

FREQUENCY OF VASCULAR RISK FACTORS AND THE IMPACT OF THEIR TREATMENT ON THE OUTCOME OF ACUTE ISCHEMIC STROKE IN PATIENTS TREATED WITH RECANALIZATION THERAPY

UČESTALOST VASKULARNIH FAKTORA RIZIKA I UTICAJ NJIHOVOG LEČENJA NA ISHOD AKUTNOG ISHEMIJSKOG MOŽDANOG UDARA KOD PACIJENATA LEČENIH REKANALIZACIONOM TERAPIJOM

Rea Mikulan¹, Lana Macura¹, Višnja Pađen^{1,2}

¹ Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija

² Univerzitetski klinički centar Srbije, Klinika za neurologiju, Beograd, Srbija

Correspondence: rea.mikulan@gmail.com

Abstract

Introduction: Stroke is one of the leading causes of death and long-term disability worldwide. Timely diagnosis and control of vascular risk factors is a priority for stroke prevention.

Aim: The aim of this study was to analyze the prevalence of vascular risk factors and the impact of their treatment on the outcome of acute ischemic stroke in patients treated with recanalization therapy.

Material and methods: A retrospective analysis of data on stroke patients treated with recanalization therapy in one year was performed. The analysis contained the characteristics of the study population, risk factors and comorbidities, and the therapy used in stroke primary prevention. Symptomatic intracerebral hemorrhage (sICH) was defined according to ECASS-2 criteria. Patients' functional outcomes after three months were assessed by using a modified Rankin scale score (mRS).

Results: The study included a total of 117 stroke patients of whom 70 (60%) were male. The average age of the study population was 65 years (64.6 ± 14), with a baseline NIHSS score of 12 (12 ± 6.7). The most often present risk factors were arterial hypertension and hypercholesterolemia. The most commonly used drugs in primary prevention were antihypertensives and antithrombotic therapy. Afterward, patients were divided into two groups (those with previous antithrombotic (AT) therapy and those without). Patients who were not on previous AT therapy were: more often male, aged 45 - 75 years or younger than 45 years, less often had previous AF, hypercholesterolemia and previous stroke ($p < 0.01$, $p = 0.014$, $p = 0.002$). They also had a trend of initially lower NIHSS scores. There were no statistical differences in the occurrence of sICH between the two groups ($p = 0.922$).

Conclusion: The identification of stroke risk factors within all age groups and their treatment is of great importance in the primary prevention of stroke. Previous use of antithrombotic therapy does not increase the likelihood of sICH occurrence in stroke patients treated with recanalization therapy.

Keywords:

acute ischemic stroke,
primary prevention,
recanalization therapy,
outcome

Sažetak

Uvod: Moždani udar (MU) vodeći je uzrok smrtnosti i dugotrajne onesposobljenosti ljudi širom sveta. Blagovremena dijagnoza i kontrola vaskularnih faktora rizika prioriteta su za adekvatnu prevenciju MU.

Cilj: Cilj ovog rada je analiza zastupljenosti vaskularnih faktora rizika i procene sveobuhvatnosti njihovog lečenja na ishod pacijenata sa akutnim ishemijskim moždanim udarom (AIMU) lečenim rekandalizacionom terapijom.

Materijal i metode: Sprovedena je retrospektivna analiza podataka pacijenata sa AIMU, lečenih rekandalizacionom terapijom u jednogodišnjem periodu na Odeljenju urgentne neurologije. Izvršena je analiza karakteristika studijske populacije, faktora rizika i komorbiditeta, kao i terapije u primarnoj prevenciji AIMU. Simptomatska intracerebralna hemoragija (sICH) definisana je prema ECASS-2 kriterijumima. Istraživanje je uključilo i procenu funkcionalnog ishoda pacijenata nakon tri meseca, koji je definisan korišćenjem modifikovanog Rankin skora (mRS).

Rezultati: Studijom je bilo uključeno ukupno 117 pacijenata sa AIMU, od kojih je 70 (60%) bilo muškog pola. Prosečna starost studijske populacije iznosila je 65 godina ($64,6 \pm 14$), a njihov inicijalni NIHSS skor (engl. *National Institute of Health Stroke Scale*) pri prijemu iznosio je 12 ($12 \pm 6,7$). Najčešći prisutni faktori rizika su bili arterijska hipertenzija i hiperholesterolemija. Najzastupljeniji lekovi u sklopu primarne prevencije su bili antihipertenzivi i antitrombozna terapija (AT). U cilju sagledavanja efekata korišćenja AT u sklopu primarne prevencije AIMU, studijska populacija je podeljena na dve grupe (onu koja je koristila prethodnu AT terapiju, i na onu koja nije). Analiza je pokazala da su pacijenti, bez prethodne AT terapije, bili: češće muškog pola, starosti 45 - 75 godina ili mlađi od 45 godina, ređe su imali prethodnu atrijsku fibrilaciju (AF), hiperholesterolemiju i prethodni AIMU ($p < 0,01$, $p = 0,014$, $p = 0,002$) i trend inicijalno nižeg NIHSS skora. Nije bilo statistički značajne razlike između dve grupe u pojavi sICH ($p = 0,922$).

Zaključak: Identifikacija faktora rizika i njihovo lečenje u svim starosnim grupama značajni su za primarnu prevenciju AIMU. Prethodna upotreba antitrombozne terapije ne povećava verovatnoću pojave sICH kod pacijenata sa AIMU lečenih rekandalizacionom terapijom.

Ključne reči:

akutni ishemijski moždani udar, primarna prevencija, rekandalizaciona terapija, ishod

Introduction

Stroke is a sudden, non-convulsive, focal neurological deficit that occurs as a result of vascular damage (1). According to the pathology underlying vascular damage, stroke can be ischemic and hemorrhagic, while, according to the speed of development and duration of symptoms, it can be divided into transient ischemic attack (TIA) and complete (stable) stroke. Within the spectrum of cerebrovascular diseases, there are also diseases of small blood vessels and vascular dementia, which are characterized by gradual course and development (1).

Acute ischemic stroke (AIS) accounts for about 85% of all strokes and is one of the most common causes of morbidity, while the mortality rate is the second leading cause of death, after coronary heart disease (2). It is estimated that about 17 million people worldwide get sick from AIS each year, about 5.7 million die, and only a third fully recover, leading to significant social and economic consequences (3).

Numerous risk factors are known to be associated with an increased incidence of stroke. They can be divided into immutable: age, race and sex (1,4). The incidence of AIS increases in older age, so patients over the age of 55 have a double risk (1,4). Men are at higher risk of disease, while the prevalence of stroke is still higher in women

because they have a longer life expectancy, which in itself carries a risk of recurrence of cerebrovascular events (5). On the other hand, the most significant variable risk factors include: hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia and atherosclerosis (especially carotid disease), obesity, alcoholism, smoking (6).

Prevention that is performed by identifying and controlling risk factors has a greater effect than other interventions that are applied after the onset of stroke. It is achieved by the control of risk factors as well as a prophylactic therapeutic approach. There are two approaches, the "high-risk patients" and the "mass" approach (1,7). The therapeutic approach in primary prevention includes the potential use of antiplatelet, oral anticoagulant, antihypertensive as well as statin therapy (1,7,8).

The only therapeutic approach for which efficacy has been shown so far and has a favorable impact on the outcome of AIS treatment is the timely recanalization of occluded blood vessels with the establishment of reperfusion of the affected tissue (9). The initial therapeutic modality, introduced in the early 2000s, involves the use of intravenous thrombolytic therapy with alteplase (IVT) in the first 3 - 4.5 hours after the onset of the first symptoms of stroke, which has been shown to reduce mortality and disability over a period of 3 - 6 months in all patients with AIS regardless of etiology 10 - 30% (10). The next step was

the publication of the results of 5 randomized clinical studies in 2015 on the use of endovascular mechanical thrombectomy (EVT) in patients with large circulatory occlusion (LVO) in the anterior circulation, which led to further improvement of the therapeutic approach in AIS treatment. (11). In subsequent years, additional studies have shown a clear benefit of EVT in patients with LVO within 6 hours of symptoms, and in special and clearly defined cases within 24 hours, resulting in the use of EVT with drug therapy becoming the standard when it comes to the treatment of patients with AIS and occlusion of large blood vessels (12). Also, neuroprotective therapy is used as well as therapy to prevent and treat complications of the disease. Secondary prevention and the use of drugs that enable this significantly prevent the indication of recurrent stroke (antithrombotic, statin therapy) (1,7,13).

The current guidelines suggest that IVT should be recommended in patients on prior antiplatelet therapy based on evidence that the benefits of alteplase outweigh the risk of symptomatic intracerebral hemorrhage (sICH) (10).

The aim of this study was to analyze the prevalence of vascular risk factors and the impact of their treatment on the outcome of acute ischemic stroke in patients treated with recanalization therapy.

Material and methods

A retrospective analysis was conducted with data from a total of 117 patients with AIS treated with recanalization therapy at the Department of Emergency Neurology, Clinic of Neurology, University Clinical Center of Serbia in 2020.

The diagnosis of AIS in these patients was made based on clinical criteria, and the clinical assessment of stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score and was made at admission (14). The established clinical diagnosis of AIS was then confirmed by CT examination which was analyzed by a neuroradiologist. At the admission, all patients underwent a non-contrast CT examination. Also, during the admission, the patient's arterial blood pressure was measured, an ECG was performed, and complete laboratory analyses were taken. The approach to the treatment of patients with AIS is based on the application of recommendations from current European and North American guidelines for the treatment of acute stroke, its secondary prevention and neurorehabilitation. Patients who met all the necessary criteria were treated with recanalization therapy, whose type (IVT, EVT or a combination of IVT + EVT) was determined after consideration of clinical and neuroimaging parameters by a multidisciplinary team (neurologist, neuroradiologist). During hospitalization, patients underwent a follow-up CT examination 12 - 72 hours after admission and, depending on the applied therapy, and in the case of clinical deterioration even earlier. A detailed analysis of the demographic characteristics of patients as well as vascular risk factors was performed (arterial hypertension, Diabetes Mellitus (DM), atrial fibrillation (AF),

hypercholesterolemia, smoking, previous coronary heart disease, myocardial infarction, peripheral arterial disease, etc.) as well as transient AIS. The therapeutic approach within the primary prevention of AIS (antiplatelet therapy (one, two or three used drugs), anticoagulant therapy (vitamin K, NOAC), antihypertensive therapy, statin therapy) was analyzed. Data were obtained anamnestic, heteroanamnestic, and with medical records. The study specifically treated patients who used antithrombotic therapy (defined as prior use of antiplatelet and/or anticoagulant therapy) in the primary prevention of AIS, and performed statistical analyses on their demographic characteristics, their associated diseases and risk factors, and an analysis of the treatment outcomes concerning the therapy used was performed.

The control assessment of the clinical status was performed by a neurology specialist after 7 days, on discharge and after 3 months from AIS. The outcome of stroke after 3 months of AIS was assessed using a modified Rankin score (mRS). Symptomatic intracerebral hemorrhage (sICH) was defined according to ECASS 2 criteria.

Statistical analysis

The results were statistically processed using the software package: SPSS, version 28.0. The data were processed by descriptive and analytical methods according to which absolute and mean values, median and frequency were obtained. The χ^2 test with Yates correction or the Fisher test was used to compare categorical variables. Numerical variables presented by the median were compared using the Mann-Whitney test. $P < 0.05$ was defined as a statistically significant value.

Results

The study involved 117 patients with AIS treated with recanalization therapy in one year, of which 70 were male (59.8%), the median age of the study population was 65 years (64.6 ± 14), and their initial NIHSS score per admission was 12 (11.97 ± 6.7). Detailed demographic and clinical characteristics and outcomes of AIS patients are shown in **table 1**.

The analysis of the presence of risk factors showed that 104 patients (88.9%) had arterial hypertension, 58 (49.6%) hypercholesterolemia, 30 subjects (25.6%) had atrial fibrillation (AF), and 21 of them (17.9%) Diabetes Mellitus. There were 29 patients (24.8%) who were active smokers. A detailed overview of the presence of risk factors is given in **figure 1**.

The examined population was also studied based on their therapeutic approach, according to the drugs used in the primary prevention of AIS. It was shown that patients in the primary prevention of AIS were most often treated with antihypertensive therapy (60.7%), followed by antithrombotic (30.8%) and statin therapy (17.1%). Oral anticoagulant therapy was used by 8 subjects (6.9%), and their INR on admission was 0.98 (0.98 ± 0.13). A detailed analysis of the therapy used in primary prevention is

Table 1. Demographic, clinical characteristics and outcome of acute ischemic stroke of the study population.

Demographic characteristics	
Male	70 (59.8%)
Age*	64.6 ± 14
< 45 years	12 (10.3%)
> 75 years	74 (54.7%)
65 - 75 years	41 (35%)
Risk factors and therapy in primary prevention	
Arterial hypertension	104 (88.9%)
Diabetes mellitus	21 (17.9%)
Atrial fibrillation (AF)	30 (25.6%)
Hypercholesterolemia	58 (49.6%)
Smoking	29 (24.8%)
Previous AIS	11 (9.4%)
Other previous vascular diseases (myocardial infarction, peripheral arterial disease, etc.)	16 (13.7%)
Antithrombotic therapy in the primary prevention of AIS	37 (30.8%)
Antiplatelet therapy in the primary prevention of AIS	29 (24.8%)
Oral anticoagulant therapy in the primary prevention of AIS in patients with previous AF	8 (6.9%)
Antihypertensive therapy in the primary prevention of AIS	71 (60.7%)
Statin therapy in the primary prevention of AIS	20 (17.1%)
Clinical and biological characteristics	
Initial NIHSS *	11.97 ± 6.7
NIHSS ** > 18	27 (23.1%)
SBP *	150.67 ± 20.33
DBP *	86.66 ± 13.2
Receiving INR values in patients who had a previous OAC	0.98 ± 0.13
Outcome	
Symptomatic intracerebral hemorrhage	3 (2.6%)
Favorable outcome (mRS *** 0-2) after 3 months	59 (50.4%)
Fatal outcome (mRS *** 6) after 3 months	16 (13.7%)

The numbers in the table represent the absolute numbers of patients (with proportion) while the data marked * represent the median.

NIHSS ** - National Institutes of Health Stroke Scale score, mRS *** - modified Rankinscale score

shown in **figure 2**.

By monitoring the study population, 59 (50.4%) had a favorable outcome (mRs 0 - 2), while 16 (13.7%) died (mRS 6). Symptomatic intracerebral hemorrhage was present in only 3 patients (2.6%).

In order to see the effects of using antithrombotic therapy in the primary prevention of AIS, the study population was then divided into two groups: one group consisted of 36 patients (31%) who received antithrombotic

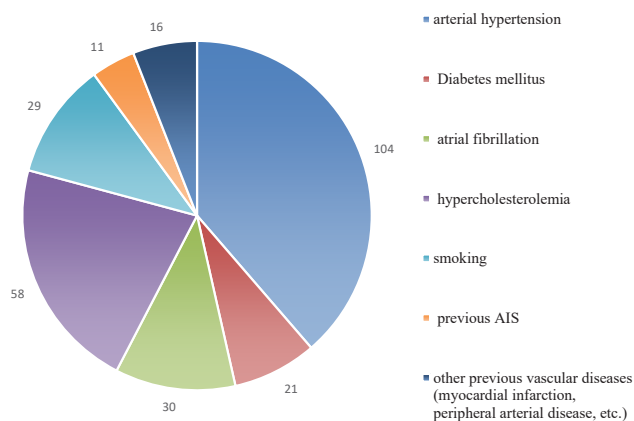


Figure 1. Review of the presence of vascular risk factors in the study population.

therapy in primary prevention, and the other group of 81 (69%) which are not. It was noticed that the majority of respondents who were not on the previous AT were male (67.9%), with an average age of 62 years. Within this group, the most common risk factors were: arterial hypertension (86.7%), hypercholesterolemia (42%) and smoking (29.6%). The average NIHSS score of these patients was 12. In the group of patients who were on previous AT therapy, the average age was 72 years, and here the patients were less often male (41.7%). The incidence of symptomatic ICH was similar in both groups and ranged below 3%. Detailed demographic and clinical characteristics and outcome of AIS patients are shown in **table 2**.

Comparing the characteristics of the two study subpopulations, it was found that patients who were not on previous AT therapy were: more often male ($p = 0.008$), aged 45 - 75 years ($p < 0.001$) or younger than 45 years ($p < 0.001$), less frequently they had previous AF ($p < 0.001$) hypercholesterolemia ($p = 0.014$) and previous AIS ($p = 0.002$), they also had a trend of initially lower NIHSS score ($p = 0.050$). It is important to note that the use of prior antithrombotic therapy in patients did not increase the likelihood of symptomatic intracerebral hemorrhage ($p = 0.922$). On the other hand, no statistically significant difference was found when it comes to the occurrence of a favorable functional outcome ($p = 0.263$). A detailed analysis of the whole spectrum of mRS scores in combination with the applied therapy is shown in **figure 3**.

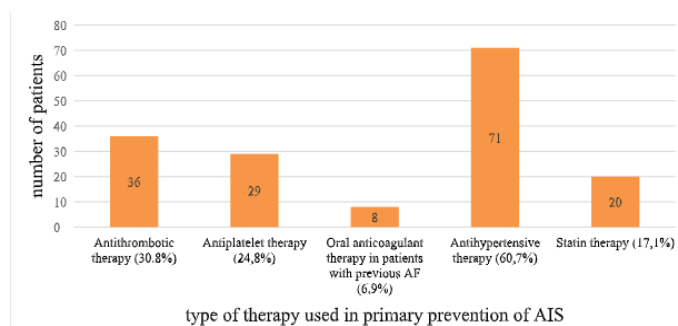


Figure 2. Review of the therapy used in the primary prevention of AIS.

Table 2. Demographic, clinical characteristics and outcome of acute ischemic stroke in patients receiving antithrombotic therapy as part of primary prevention vs patients who are not.

	Patients with previous antithrombotic therapy (n = 36)	Patients without previous antithrombotic therapies (n = 81)	P values
Demographic characteristics			
Male	15 (41.7%)	55 (67.9%)	0.008
Age*	71.6 ± 10	61.6 ± 14.5	< 0.001
Age > 75 years	17 (58.6%)	12 (41.4%)	
Age 45 - 75 years	19 (25%)	57 (75%)	< 0.001
Age < 45 years	0 (0%)	12 (100%)	
Clinical and biological characteristics			
NIHSS ** on admission *	13.8 ± 6.3	11.2 ± 6.9	0.050
NIHSS ** > 18	10 (37%)	17 (63%)	0.478
SBP *	149.5 ± 20.4	151.1 ± 20.4	0.681
DBP *	82.6 ± 11.6	88.4 ± 16.5	0.028
Outcome			
Symptomatic intracerebral hemorrhage	1 (33.3%)	2 (66.7%)	0.922
Favorable outcome (mRS *** 0-2) after 3 months	13 (33.3%)	46 (56.7%)	0.263
Fatal outcome (mRS *** 6) after 3 months	6 (37.5%)	10 (62.5%)	0.263

The numbers in the table represent the absolute numbers of patients (with proportion) while the data marked * represent the median. NIHSS ** - National Institutes of Health Stroke Scale score, mRS *** - modified Rankin scale score

Discussion

The best form of prevention is to control risk factors in this context identification of risk factors and their treatment in all age groups is important for the primary prevention of AIS.

In previous studies, as well as in this one, the connection between age and the development of AIS has been proven. Evidence suggests that the risk of AIS doubles after age 55 (1,4). In this study population, the average age of patients was 65 years, while the highest incidence of AIS

was recorded in persons older than 75 years (54.7%), younger than 45 accounted for 10.3% of the study population, which is also evidenced by the already mentioned (4). Gender differences speak in favor of the already proven age risk, and they complement each other. In the younger population, AIS is more common in women, which is related to hormonal variations, pregnancy, and use of oral contraceptives, while in the older population, AIS is more common in men, as evidenced by this study (4,15). The previously mentioned age of our patients is related to the fact that 59.8% of the study population was male.

Vascular risk factors for the development of AIS are well known and clearly defined (15). In particular,

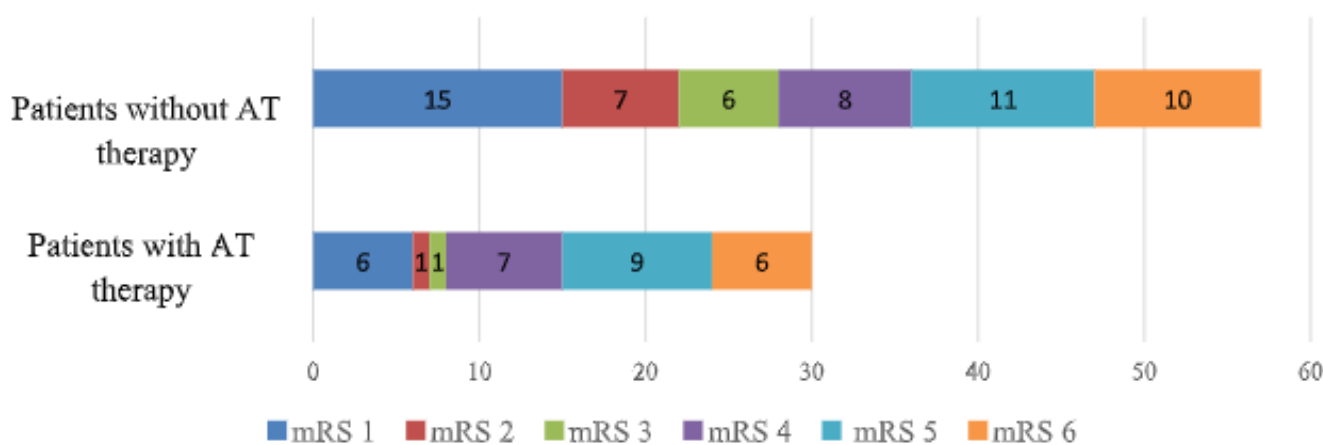


Figure 3. Outcome after 3 months in patients who used AT therapy (n = 36) and those who did not use AT therapy (n = 81). The outcome was estimated using a modified Rankin score (mRS) where the score value is 0 represents the absence of disability, and the value 6 is fatal. Values shown in each categories are percentage.

arterial hypertension is mentioned as the most important risk factor in various studies, and a significant number of patients had this comorbidity in this one, 104 of them (88.9%). Reducing systolic blood pressure (SBP) by 2 mmHg has been shown to reduce the risk by 25%, while reducing diastolic blood pressure (DBP) reduces this risk by as much as 50% (16). In these respondents, these values were 150.67 ± 20.33 for SBP and 86.66 ± 13.2 for DBP. Hypercholesterolemia as a risk factor is primarily associated with myocardial infarction or coronary atherosclerosis, but is also associated with AIS. Also, the effectiveness of statins as drugs in the secondary prevention of AIS has long been proven, but their role in primary prevention is being considered. It is stated that in people with known vascular disease, they may have beneficial effects, not only on reducing the incidence but also on a better outcome in developed AIS (17). It is recommended to continue to use them in combination with other, also effective drugs in primary prevention in the population of people who have a vascular disease (16). In this study, 20 subjects (17.1%) used statin therapy. Current guidelines recommend that patients with atrial fibrillation be stratified for the risk of thromboembolic events, including AIS, using appropriate scores (CHADS2 and CHA2DS2-VASc) to define those patients in whom oral anticoagulant therapy is indicated. (23). However, the use of oral anticoagulant therapy has been shown to remain underused (18). The most common reasons for this are the overestimated risk of bleeding caused by warfarin, and the underestimation of its importance in the prevention of AIS. On the other hand, the positive effect of aspirin is overestimated, and its influence on the risk of bleeding is underestimated (19). It is estimated that about 50% of patients with AF on warfarin therapy are in primary prevention, and that these patients generally have ineffective or unsafe levels of warfarin in their blood for almost half the time, and that in fact only 25% of patients receive adequate treatment to reduce the risk of developing AIS (20). The study showed that 6.9% of patients who knew about AF were on previous anticoagulant therapy, however, this group was very poorly anticoagulated because the average INR was $0.98 (\pm 0.13)$. Diabetes Mellitus is an important risk factor for the development of AIS. It has been shown that in combination with antihypertensive therapy and control of dyslipidemia, patients with regulated DM will develop vascular disease to a lesser extent compared with patients with unregulated glycemia (16). Smoking, whether active or passive, it has also been linked to an increased risk of developing AIS as an "enhancer" of already known risk factors such as arterial hypertension and dyslipidemia. Previous studies state that smoking cessation reduces the risk by as much as 50% after one year, ie after 5 years the risk is the same as in non-smokers (24). In this study, 29 respondents (24.8%) were smokers.

Numerous studies have highlighted the importance of aspirin in both primary and secondary prevention of cerebrovascular disease (13,25-27). Studies have shown that the use of aspirin in the primary prevention of AIS is associated with a lower absolute risk of ischemic stroke

compared with controls in 10 randomized studies (1.27% aspirin vs 1.48% without aspirin; HR: 0.81; 95% CI: 0.76 – 0.87, absolute risk reduction [ARR]: 0.19%; 95% CI: 0.06% – 0.30%), and on the other hand a similar risk for intracranial hemorrhage in 12 randomized studies (0.43% aspirin vs 0.32% aspirin-free; HR: 1.34; 95% CI: 1.14 to 1.57; ARR: 0.11%; 95% CI: 0.04% – 0.18%) (25). When it comes to the use of vitamin K antagonists, studies have shown that the use of these OACs in patients with AF increases the risk of major bleeding by 0.3 – 0.5% per year (28). This study showed that the use of previous antithrombotic therapy (aspirin or VKA) in patients does not increase the likelihood of symptomatic hemorrhage. There were no patients in the study population who were on previous NOAC. On the other hand, there is no statistically significant difference when it comes to the appearance of a favorable functional outcome, but this result should be viewed through the prism that patients who were not on previous antithrombotic therapy were on average 10 years younger.

Conclusion

Recognition of vascular risk factors, their control and treatment are of immense importance in the primary prevention of AIS. Their influence has been proven to all age groups and it is necessary to continue working on their identification and treatment. Previous use of antithrombotic therapy does not increase the likelihood of sICH in patients with AIS treated with recanalization therapy.

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