

## CAROTID ARTERY STENOSIS AS A RISK FACTOR FOR THE OCCURRENCE OF ISCHEMIC STROKE

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Carotid artery stenosis is a widespread disease and it is one of the most significant risk factors for the development of ischemic stroke. The risk of ischemic stroke increases with the increase in the degree of carotid artery stenosis. Although the relation between carotid artery stenosis and other risk factors (arterial hypertension, hyperlipidemia, diabetes, etc.) has not been precisely determined in relation to the development, course and outcome of the ischemic stroke, the degree of this association is considered important for the development of ischemic stroke.

The aim of the study was to determine the significance of carotid artery stenosis in patients with ischemic stroke and to estimate the degree of association between carotid artery stenosis and other risk factors in the development of ischemic stroke.

The study included patients with ischemic stroke treated at the Cerebrovascular Diseases Department of the Neurology Clinic. The data were obtained from histories and from color Doppler (CD) examination of extracranial blood vessels of the neck.

The highest percentage of patients with stroke had carotid artery stenosis ( $p < 0.05$ ). Of these patients, the highest percentage were with stenosis degree less than 60% ( $p < 0.05$ ). The patients with more than two risk factors, in addition to stenosis, more often had ischemic stroke ( $p < 0.05$ ). In the group without carotid artery stenosis, patients with large number of risk factors also had a higher risk of developing the disease, compared to those who did not have the combined risk factors ( $p < 0.05$ ). However, patients with ischemic stroke without carotid artery stenosis who had several other risk factors also had the same risk of developing ischemic stroke as the patients with carotid artery stenosis without combined risk factors.

Carotid artery stenosis is a risk factor in ischemic stroke. In patients with several risk factors, stenosis is a high risk factor for ischemic stroke. Patients without stenosis but with several other risk factors have the same risk of developing ischemic stroke as patients with stenosis and without other risk factors. *Acta Medica Medianae* 2016;55(2):40-45.

**Key words:** carotid artery stenosis, ischemic stroke, risk factors

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### Introduction

Stroke is one of the leading causes of morbidity, mortality and permanent deterioration of the quality of life (1). There are two clinical phenotypes of stroke - ischemic (80-85%) and hemorrhagic (15-20%). On the other hand, according to

the TOAST criteria (Trial of Org in Acute Stroke Treatment), there are five subtypes of ischemic stroke: stroke caused by atherosclerosis of a large vessel, cardioembolic stroke, stroke caused by occlusion of small vessels on the branch, stroke caused by other etiological factors, and stroke with unknown primary etiology (2). The etiological basis of ischemic stroke is important in primary and secondary prevention within a population at risk of developing ischemic stroke. The key measures of prevention include prevention, reduction and modification of risk factors which are important in the process of initiating complex pathogenic cascade of ischemic stroke. Risk factors are classified into constitutional, whose expression cannot be influenced, and those which are more numerous but whose effects can be prevented by various measures. This group includes bad hygienic and dietary habits, physical inactivity, smoking, high serum lipoproteins, triglycerides, high

homocysteine level, diabetes, high blood pressure or atherosclerosis of main blood vessels of the brain, carotid and/or vertebrobasilar arterial system of the brain (3). Although there are studies which confirm high pathogenic potential of every ischemic stroke risk factor (4), a small number of them compare their individual or cumulative pathogenic potential in the development of ischemic stroke. Carotid artery stenosis is the most common risk factor in the development of ischemic stroke although it is often combined with other stroke risk factors (3, 4). The risk of ischemic stroke is multiplied if the degree of stenosis is higher, both in patients with different clinical manifestation of stenosis (symptomatic stenosis) and in asymptomatic people. Combination of carotid artery stenosis and other risk factors (hypertension, hyperlipidemia, atrial fibrillation, cardiomyopathy, etc.) significantly increases the risk of developing ischemic stroke.

### Aims

The aim of this study was to investigate the pathogenic significance of carotid artery stenosis in patients with ischemic stroke, as well as to determine the degree of association between stenosis and standardized risk factors in estimating individual and cumulative effect of these factors in the development of ischemic stroke.

### Material and methods

This retrospective study was granted by the Ethics Committee of the Faculty of Medicine, University of Niš. The study included the analysis of all relevant demographic, clinical and paraclinical data obtained from histories of patients with ischemic stroke in the carotid system treated at the Neurology Clinic of the Clinical Center in Niš from December 2009 to December 2010.

The study included patients with acute neurological symptoms and signs – motor, sensitive, visual or speech impairments, provided that the patients did not have similar discomforts earlier in life. Computerized tomography of the endocranium with examination of the intracranial blood vessels was conducted during a period of 24 to 72 hours. The findings were interpreted by a neuroradiologist who only examined the clinical manifestations of the disease and had no knowledge about the group into which the patients had been randomized for the needs of the research.

The classification of ischemic stroke in the carotid was done according to the TOAST criteria (2). All patients underwent Color Doppler ultrasound (CDU) of extracranial blood vessels of the neck. The procedure was performed using Esaote MyLab 75 apparatus. A linear probe 7.5 Hz frequency was used as it provides the best spatial resolution. The diagnosis of carotid artery stenosis was set on the NASCET criteria.

The examination also included the presence of other combined risk factors and comorbidities,

arterial hypertension, diabetes, hypertriglyceridemia, hyperlipoproteinemia, etc., according to previously standardized criteria for ischemic stroke risk factors (6).

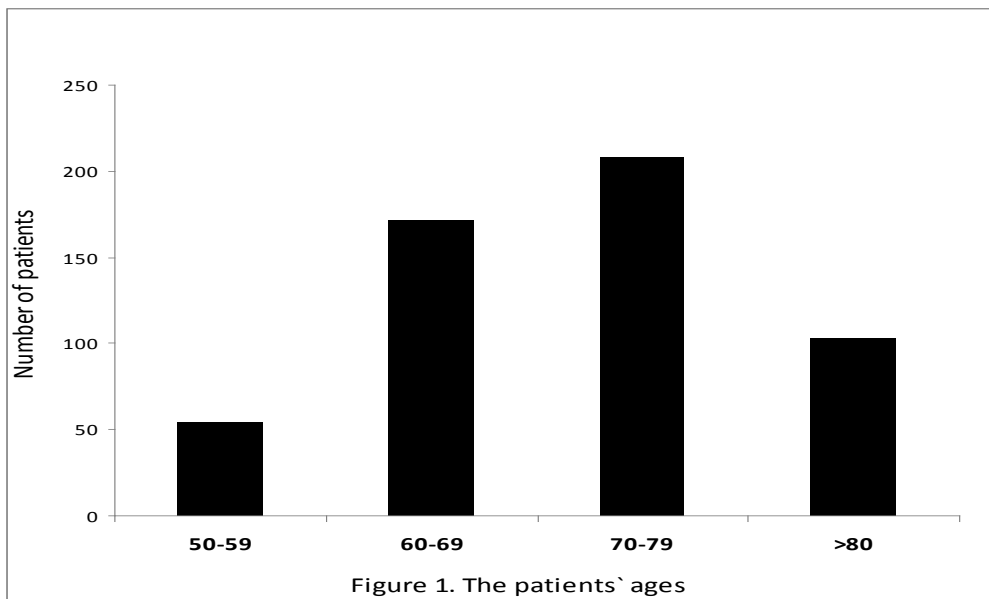
The patients were classified into four groups. The first group included patients without carotid artery stenosis with two and more combined risk factors. The second group was composed of patients without carotid artery stenosis with one risk factor for ischemic stroke. The third group included patients with stenosis and more combined risk factors ( $\geq 2$ ), whereas the fourth group included patients with ischemic stroke, with only one risk factor and with carotid artery stenosis.

The results are shown in figures as mean values  $\pm$  statistical error. Non-parametric statistical tests were used after determining the distribution of the tested variables within patient groups. Spearman's rank correlation coefficient was used for estimating the degree of association of the tested variables. Values of  $p < 0.05$  were considered statistically significant. Statistical analysis of data was done by SPSS, version 13 statistical package.

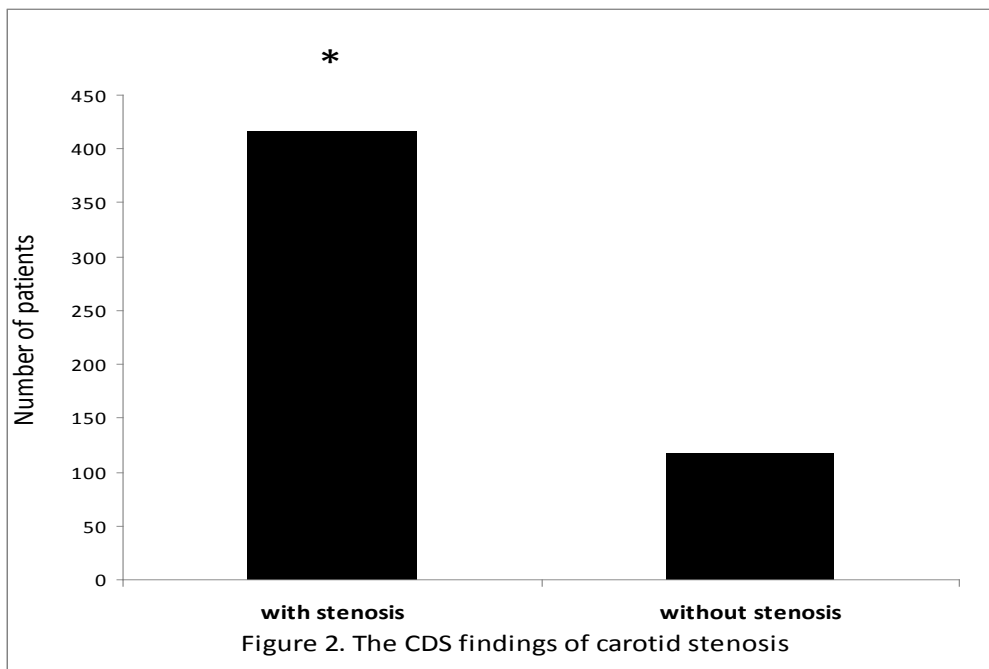
### Results

The study included 534 patients, of whom 331 were female and 201 were male, aged 50 to 86 years, diagnosed with ischemic stroke in the carotid system. The highest percentage of patients (89%) were above 60 years of age ( $p < 0.01$ ) (Figure 1). Carotid artery stenosis was observed in 78% ( $p < 0.01$ ) (Figure 2). With respect to the carotid artery stenosis, further group stratification was performed as shown in Figure 3. It was observed that the highest percentage of patients with ischemic stroke (60%) had carotid artery stenosis below 60% ( $p < 0.01$ ).

Analysis of association between stenosis and other factors showed that the group without stenosis (22% of patients with stroke) had three times more patients with more than one risk factor for the development of ischemic stroke (most commonly found were arterial hypertension, hyperlipoproteinemia, and diabetes), compared to those with only one risk factor (arterial hypertension) or without risk factors. The comparison of these two groups with ischemic stroke showed that a combination of ischemic stroke and other risk factors without carotid artery stenosis was present in 73% of patients ( $p < 0.01$ ). On the other hand, in the group with carotid artery stenosis (78%), patients with more than one standard risk factor were three times more prone to developing ischemic stroke, compared to patients with carotid artery stenosis and only one risk factor ( $p < 0.01$ ). It is interesting to point out that a comparison of all groups with respect to the presence or absence of carotid artery stenosis and other risk factors (Figure 4) showed that the risk of ischemic stroke is almost identical ( $p > 0.05$ ) in patients with ischemic



**Figure 1.** Distribution of patients with ischemic stroke in relation to age



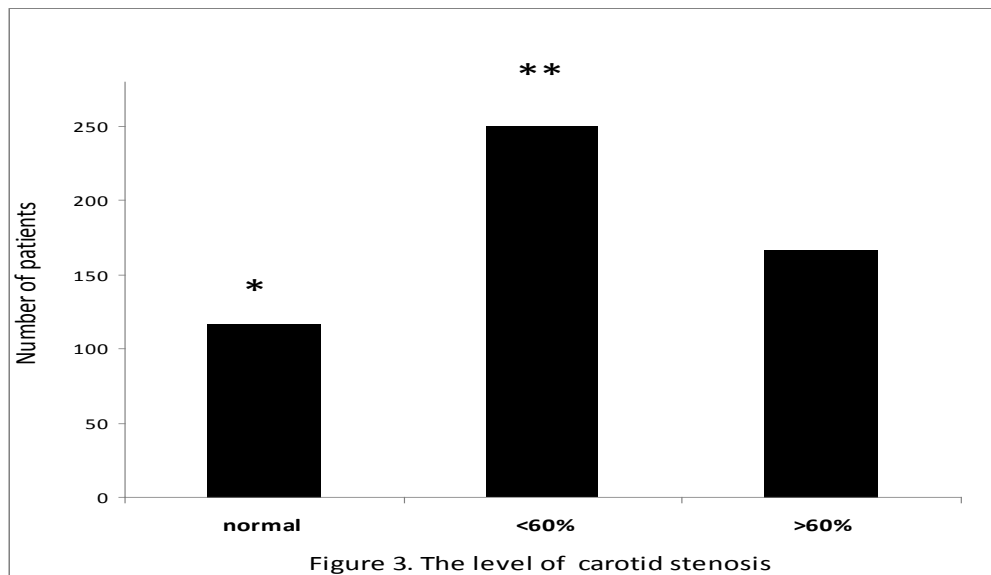
**Figure 2.** Distribution of CDU findings in patients with ischemic stroke \*vs without stenosis –  $p < 0.05$

stroke who had carotid artery stenosis with one risk factor or absence of other risk factors and those who had several other standardized risk factors without carotid artery stenosis.

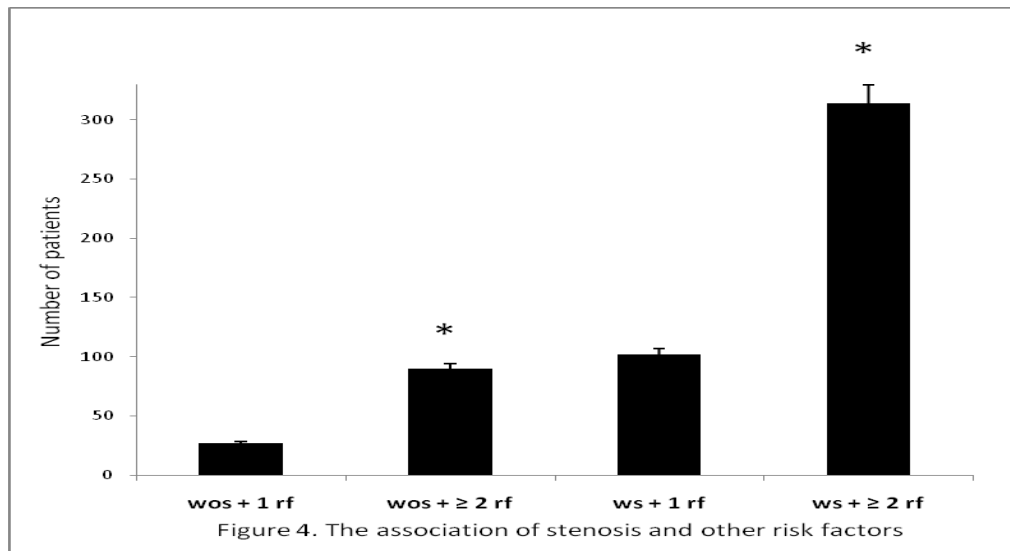
A comparison of analyzed data with respect to other demographic, clinical and paraclinical characteristics of patients did not show statistically significant differences ( $p > 0.05$ ). The data are not presented.

## Discussion

Ischemic stroke is most frequent in the elderly population. Its incidence is increasing and its specific mortality rate doubles every five years. However, about one third of patients are younger than 65 (7). Figure 1 shows the age of our patients. The largest number (89%) of patients is over 60 years of age.



**Figure 3.** Distribution of CDU findings in patients with ischemic stroke in relation to severity of pathological findings \*vs < 60%; vs >60% -  $p < 0.05$



**Figure 4.** Distribution of patients with and without stenosis with respect to the presence of other (standardized<sup>#</sup>) risk factors  
<sup>#</sup>arterial hypertension, diabetes, hyperlipoproteinemia/hypercholesterolemia (frequency of findings)  
 \*vs wos+≥2rf; vs ws+≥2rf -  $p < 0.05$  ws - with stenosis wos - without stenosis rf - risk factor

There are a lot of literature data about the problem of carotid atherosclerosis. The frequency of this disease in general population aged 19-99 years is around 25% (8), but it increases with age. In general population over 65 years of age, carotid atherosclerosis is present in 60-75% of cases (9). In our group of patients, atherosclerosis which could be expressed in percentage of lumen narrowing was 78%, which is in line with literature data (Figure 2).

Carotid artery occlusive disease, especially in developed countries, presents one of the most significant causes of ischemic stroke. Attempts to associate the degree of carotid stenosis with a particular degree of risk for ischemic stroke did

not provide definite results. However, it is clear that the risk of ischemic stroke undoubtedly increases along with the increase in the percentage of carotid stenosis in both symptomatic and asymptomatic patients. Several studies have shown that the degree of stenosis of internal carotid artery was the only criterion for classifying patients into the high risk group for developing ischemic stroke (7). In general population, the percentage of hemodynamically significant stenosis is around 5-7% according to literature data (9). In our patient group, this percentage is higher. With respect to patients with stenosis of a certain degree, the percentage of hemodynamically significant carotid artery stenosis is 40%. With respect to the whole

group of patients with ischemic stroke, the percentage is 29%. We believe that the high percentage of hemodynamically significant stenosis is caused by the age structure of the patient group (Figure 3).

The most common risk factors for the development of ischemic stroke are: arterial hypertension (AH), atrial fibrillation (FA), recent myocardial infarction (MI), diabetes (DM), hyperlipidemia (HL), coronary disease, obesity, age, gender, physical inactivity. Majority of these factors also cause the development of atherosclerosis of the major blood vessels. While some risk factors directly cause its development, the association with other factors is not completely known. The risk of atherosclerosis can be reduced by prevention of the risk factors. The frequency of some risk factors in patients with ischemic stroke or isolated carotid artery stenosis reported in literature is in line with our findings – arterial hypertension in 84 %, hyperlipidemia - 30%, diabetes mellitus – 22 %, coronary disease in 51% of patients (10). In our patient group, we also investigated a simultaneous presence of two and more risk factors for ischemic stroke with carotid artery stenosis and their total risk for the development of ischemic stroke, as well as the risk for ischemic stroke in

patients with carotid artery stenosis without associated risk factors and patients with several risk factors and without carotid artery stenosis. Literature data show that the risk for ischemic stroke increases when several associated risk factors are present (11) and the data are in accordance with the results of our study.

### Conclusion

Considering the results of the study, it can be concluded that in the patient group carotid artery stenosis is a significant individual factor for ischemic stroke, and that it is also a risk factor for ischemic stroke in association with other standardized risk factors. On the other hand, patients without carotid artery stenosis but with several other risk factors have the same risk of developing ischemic stroke as patients with stenosis and one or without any other risk factors.

In order to verify the data presented in this study, a suggestion for further research would refer to testing the parameters in relation to ischemic stroke subtypes with the aim of defining the pathogenic significance of carotid artery stenosis in the development, course and outcome of ischemic stroke, as well as other risk factors.

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## STENOZA KAROTIDNIH ARTERIJA KAO FAKTOR RIZIKA ZA NASTANAK ISHEMIČNOG MOŽDANOG UDARA

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Stenoza karotidnih arterija (SKA) je veoma rasprostranjena i predstavlja jedan od najznačajnijih faktora rizika za nastanak ishemijskog moždanog udara (IMU). Rizik od IMU raste sa povećanjem stepena SKA. Iako nije sasvim precizno utvrđen značaj povezanosti SKA i drugih standardnih faktora rizika (arterijska hipertenzija, hiperlipidemija, šećerna bolest) u pojavi, toku i ishodu IMU, stepen te povezanosti smatra se značajnim za nastanak IMU.

Cilj rada bio je utvrđivanje značaja nalaza SKA kod bolesnika sa IMU kao i procena stepena povezanosti SKA i ostalih faktora rizika u nastanku IMU.

Istraživanjem su obuhvaćeni oboleli od IMU koji su lečeni na Odeljenju za cerebrovaskularne bolesti Klinike za neurologiju. Korišćeni su podaci dobijeni iz istorija bolesti i nalaz color doppler sonografije (CDS) ekstrakranijalnih krvnih sudova vrata.

Najveći procenat bolesnika sa moždanim udarom imao je određeni stepen SKA (78%) ( $p < 0,05$ ), od kojih je najveći procenat imao stepen stenoze manji od 60% ( $p < 0,05$ ). Bolesnici koji su osim SKA imali više od dva faktora rizika, značajno su češće imali IMU ( $p < 0,05$ ). U grupi onih koji nisu imali SKA, oboleli sa većim brojem faktora rizika bili su u većem riziku oboljevanja u odnosu na one koji nisu imali udružene faktore rizika ( $p < 0,05$ ). Ipak, oboleli od IMU bez SKA, koji su imali više drugih faktora rizika, bili su u istom riziku za nastanak IMU kao i bolesnici sa SKA bez udruženih faktora rizika.

SKA predstavlja faktor rizika za pojavu IMU. Bolesnici koji imaju više faktora rizika, SKA predstavlja faktor visokog rizika za nastanak IMU. Bolesnici bez SKA, koji imaju više drugih faktora rizika, imaju isti rizik za nastanak IMU kao i oni sa SKA bez drugih faktora rizika. *Acta Medica Medianae 2016;55(2):40-45.*

**Ključne reči:** stenoza karotidnih arterija, ishemijski moždani udar, faktori rizika