

The Influence of COVID-19 Pandemic on Secondary Prevention in Non-COVID Patients With Cardioembolic Stroke

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SUMMARY

Introduction: Since March 2020, when the World Health Organization declared the global pandemic of the Coronavirus disease 2019 (COVID-19), an era of great challenges for the entire healthcare system has begun. A new organization of the healthcare system was needed to balance care not only for cases tested positive for COVID-19, but also for those that did not. Data indicate a reduction in the functioning of stroke units, a decrease in neuroimaging diagnostic procedures, and changes in therapeutic interventions for stroke patients.

Aim: This research investigates the assumption that these changes in medical care have affected the secondary prevention of cardioembolic stroke (CS) in non-COVID patients.

Material and Methods: A cross-sectional study was conducted among 338 out of 1,928 non-COVID patients with CS and non-valvular atrial fibrillation (NVAF), comparing demographic, therapeutic recommendations between the period before and during the COVID-19 pandemic. Over a five-year period, data of the possible complications of therapeutic management for secondary stroke prevention were collected.

Results: Among two groups, only chronic renal insufficiency emerged as a significant risk factor during COVID-19 ($p=0.0365$), while previous stroke was characteristic of the first period, before COVID-19 pandemic ($p=0.0081$). The most common therapeutic recommendations for secondary prevention of CS with NVAF included apixaban ($p=0.0336$) and bridging therapy: low-molecular weight heparin with acetylsalicylic acid (LMWH+ASA) ($p=0.0011$), both during the COVID-19 period. Complications were registered in 20 (8%) patients. Although not statistically significant, the highest proportion of systemic and neurological complications occurred in patients using dabigatran (25%) Recurrent stroke was registered in 20% of patients using apixaban, while 15% patients using rivaroxaban had systemic bleeding (15%).

Conclusion: Our results demonstrate preserved stroke care quality during the COVID-19 time period. It is crucial to carefully evaluate the possible causes of any ischemic stroke, anticoagulant therapy with direct oral anticoagulants is the mainstay of NVAF management

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of CS stroke with the dominance of apixaban and bridging therapy. No intracranial bleeding was noted.

Keywords: Coronavirus Disease 2019, Stroke, Atrial Fibrillation, Management, Oral Anticoagulation, Prevention

INTRODUCTION

The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) as a pandemic on March 11, 2020. Since then, the healthcare system has faced significant challenges both globally and in Serbia.

Standard medical care and treatment globally have been substantially disrupted due to the reallocation of hospital resources and health personnel towards the COVID-19 pandemic. A new organization of the health system was needed in order to balance the care of both patients with and without COVID-19 [1].

In addition, this pandemic has imposed containment and social distancing measures, with potential subsequent social isolation, that may have contributed to a drop in stroke admissions. There is also evidence of reduced functioning in stroke care units, reduced number of neuroimaging diagnostic procedures (computed tomography, magnetic resonance, neuro-ultrasonography, etc.) [2-4].

The frequency of ischemic stroke in patients with COVID-19 varies from study to study. According to some authors, the occurrence of stroke was less frequent (1.3%) [5,6] or between 2.8% and 5.4% among confirmed and hospitalized COVID-19 patients [7,8].

Evidence suggests that the COVID-19 pandemic had a negative impact on the application of reperfusion therapy (thrombolysis and/or mechanical thrombectomy), around 25% [5,9,10].

However, there is limited data on how the COVID-19 pandemic has affected the therapeutic approach to non-COVID patients with acute stroke.

AIM

This research aims to investigate the assumption that the changes in medical care during the pandemic similarly impacted the second-

ary prevention of cardioembolic stroke in non-COVID patients, was the interest of this research.

MATERIAL AND METHODS

A cross-sectional study of adult patients treated at the Clinic of Neurology, University Clinical Center of Vojvodina, Novi Sad, due to cardioembolic stroke (CS) with non-valvular atrial fibrillation (NVAf) and without COVID-19 infection, was conducted.

In the first group we included patients with CS and NVAf treated before the COVID-19 pandemic (January 1, 2019 - March 15, 2020), while in the second group we included those with CS and NVAf treated during COVID-19 pandemic (March 16, 2020 - December 31, 2021). The period of the COVID-19 pandemic was defined by the start and duration of the redirection of hospital resources and health personnel from the Neurology Clinic towards the COVID-19 pandemic.

All hospitalized patients had a negative polymerase chain reaction (PCR) test for the SARS-CoV-2 virus. We reviewed electronic medical records and patient histories from before and during the COVID-19 pandemic, identifying patients based on their discharge diagnoses (ICD: I63.4).

The recommended therapy for secondary prevention of recurrent stroke on the discharge letter was noted and afterwards compared between two specified time periods. Demographic data on gender, age, vascular risk factors, in-hospital mortality were recorded. In order to categorize the risk of ischemic stroke, the CHA2DS2-VASc score was analyzed, while the HAS-BLED score was used to predict the risk of bleeding after prescribed anticoagulant therapy.

The occurrence of complications due to prescribed therapy was monitored: the occurrence of recurrent ischemic stroke, cere-

Characteristic or Investigation	Before COVID-19 (n=114)	During COVID-19 (n=224)	Total (n=338)	p value
Age <65, n (%)	12 (10,53)	19 (8,48)	31 (9,17)	0,5537
Age ≥65, n (%)	102 (89,47)	205 (91,52)	307 (90,83)	
Male, n (%)	45 (40)	90 (40,18)	135 (39,94)	1,000
Female, n (%)	69 (60)	134 (59,82)	203 (60,06)	
Hypertension, n (%)	101 (87,83)	197 (87,95)	298 (88,16)	1,000
Diabetes mellitus, n (%)	25 (21,74)	58 (25,89)	83 (24,56)	0,5042
Dyslipidemia, n (%)	30 (26,09)	75 (33,48)	105 (31,07)	0,2139
Chronic kidney disease, n (%)	6 (5,22)	29 (12,95)	35 (10,36)	0,0365
Previous stroke/TIA, n (%)	7 (6,09)	2 (0,89)	9 (2,66)	0,0081
In-hospital mortality, n (%)	32 (27,83)	57 (25,45)	89 (26,33)	0,6040

Table 1. Baseline characteristics of patients before and during COVID-19 pandemic

COVID - COronaVirus Disease
TIA - Transient Ischemic Attack

bral hemorrhage and/or systemic bleeding in the hospital and post-hospital period (by reviewing the clinical information system). The post-hospital period included the period from the end of hospitalization, until December 31, 2023, for both groups.

Severe systemic bleeding was defined as any gastrointestinal, intra-abdominal, or external bleeding necessitating transfusion. Exclusion criteria were COVID-19 positive test as well as other subtypes of ischemic stroke (according to the TOAST classification): atherosclerotic, lacunar, embolic stroke of unknown cause and stroke caused by other causes, as well as transient ischemic attack (TIA). Some of the mentioned subtypes of ischemic stroke was used only in the numerical presentation of their distribution in the observed time periods.

The study was approved by the Ethics Committee of the University clinical centre of Vojvodina (No. 00-206/2023).

Descriptive variables are presented in the form of absolute numbers and percentages. Fisher’s exact test was used to compare categorical variables. A p value of 0.05 and less indicates the existence of a significant difference between the observed results. Statistical analysis was performed using the RStudio program, version RStudio 2023.12.0+369 „Ocean Storm” Release.

RESULTS

A total of 1928 patients were treated at the Clinic of Neurology due to ischemic stroke for both time periods (before and during the COVID-19 pandemic). According to the TOAST classification, large-artery atherosclerosis was registered in 778 (40.35%), the second most

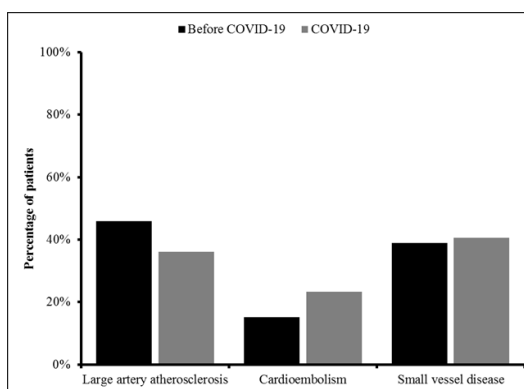


Figure 1. TOAST classification of stroke, before and during COVID-19 pandemic

frequent was small blood vessel disease (lacunar subtype) in 768 (39.83%), while CS stroke with NVAf was third, with 382 (19.81%) patients (Figure 1).

The frequency of atherosclerotic ischemic stroke was statistically significantly lower during the COVID-19 pandemic (390; 35.94%) ($p < 0.0001$), while the cardioembolic subtype was significantly more prevalent during the COVID-19 pandemic (256; 23, 6%) ($p < 0.0001$).

The research included 338 stroke patients with CS and NVAf, 114 of which were in the first group (before COVID-19 pandemic was declared), and 224 in the second group (during the COVID-19 pandemic). Their demographic and clinical characteristics are shown in Table 1.

Cardioembolic stroke was more common in women, 203/338 (60.06%) with an average age of 76.13 ± 9.16 , with no significant difference in both observed periods. However, when CS patients without COVID-19 were compared, there were minimal differences in demographic and clinical characteristics.

A statistically significant difference was shown in patients during the COVID-19

Figure 2A. CHA2DS2-VASc scoring system in observed groups

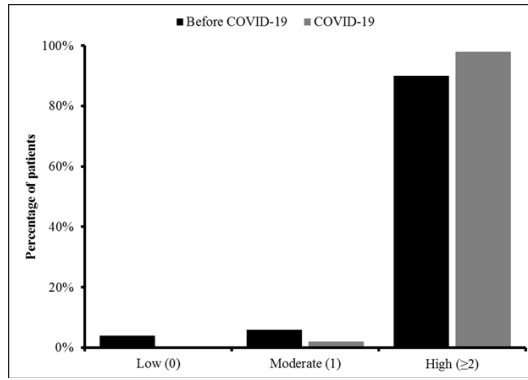
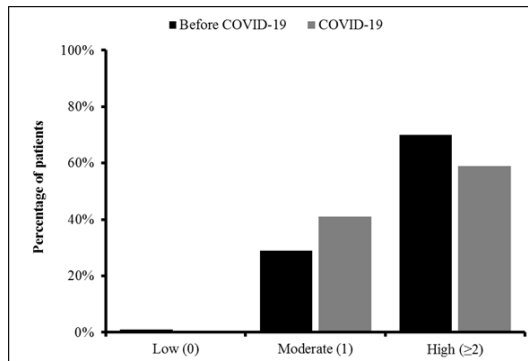


Figure 2B. HAS-BLED scoring system in observed groups



pandemic, with a higher prevalence of chronic kidney disease in 29/224 (12.95%) (p=0.0365), while significantly more patients had a previous ischemic stroke in the first group, (before COVID-19 pandemic), 7/114 (6.09%) (p=0.0081).

Almost one in four patient, 89/338 (26.33%), died during hospitalization, observed in both time periods.

Among patients who survived, a high CHA2DS2-VASc (≥2) score was noted in the group during the COVID-19 pandemic, 164/167 (98.2%) (p=0.0069) (Figure 2A).

High HAS-BLED score (≥3) was not significantly different in both observed peri-

ods, (156/249) 62.65% patients (Figure 2B).

The most frequently recommended drug at discharge, as a secondary prevention of CS with NVAf in both time periods, was apixaban, with 68/249 (27.31%) of patients taking it, with significantly higher prescribing during the COVID-19 pandemic (p=0.0336). In second place was the combination of low weight molecular heparine (LMWH) and acetylsalicylic acid (ASA), in 43/249 (17.27%), with also significantly higher recommendation during the COVID-19 pandemic (p=0.0011).

Although there was no significant difference before and during the COVID-19 pandemic, the following, in terms of frequency of recommendations, were: dabigatran in 33/249 (13.25%), warfarin in 19/249 (7.63%), LMWH as monotherapy in 18/249 (7.23%), ASA in 18/249 (7.2%) and rivaroxaban in 12/249 (4.82%) patients (Table 2).

In the post-hospital period, no statistically significant difference was found in the occurrence of complications due to recommended therapy, 20/245 (8%). Although without statistical significance, the largest number of systemic and neurological complications was registered in patients using dabigatran 5/20 (25%), among which 3 had systemic bleeding and 2 experienced a new ischemic stroke. In patients who used apixaban, only neurological ischemic complications were registered, 4/20 (5%). In those who used rivaroxaban, systemic bleeding was recorded (2/8 patients), and in those who used warfarin, a new ischemic stroke was more common (2/12 patients). None of the patients experienced cerebral hemorrhage. Observed complications were not recorded in those using clopidogrel or LMWH as monotherapy (Table 3).

Table 2. Recommended therapy at discharge

COVID - COronaVirus Disease
 ASA - acetylsalicylic acid
 LMWH - low molecular weight heparin

Characteristic or Investigation	Before COVID-19 (n=82)	During COVID-19 (n=167)	Total (n=249)	p value
ASA, n (%)	8 (9,76)	10 (5,99)	18 (7,2)	0,3036
clopidogrel, n (%)	3 (3,66)	2 (1,2)	5 (2)	0,3349
LMWH, n (%)	6 (7,32)	12 (7,19)	18 (7,23)	1,000
rivaroxaban, n (%)	1 (1,22)	11 (6,59)	12 (4,82)	0,1107
apixaban, n (%)	15 (18,3)	53 (31,7)	68 (27,31)	0,0336
warfarin, n (%)	8 (8,76)	11 (6,6)	19 (7,63)	0,4472
dabigatran, n (%)	15 (18,3)	18 (10,78)	33 (13,25)	0,1135
ASA+ clopidogrel, n (%)	0 (0)	1 (0,39)	1 (0,4)	1,000
LMWH + ASA, n (%)	5 (6,1)	38 (22,75)	43 (17,27)	0,0011
LMWH + clopidogrel, n (%)	3 (3,66)	6 (2,34)	9 (3,61)	1,000

Characteristic or Investigation	Systemic bleeding (n=8)	Neurological complication (n=12)	Total (n=20)	p value
apixaban, n (%)	0 (0)	4 (33,33)	4 (20)	0,1166
rivaroxaban, n (%)	2 (25)	1 (8,33)	3 (15)	0,5368
ASA, n (%)	1 (12,5)	1 (8,33)	2 (10)	1,000
LMWH, n (%)	0 (0)	0 (0)	0 (0)	0
dabigatran, n (%)	3 (37,5)	2 (16,67)	5 (25)	0,3473
warfarin, n (%)	1 (12,5)	2 (16,67)	3 (15)	1,000
clopidogrel, n (%)	0 (0)	0 (0)	0 (0)	0
LMWH + ASA, n (%)	0 (0)	2 (16,67)	2 (10)	0,4947
LMWH + clopidogrel, n (%)	1 (12,5)	0 (0)	1 (5)	0,4000

Table 3. Complications of recommended therapy

COVID - COronaVirus Disease
ASA - acetylsalicylic acid
LMWH - low molecular weight heparin

DISCUSSION

To the best of our knowledge, our study is the first to compare the effects of therapeutic strategy among patients with CS and NVAf before and during the COVID-19 pandemic.

The results indicate significant increase in CS during the COVID-19 pandemic. We assume that the more severe clinical picture in the elderly (8th decade of life), along with numerous comorbidities and risk factors, had a significant role in the incidence of this subtype. Nevertheless, Akhtar et al. noted a discrete increase in CS during the COVID-19 pandemic [11]. In our country, CS is more common in women due to the higher risk of atrial fibrillation [12,13].

The association between chronic kidney disease and CS confirms the high comorbidity profile in patients with renal dysfunction [14,15]. Thus, accelerated atherosclerosis, chronic uremia, tendency to prothrombotic process and atrial fibrillation (AF) increase the risk of ischemic stroke. The prevalence of AF in the population with chronic kidney disease is twice as high as in the general population, with a higher risk of thromboembolism [11,13].

While the healthcare system has been disrupted during the COVID-19 pandemic outbreak, leading to a massive redistribution of healthcare resources, but therapeutic strategy in patients with stroke should have been the same or similar.

It is well known that the risk of early recurrence of ischemic stroke is higher in those with NVAf than in those without it, thus it would be reasonable to introduce anticoagulant therapy as soon as possible [16].

The advantage of modern direct oral anticoagulants (DOAC) therapy is their fast

acting (2-3 hours for dabigatran, 2-4 hours for rivaroxaban, 3-4 hours for apixaban), while their standard doses do not require titration, unlike vitamin K antagonists (VKA) [17]. In our study, apixaban was most often recommended, especially during the COVID-19 pandemic, while in the pre-COVID-19 period that were both dabigatran and apixaban.

Interestingly, rivaroxaban was the least prescribed, with only 12 patients receiving it. This may be attributed to its high cost in our market or the personal preferences of the treating physicians. Over the following five-year observation period, no significant number of systemic or neurological complications was recorded (only 8%, with no intracranial hemorrhage recorded). The same is noted in the literature: the RAF study concluded that the incidence of recurrent ischemic events (ischemic stroke or TIA) was 7.6%, while the incidence of symptomatic cerebral bleeding was 3.6% with 1.4% of major bleeding [18]. However, in our study, patients who used dabigatran and rivaroxaban had a tendency towards systemic bleeding, especially before COVID-19 period, which correlates with a high HAS-Bled score. According to the results of the RE-LY [19] and ROCKET-AF [20] studies comparing the efficacy and safety of dabigatran (150 mg) and rivaroxaban (20 mg/15 mg), a similar risk of bleeding was observed. When interpreting the results, differences in the demographic and other characteristics of the patients should be taken into account, thus those from the ROCKET-AF study had a significantly more severe clinical picture.

Among the patients using apixaban, 5% had a recurrent ischemic stroke, while there were no symptomatic and massive hemorrhages. AREST (Apixaban for Early Prevention of Recurrent Embolic Stroke and Hem-

orrhagic Transformation) study revealed that apixaban had statistically similar, yet generally numerically lower rates of recurrent strokes/TIA (14.6% versus 19.2%) and symptomatic hemorrhages (0% versus 2.1%), compared to warfarin [23].

The results of a comparative study showed a significantly lower risk of major bleeding in patients who used apixaban compared to those who used rivaroxaban or dabigatran [24], as was also shown in our research.

In our sample, during the COVID-19 pandemic, the combination of LMWH and ASA (aspirin, 100 mg per day) was the most common. Although current guidelines recommend initiation of anticoagulant therapy within 4-14 days of the index event [25], we hypothesize that this decision on bridging therapy to OAK or DOAK was due to factors that may lead to delayed initiation (large ischemic lesion or early hemorrhagic transformation) or a short hospitalization period.

On the other hand, due to the impossibility of continuous post-hospital follow-up, we have no insight into whether the transfer to OAK or DOAK was completed and on which dosage regimen. Bridging therapy resulted in recurrent ischemic stroke only in those patients hospitalized during the COVID-19 period, nearly 17% of all complications which is higher than 7.8% or 1% reported by other authors [17, 26]. The authors noted that bridging therapy for the COVID-19 period did not include full-dose LMWH compared to the period before COVID-19 pandemic, which may explain the tendency towards recurrent ischemic stroke (subdosing).

Similarly, unregistered symptomatic intracranial hemorrhages in a patients using this combined therapy can be explained, which is supported by the results of other studies as well [27,28].

It is well known that it takes several days for VKA to achieve an anticoagulant effect, measured by INR. In our study, fewer recommendations for VKA were made during the COVID-19 period with similar assumptions: short hospitalization (VKA administration takes time) and/or possible hemorrhagic transformation.

The decision for ASA or clopidogrel as the secondary prevention of CS in both time periods is surprising. Despite clearly defined specific recommendations of different European, American and World Associations

for the treatment and secondary prevention of CS with NVAf [15,16,29], the authors find a possible explanation in poor patient compliance or caution due to complications. Notably, no complications were recorded in patients who used clopidogrel, while systemic bleeding was observed in one case, as well as recurrent stroke in the group on ASA.

Our study has some limitations. Not all data were complete: results of diagnostic tests (neuroimaging and laboratory tests), as well as intrahospital occurrence of hemorrhagic transformation and/or intracranial bleeding, could all have influence on choice of drug or dose. Furthermore, not all categories of the TOAST classification were included, because they were not classified as such at discharge, especially during the COVID-19 pandemic: no additional diagnostics were performed, which would eventually define another etiology of CS, like patent foramen ovale with atrial septal aneurysm, or left ventricular dysfunction. We didn't compare COVID and non-COVID stroke patients, which could contribute to a better quality of our study. The existing number of patients in our study was not sufficient to demonstrate absolute differences of less than 15%. Additionally, our study lacks long-term follow-up (like 30 or 90 days) that could evaluate the optimality of post-discharge management, or NIHSS on admission, which could have an influence on certain therapeutic decisions of the neurologists.

CONCLUSION

The healthcare system was significantly disrupted during the COVID-19 pandemic, leading to a massive redistribution of healthcare resources. Our results demonstrate preserved stroke care quality during the COVID-19 pandemic, even in the period of shortage of vascular neurologists.

Carefully evaluating, which is mandatory to determine the possible causes of any ischemic stroke, anticoagulant therapy with DOACs is the mainstay of NVAf management of cardioembolic stroke with the dominance of apixaban and bridging therapy. Among complications of the recommended therapy, no intracranial bleeding was noted.

Due to small number of patients, the main conclusion is conditioned by the high probability of statistical error of the second type and results should be analyzed with cau-

tion.

As we continue to learn about the impact of the COVID-19 pandemic on stroke evaluation and treatment, we anticipate that best practice guidelines for anticoagulant therapy will evolve, informed by streamlined protocols developed from cumulative experiences. This evolution will be crucial if we encounter similar situations in the future.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Uticaj COVID-19 pandemije na sekundarnu prevenciju non-COVID pacijenata sa kardoembolijskim moždanim udarom

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KRATAK SADRŽAJ

Uvod: Od marta 2020. godine, kada je Svetska zdravstvena organizacija proglasila globalnu pandemiju korona virusa 2019 (SARS-CoV 2), počela je era velikih izazova za ceo zdravstveni sistem. Nova organizacija zdravstvenog sistema bila je potrebna da bi se izbalansirala briga ne samo za pacijente koji su bili pozitivni na COVID-19, već i za one koji nisu. Postoje podaci o smanjenom funkcionisanju jedinica za moždani udar, smanjenom broju neuroimidžing dijagnostičkih procedura, kao i promenama u terapijskom delovanju kod pacijenata sa moždanim udarom (MU).

Cilj: Pretpostavka da su pomenute promene u medicinskom pristupu uticale na sekundarnu prevenciju kardoembolijskog MU kod pacijenata koji nisu oboleli od COVID-a, bila je interes ovog istraživanja.

Materijal i metode: Studija preseka sprovedena je među 338/1928 pacijenata bez COVID-a sa kardoembolijskim MU i nevalvularnom atrijskom fibrilacijom (NFAF), upoređujući demografske karakteristike, terapijske preporuke između perioda pre i tokom pandemije COVID-19. Tokom petogodišnjeg perioda prikupljeni su podaci o mogućim komplikacijama terapijskog pristupa u sekundarnoj prevenciji MU.

Rezultati: Između dve grupe, samo se hronična bubrežna insuficijencija pojavila kao značajan faktor rizika tokom COVID-19 ($p=0,0365$), dok je prethodni MU bio karakterističan za period pre pandemije COVID-19 ($p=0,0081$). Najčešće terapijske preporuke za sekundarnu prevenciju kardoembolijskog MU sa NFAF uključivale su apiksaban ($p=0,0336$) i terapiju premoščavanja: heparin niske molekularne težine sa acetilsalicilnom kiselinom (LMVH+ASA) ($p=0,0011$), obe tokom perioda COVID-19. Komplikacije su registrovane kod 20 (8%) pacijenata. Iako bez statističke značajnosti, najveći broj sistemskih i neuroloških komplikacija registrovan je kod pacijenata koji su uzimali dabigatran (25%), rekurentni MU registrovan je kod 20% onih na apiksabanu, dok je 15% pacijenata na rivaroksabanu imalo sistemsko krvarenje (15%).

Zaključak: Naši rezultati pokazuju očuvan kvalitet terapijskog pristupa pacijentima sa MU tokom COVID-19. Pažljiva procena, koja je obavezna da bi se utvrdili mogući uzroci bilo kog ishemijskog MU uz primenu direktnih oralnih antikoagulanasa, glavno je uporište u terapiji onih sa kardoembolijskim MU i NFAF uz dominaciju apiksabana i terapije premoščavanja. Nije zabeleženo intrakranijalno krvarenje.

Ključne reči: koronavirusna bolest 2019, moždani udar, atrijska fibrilacija, terapija, oralni antikoagulansi, prevencija

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