE

In the group of patients with newly diagnosed AF (174 subjects), arrhythmia was mostly detected by a 12-lead ECG, while 24-h Holter monitoring detected AF in 22 patients (12.5%), and a cardiac electronic device (ICD-DR) detected AF in one patient.

24-h Holter monitoring was performed in 400 patients. Among all the patient records examined in the study, 15 (4%) were lacking results from a 12-lead ECG. Of these 15 patients, 13 were in sinus rhythm (87%), while 2 (13%) patients had been previously diagnosed with AF according to medical records.

24-h Holter monitoring was performed in 96 patients (24%) in whom AF had already been diagnosed by 12-lead ECG. The recorded rhythm was AF in 78 (81%) of these patients, while 18 (19%) patients were in sinus rhythm.

Finally, 24-h Holter monitoring was performed in 289 patients with sinus rhythm according to the initial 12-lead ECG. Previously unknown AF was detected in 22 patients (8%), accounting for 5.5% of the total number of subjects (n = 400) in whom 24-hour Holter monitoring was performed (**Figure 1**).

DIAGNOSIS OF ATRIAL FIBRILLATION IN THE SUB-GROUP OF PATIENTS WITH FIRST ISCHEMIC STROKE

In the group of patients with first stroke (424 subjects), 163 patients (38.4%) had AF, of whom 93 (57.0%) were newly diagnosed. Newly diagnosed AF was mostly detected by a 12-lead ECG (82.7%), while 24-h Holter monitoring detected AF in 15 patients (16%), and a cardiac electronic device (ICD-DR) detected AF in one patient (1.3%).

24-h Holter monitoring was performed in 217 patients with first stroke (n=424). 5 (2.3%) patient records were lacking a 12-lead ECG examination. Of these 5 patients, all five were in sinus rhythm (100%).

24-h Holter monitoring was performed in 51 patients (23.5%), in whom AF was already diagnosed by a 12-lead ECG. In 40 (78.0%) of these patients, the recorded rhythm was AF, while 11 (22%) patients were in sinus rhythm.

U njih 17 (10,5 %) detektirana je nova FA, što je 7,8 % od ukupno-ga broj ispitanika (n = 217) sa snimljenim 24-satnim EKG-om (**Slika 2**).

Finally, 24-h Holter monitoring was performed in 161 patients (74.2%) with sinus rhythm according to the initial 12-lead ECG. Previously unknown AF was found in 17 patients (10.5%), accounting for 7.8% of the total number of subjects (n = 217) in whom 24-hour Holter monitoring was performed (**Figure 2**).
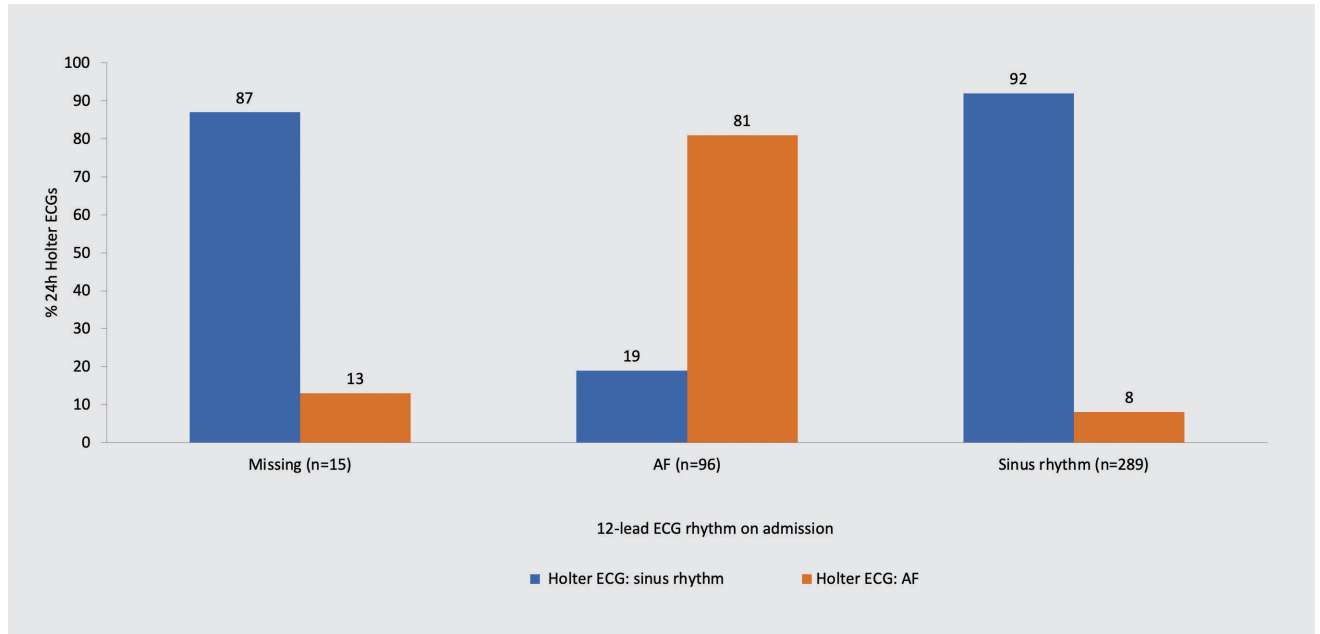

FIGURE 1. Rhythm in 24-hour Holter monitoring in comparison with rhythm in standard 12-lead ECG on admission in all the patients with ischemic stroke.
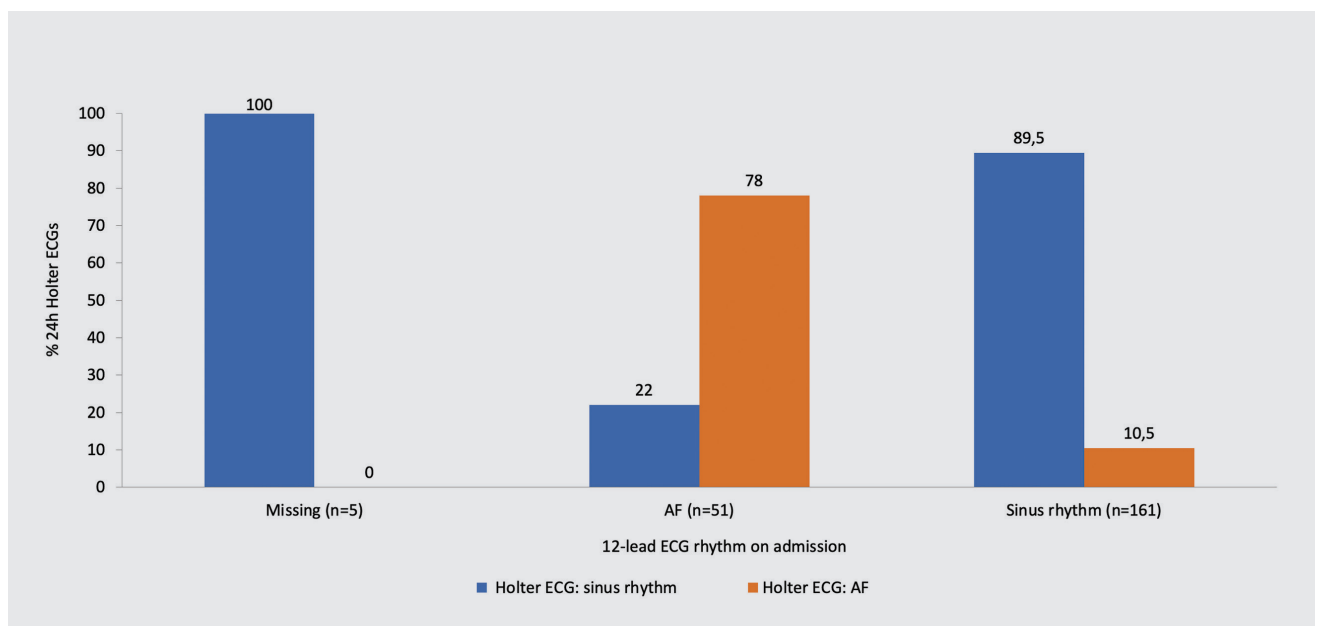**AF – atrial fibrillation**

FIGURE 2. Rhythm in 24-hour Holter monitoring in comparison with rhythm in standard 12-lead ECG on admission in a sub-group of patients with first ischemic stroke.
AF – atrial fibrillation

Rasprava

U 39 % ispitanika s ishemijskim MU-om dijagnosticirana je FA, a od ukupnoga broja ispitanika s FA-om samo je 50 % njih znalo za svoje stanje. Poražavajući podatci iz ovog istraživanja, gotovo 20 godina nakon istraživanja *AFFIRM*, pokazuju da čak 73 % bolesnika s anamnestički poznatom FA nije bilo adekvatno antikoagulirano kako bi se izbjegli tromboembolijski incidenti[16]. U Europi postoji rastući trend propisivanja NOAK-a te je u istraživanju *GLORIA-AF* 52,3 % bolesnika s novo-otkrivenom FA dobilo NOAK[17]. Samo 23,8 % bolesnika u ovom je istraživanju uzimalo NOAK, ali u obzir treba uzeti razliku u cijeni zbog koje mnogi bolesnici i dalje odabiru varfarin.

U starijim dobnim skupinama u ovom istraživanju incidencija FA-a rasla je tri puta. Ovakvi su rezultati sukladni Rotterdamskoj studiji u kojoj je prevalencija FA-a također rasla sa svakom sljedećom dobnom skupinom[18]. Incidencija FA-a u ovoj studiji bila je dvaput veća u žena nego u muškaraca. Moramo uzeti u obzir da su žene u studiji bile starije, što je bitan zbunjujući čimbenik. U Fribergovom istraživanju FA je također bila češća u žena s ishemijskim MU-om, čija je srednja dob bila 5,1 godinu veća od srednje dobi muškaraca[19]. Nedostatak značajne razlike u prevalenciji prethodnih ishemijskih MU-a između skupine s i bez FA u ovom istraživanju mogao bi se objasniti velikim brojem lakunarnih incidenata. Oni se uglavnom pripisuju bolesti malih krvnih žila, a ne kardioemboliji, dok su u ovom istraživanju vođeni kao prethodni moždani udar[20]. Ispitanici su u ovom istraživanju i visokog medijana životne dobi u kojoj raste prevalencija lakunarnih moždanih udara. U istraživanju Bejot *i sur.* anamnestički podatak o FA-u bio mnogo češći u bolesnika s nelakunarnim (31 %) nego s lakunarnim infarktima (15 %). Isto istraživanje dokazalo je i znatan porast prevalencije lakunarnih infarkta nakon sedamdesete godine života[21]. Također, u istraživanju Grau *i sur.* učestalost arterijske hipertenzije u bolesnika s ishemijskim MU-om bila je veća u grupi bolesnika s mikroangiopatijom i makroangiopatijom nego s kardioembolijom, dok je učestalost šećerne bolesti bila veća u grupi s mikroangiopatijom nego u grupi s kardioembolijom, što može objasniti izostanak statistički značajne razlike među skupinama u ovom istraživanju[22].

FA je česta u bolesnika sa ZS-om[23]. U ovom je istraživanju ZS statistički značajno povećavalo izglede za razvoj FA-a, što je u skladu s patofiziološkim mehanizmima ovih stanja. Poznato je da FA povećava rizik od kardiovaskularne i ukupne smrtnosti[24]. U ovom je istraživanju smrtni ishod bio triput izgledniji u bolesnika s FA-om u usporedbi s bolesnicima bez FA, što je sukladno istraživanju Kellera *i sur.*[25].

Bodovni sustav CHA_2DS_2-VASc u ovom je istraživanju promatran kao skupni čimbenik tromboembolijskog rizika te smo ga izračunavali svim bolesnicima, uključujući i one u sinusnom ritmu. U istraživanju Rende *i sur.* kumulativna incidencija ishemijskih MU-a u bolesnika bez FA s vrijednostima ≥4 prema CHA_2DS_2-VASc bodovnom sustavu bila je slična incidenciji ishemijskoga moždanog udara u bolesnika s FA-om i vrijednosti 2 prema CHA_2DS_2-VASc. Vrijednost ≥2 također je bila neovisni prediktor smrtnog ishoda i incidencije FA[26]. U ovom istraživanju, bolesnici s FA-om, kao i oni sa smrtnim ishodom, imali su viši medijan prema bodovnom sustavu CHA_2DS_2-VASc nego oni bez FA-a. Ovi su rezultati važni jer se u literaturi spominje mogućnost uvođenja antikoagulan-

Discussion

AF was diagnosed in 39% of the patients with ischemic stroke, and only 50% the total number of patients diagnosed with AF already knew about their condition. The very concerning data obtained from this study, almost 20 years after the AFFIRM study, is that 73% of patients with previously diagnosed AF were not adequately treated to prevent thromboembolic events[16]. There is a growing trend in prescribing NOAC in Europe, and in the GLORIA-AF study, 52.3% of patients with newly-diagnosed AF received NOAC[17]. Only 23.8% of patients were on NOAC in this study, but one should consider the difference in the price due to which many patients in this community still opt for warfarin.

The incidence of AF was increased threefold in the older age groups in this study. This finding is consistent with the Rotterdam study in which the prevalence of AF also increased with each subsequent age group[18]. The incidence of AF was twice as high in women as in men. We must consider that women with stroke in this study were older, which is an important confounding factor. In Friberg's study, AF was also more common in women with ischemic stroke whose mean age was 5.1 years higher than the mean age of men[19].

The lack of a statistically significant difference in the prevalence of previous ischemic strokes may be explained by a large proportion of lacunar incidents. These are mainly attributed to small blood vessel disease, not cardio embolism, and in this study they were classified as a previous stroke[20]. Subjects in this study had high age median, so an increase in the prevalence of lacunar strokes is expected. In a study by Bejot *et al.*, history of AF was significantly more common in patients with non-lacunar infarction than those with lacunar infarction. The same study showed a significant increase in the prevalence of lacunar infarction after the age of seventy[21]. Additionally, in a study by Grau *et al.*, the incidence of hypertension and diabetes in patients with ischemic stroke was higher in the group of patients with micro and macroangiopathy than in those with cardio embolism, which may explain the absence of statistically significant differences between the groups[22].

AF is common in patients with HF[23]. In this study, HF statistically significantly increased the chance of developing AF, which is consistent with the pathophysiological mechanism of the diseases themselves. AF is known to increase the risk of cardiovascular and overall fatal outcomes[24]. In this study, fatal outcomes were three times more likely in patients with AF compared with patients without AF, which is consistent with the research of Keller *et al.*[25].

We found CHA_2DS_2-VASc to be a cumulative factor of thromboembolic risk in all patients, including those in sinus rhythm. In a study by Rende *et al.*, the cumulative incidence of ischemic stroke in patients without AF with a CHA_2DS_2-VASc score ≥4 was similar to the incidence of ischemic stroke in patients with AF and a CHA_2DS_2-VASc score of 2. A CHA_2DS_2-VASc score ≥2 was also shown to be a predictor of fatal outcome and AF incidence[26]. In this study, patients with AF, as well as with a fatal outcome, had a higher median CHA_2DS_2-VASc score than the group without AF. These results are important because the literature mentions the possibility of introducing anticoagulant therapy after ischemic stroke in patients who have a high CHA_2DS_2-VASc score even though they have not been diagnosed with AF.

tne terapije nakon ishemijskog MU-a bolesnicima koji imaju visoku vrijednost prema CHA_2DS_2-VASc bodovnom sustavu, iako nemaju dijagnosticiranu FA. Komponente tromboembolijskog rizika ujedno su i čimbenici rizika od nastanka same FA te ovi rezultati upućuju na potrebu za opreznijim pretraživanjem FA-a u bolesnika s većim vrijednostima prema CHA_2DS_2-VASc bodovnom sustavu[27].

Od 400 učinjenih 24-satnih EKG-a u bolesnika s ishemijskim MU-om u ovom centru, 5,5 % detektiralo je dotad nepoznatu FA koja nije bila zabilježena na standardnom 12-kanalnom EKG-u pri prijmu. Treba napomenuti da je 4,75 % 24-satnih EKG-a pokazalo sinusni ritam, dok je paroksizam fibrilacije zabilježen isključivo 12-kanalnim EKG-om. Četvrtina 24-satnih EKG-a snimljena je u bolesnika koji su već u standardnom 12-kanalnom EKG-u imali FA, što je, prema smjernicama ESC-a, dostatno za dijagnozu[4].

Nedavno istraživanje Huanga *i sur.* fokusiralo se upravo na ovu problematiku, usporedivši učinkovitost detekcije FA-a u bolesnika hospitaliziranih zbog ishemijskoga moždanog udara 24-satnim EKG-om i serijskim snimanjem 12-kanalnog EKG-a tijekom pet uzastopnih dana. Nije pronađena statistički značajna razlika između stopa detekcije ovim dvjema metodama. Ovakav je pristup pragmatičniji i trebao bi se uzeti u obzir kao metoda prvog izbora za dijagnozu paroksizmalne FA u starijih bolesnika s ishemijskim MU-om[28].

Ovo istraživanje ima nekoliko ograničenja. Ponajprije, podatci su prikupljani retrospektivno. Podatci o klinički dokumentiranim prethodnim ishemijskim MU-om ne govore o njihovim obilježjima pa analiza subtipova nije bila moguća. Tihi lakunarni ishemijski MU-i, koji su u starijoj populaciji vrlo česti, također su se vodili kao prethodni ishemijski incident, iako su češće povezani s mikroangiopatijom[20]. Anamnestički podatci o redovitom uzimanju antikoagulantne terapije nisu potpuno pouzdani pa postoji mogućnost da je suradljivost ispitanika u ovom istraživanju još manja.

Ovo je istraživanje pokazalo da su bodovni sustav CHA_2DS_2-VASc i FA neovisni čimbenici rizika za smrtni ishod. Visoka vrijednost, prema CHA_2DS_2-VASc nije prediktivna za loš ishod samo u bolesnika s FA-om već i u bolesnika u sinusnom ritmu. Stoga bi se buduća istraživanja trebala usmjeriti na potencijalnu korist antikoagulantne terapije u ovoj skupini bolesnika. Vrijednost prema CHA_2DS_2-VASc je bila viša u bolesnika s FA-om, što upućuje na potrebu za opreznijim nadzorom nad bolesnicima s ishemijskim MU-om i visokim vrijednostima CHA_2DS_2-VASc bodovnog sustava, u kojih je veća vjerojatnost nedijagnosticirane FA[29].

Components of thromboembolic risk are also risk factors for AF itself, and these results suggest the need for more frequent screening of AF in patients with a higher CHA_2DS_2-VASc score[27].

Of the 400 24-hour Holter monitoring examinations performed in patients with stroke at this center, 5.5% of them detected unknown AF that was not observed on 12-lead ECG at admission. It should be noted that 4.75% of 24-hour Holter monitoring examinations showed sinus rhythm, and AF was detected only by a 12-lead ECG. A quarter of 24-hour Holter monitoring examinations were performed in patients who already had AF in a 12-lead ECG, which is sufficient for diagnosis according to ESC guidelines[4].

A recent study by Huang **et al**. focused on this issue, comparing the effectiveness of detecting AF in patients admitted for ischemic stroke with a 24-hour Holter monitoring and serial recording of a 12-lead ECG for five consecutive days. No statistically significant difference was found between these two methods. This approach is more pragmatic and could be considered the first-choice method for the diagnosis of paroxysmal AF among elderly patients with ischemic stroke[28].

This study has several limitations. Firstly, data were collected retrospectively. Data and clinically documented previous ischemic strokes do not detail their characteristics, so analysis of stroke subtypes was not possible. Silent lacunar ischemic strokes, which are very common in the elderly population, have also been reported as a previous ischemic incident, although more commonly associated with microangiopathy[20]. History on the regular use of anticoagulant therapy was not completely reliable, so there is a possibility that the compliance of subjects in this study was even lower.

This study has shown that CHA_2DS_2-VASc score and AF are independent risk factors for death. A high CHA_2DS_2-VASc score is not predictive of poor outcomes only in patients with AF, but also in patients in sinus rhythm. Therefore, future research should focus on the potential benefits of anticoagulant therapy in this group of patients. The CHA_2DS_2-VASc score was higher in patients with AF, suggesting the need for more careful monitoring of patients with ischemic stroke and high CHA_2DS_2-VASc scores, who are more likely to have occult AF[29].

LITERATURE ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||

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