

## EPIDEMIOLOGICAL ASPECTS OF CAROTID DISEASE

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### Abstract

**Citation:** Paljoskovska Jordanova S. Epidemiological aspects of carotid disease. Arch Pub Health 2021; 13 (1).

doi.org/10.3889/aph.2021.5993

**Key words:** carotid artery, carotid artery disease, risk factors, atherosclerosis

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**Received:** 20-Dec-2020; **Revised:** -Mar-2021; **Accepted:** 10-Mar-2021; **Published:** 20-Jun-2021

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**Competing Interests:** The author have declared that no competing interests

Carotid artery disease most commonly manifests as atherosclerotic carotid artery disease, which can lead to an ischemic stroke. Our aim was to present the epidemiological aspects of carotid disease and to demonstrate the association of risk factors with carotid disease. For that purpose, we prospectively followed 1031 patients at the University Clinic for Cardiology in Skopje, who were examined for carotid stenosis and its correlation with risk factors such as hypertension, smoking, hyperlipidemia, diabetes, obesity and peripheral arterial disease. Results: Carotid stenosis was correlated with arterial hypertension, hyperlipidemia, diabetes mellitus, smoking, and peripheral arterial disease. Conclusions: Our study found that conventional risk factors such as hypertension, diabetes, smoking, and dyslipidemia were independently associated with significant carotid artery disease and peripheral arterial disease.

### Клинички истражувања

## ЕПИДЕМИОЛОШКИ АСПЕКТИ НА КАРОТИДНАТА АРТЕРИСКА БОЛЕСТ

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### Извадок

**Цитирање:** Палошковска Јорданова С. Епидемиолошки аспекти на каротидната артериска болест. Арх Ј Здравје 2021;13(1)

doi.org/10.3889/aph.2021.5993

**Клучни зборови:** каротидна артерија, болест на каротидна артерија, фактори на ризик, атеросклероза.

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**Примено:** 20-дек-2020; **Ревидирано:** 1-мар-2021; **Прифатено:** 10-мар-2021; **Објавено:** 20-јун-2021

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**Конкурентски интереси:** Авторот изјавува дека нема конкурентски интереси.

Болеста на каротидната артерија најчесто се манифестира како атеросклеротична болест на истоимената артерија, што може да доведе до исхемичен мозочен удар. Целта на оваа студија беше да ги претставиме епидемиолошките аспекти на каротидната болест и да ја демонстрираме поврзаноста на факторите на ризик со каротидната болест. Материјал и методи: Проспективно следевме 1031 пациент на Универзитетската клиника за кардиологија во Скопје, кај кои беа направени испитувања за каротидна стеноза и нејзината корелација со ризик-факторите како што се: артериската хипертензија, пушењето, хиперлипидемијата, дијабетот, дебелината и периферната артериска болест. Резултати: Каротидната стеноза беше во корелација со артериската хипертензија, дебелината, хиперлипидемијата, дијабетот, пушењето и периферната артериска болест. Заклучок: Со оваа студија утврдивме дека конвенционалните фактори на ризик како што се хипертензија, дијабет, пушење и дислипидемија, периферната артериска болест се независно поврзани со значајна каротидна артериска болест.

## Introduction

Carotid artery disease most commonly manifests as atherosclerotic disease of the carotid artery, which can lead to an ischemic stroke with a mortality rate of 10% to 20%<sup>1</sup>.

The knowledge that 50% of the causes of all ischemic strokes originate from emboli or as a consequence of thrombosis of extracranial segments of the carotid and vertebral arteries brought to the fore duplex ultrasonography of the carotid and vertebrobasilar basin, so that this method imposed itself as the cerebrospinal fluid standard<sup>2</sup>.

Studies on a large number of patients have shown that a high percentage of patients with atherosclerosis of the carotid arteries, no transient ischemic attack (TIA), which would warn of the disease, have long been asymptomatic to end in stroke. This is certainly one of the important facts, which explains the insufficient efficiency of the timely diagnosis of cerebrovascular atherosclerosis<sup>3</sup>.

Since preventive measures such as blood pressure regulation, treatment of disorders of glucose and lipid metabolism, surgical and endovascular interventions to eliminate significant atheromatous changes can significantly reduce the occurrence of vascular disease, it is necessary to conduct control examinations in order to find patients at an increased risk<sup>4</sup>.

Atherosclerosis, the main cause of increased mortality in modern humanity, is a diffuse, multifactorial process, involving large (elastic) and medium (muscular) arterial blood vessels, and having pathological characteristics of smooth muscle cell proliferation, lipid accumulation, cell necrosis, fibrosis and calcification<sup>5</sup>.

Based on numerous epidemiological studies, cardiovascular diseases, especially coronary heart disease and cerebrovascular disease, are the main cause of mortality and even morbidity of the population, and one of the most important social and medical problems present<sup>6</sup>.

Carotid artery disease (CAD) is the leading cause of illness in the world, the third leading cause of death in developed countries, and the second leading cause of death in the world in general. CAD is the first cause of death in women<sup>7</sup>. The incidence of CAD varies by area and ranges from 100 to 300 new cases per 100,000 population per year, while the prevalence ranges from about 600 per 100,000 population in developed countries to as many as 900 in underdeveloped countries<sup>8</sup>. Mortality varies from 63.5-273.4 deaths per 100,000 inhabitants per year.

Timely diagnosis and treatment of complications that accompany CAD, as well as improvement of the functional status of patients by applying early and late rehabilitation measures, also contribute to lower mortality. Sacco et al. in their study found that patients after 6 months of IMU in 48% of cases have hemiparesis, 22% of patients are not independently mobile, 24 - 53% show complete or partial dependence on the scale of daily activities, 12 - 18% have aphasia, 32% have clinical signs of depression and 26% require institutional care<sup>9</sup>.

Atherosclerosis syndrome is the cause of the most common hospital treatment, the highest consumption of drugs and expenses in relation to all other diseases. The main goals of the epidemiology of cardiovascular and cerebrovascular diseases are to establish risk factors, which contribute to

a higher prevalence and frequency of the disease.

Leading epidemiological studies have shown that about 20 risk factors are independently associated with a higher incidence of the disease<sup>10</sup>.

The prevalence and severity of carotid atherosclerosis in the general population correlate significantly with age, total cholesterol, and cardiovascular ischemic changes. Data on the prevalence of carotid atherosclerosis come from the results of studies that included mostly inhomogeneous groups of subjects, in different environments and time periods, using different methodologies and technologies.

Numerous studies indicate that asymptomatic carotid atherosclerotic plaques can be detected in a third of the elderly by ultrasound<sup>(11)</sup>. Significant atherosclerotic disease of extracranial carotid segments is present in 25-30% of persons in whom surgical treatment is indicated due to occlusive disease of peripheral arteries<sup>12</sup>.

Our aim was to present the epidemiological aspects of carotid disease and to demonstrate the association of risk factors with carotid disease. For that purpose, in our prospective study, a comparative analysis of the relationship between risk factors was made.

## Material and methods

The study included 1031 respondents hospitalized in the University Clinic for Cardiology or randomly assigned outpatients, men and women, with proven coronary artery disease, previously defined as high cardiovascular risk patients. The examination was conducted in the period from 2017 to 2020.

Selected demographic data (gender, age, history of smoking, dyslipidemias, hypertension), laboratory values for hypertriglyceridemia, diabetes and clinical data (comorbidities and risk) were collected from each patient. Carotid ultrasound was used to assess intima media thickness (IMT), plaque, or stenosis.

Intima thickness of the common carotid artery can be detected accurately by B-mode ultrasonography. It is a reliable technique and has a high degree of accuracy and reproducibility in estimating the arterial wall thickness. Intima-media thickness (IMT), also called intima-medial thickness, is a measure of the thickness of the intima tunic and tunica-media, the deepest two layers of the artery wall. The measurement is usually made with external ultrasound, and occasionally with internal, invasive ultrasound catheters. Measurement of total ves-

| Degree of stenosis, %             | Primary parameters         |                              | Additional parameters |                 |
|-----------------------------------|----------------------------|------------------------------|-----------------------|-----------------|
|                                   | ICA PSV, cm/sec            | Plaque estimate*, %          | ICA/CCA PSV ratio     | ICA EDV, cm/sec |
| Normal                            | < 125                      | None                         | < 2.0                 | < 40            |
| < 50                              | < 125                      | < 50                         | < 2.0                 | < 40            |
| 50–69                             | 125–230                    | ≥ 50                         | 2.0–4.0               | 40–100          |
| ≥ 70 but less than near occlusion | > 230                      | ≥ 50                         | > 4.0                 | > 100           |
| Near occlusion                    | High, low, or undetectable | Visible                      | Variable              | Variable        |
| Total occlusion                   | Undetectable               | Visible, no detectable lumen | Not applicable        | Not applicable  |

\*Plaque estimate (diameter reduction) with gray-scale and color Doppler ultrasound.  
CCA—common carotid artery; EDV—end-diastolic velocity; ICA—internal carotid artery; PSV—peak systolic velocity.  
(From Grant et al. [25]; with permission.)

sel wall thickness can also be made by using other imaging modalities.

Criteria for carotid stenosis: Grey-Scale

CP Oates, AR Naylor, T. Hartshorne. Joint Recommendations for Reporting Carotid Ultrasound Investigations in the United Kingdom *Eur J Vasc Endovasc Surg.*2009; 37, 251e261)

The following statistical methods were used in the study: analysis of numerical arrays, arithmetic mean, median, indices, mean, sample method; graphical representation of statistical data, histograms, rectangular or

bar chart, structural circles, line diagram and correlation (linear, correlation, curvilinear, partial correlation).

Univariate analysis was done to define risk factors associated with carotid artery disease.

**Results**

A total of 1031 patients with a mean age of 65.2 years (34-88 years), of which 33.5% (345) women and 66.6% (686) men with coronary artery disease were included in the study (Table 1).

| Total | %   | Men | %    | Women | %    |
|-------|-----|-----|------|-------|------|
| 1031  | 100 | 686 | 66.6 | 345   | 33.4 |

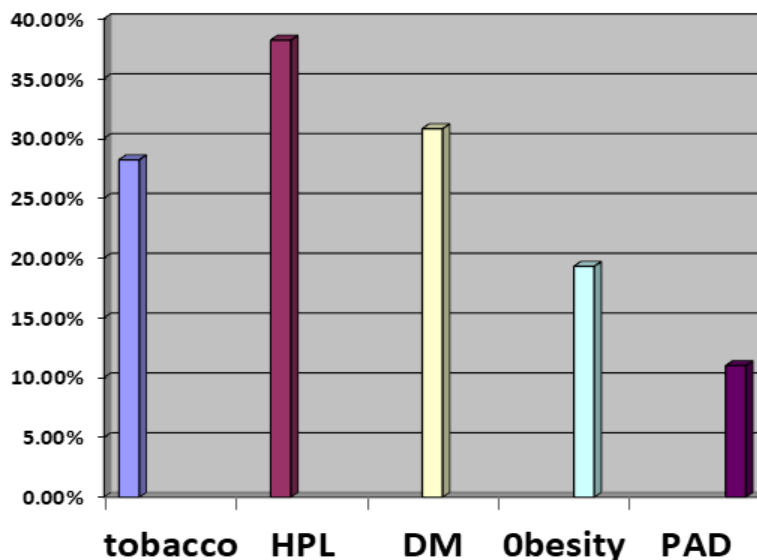
**Table 1:** Gender distribution of patients

Of all included participants, 28.2% (270) used tobacco, 38.1% (341) had hyperlipidemia (HLP), 30.8% (316) had diabetes mellitus (DM), 19.3% had obesity, and 11.0% had peripheral artery disease (PAD). Increased IMT was

observed in 673 or 68.5% of patients (Figure 1).

Based on the analysis of the results obtained, of the total number of patients 145 or 14.1% had carotid stenosis.

**Figure 1:** Relevant risk factors in the study group



PAD was a risk factor for increased IMT > 0.8 with a score of 3.23 for  $p < 0.05$ . Risk factors for stenosis are all those where the significant val-

ue is less than 0.05. Less significant value than 0.05 was observed in the section for HTA 1 and HLP (Table 2).

| Source          | Score  | of | Mean Square | F      | Sig. |
|-----------------|--------|----|-------------|--------|------|
| Corrected Model | 12.994 | 49 | .265        | 1.451  | .035 |
| Intercept       | .605   | 1  | .605        | 3.309  | .070 |
| HTA             | 2.047  | 1  | 2.047       | 11.199 | .001 |
| HLP             | 1.001  | 1  | 1.001       | 5.473  | .020 |
| OBESITY         | .051   | 1  | .051        | .280   | .597 |
| SMOKER          | .367   | 2  | .367        | 1.002  | .368 |
| PAD             | .001   | 1  | .001        | .004   | .952 |
| DM              | .037   | 1  | .037        | .200   | .655 |

## Discussion

There are numerous risk factors for the development of atherosclerosis and while some directly affect this process, the connection with others is not completely clarified. It has been shown that it is possible to reduce the incidence of atherosclerosis if preventive actions on risk factors for its occurrence are being undertaken<sup>15</sup>.

The main risk factors for atherosclerosis are arterial hypertension, lipoproteinemia, diabetes and smoking. The newly discovered risk factors that are being intensively studied are C-reactive protein, lipoprotein (a), fibrinogen, homocysteine, and genetic causes<sup>14</sup>.

Hypertension accelerates the appearance and development of atherosclerosis due to an increased physical stress on the walls of the arteries and increased use of fatty substances. Thickening of the intima-media complex (IMT) significantly corre-

lates with higher values of systolic pressure regardless of race, sex and taking drugs with antihypertensive action<sup>15</sup>. A negative correlation with diastolic pressure values suggests that pulse pressure may be an important marker of atherosclerosis<sup>16</sup>.

Macroangiopathy is significantly more common in patients with severe hypertension than in subjects with controlled hypertension, especially if other risk factors are associated<sup>17</sup>. Among several known risk factors for the development of atherosclerosis, hypercholesterolemia occupies a special place, which is probably sufficient to lead to the development of atherosclerosis on its own and without the presence of other risk factors<sup>18</sup>.

Several large epidemiological studies have confirmed the link between diabetes and vascular disease. A special accent has been given in the Framingham study where the importance of diabetes as a risk factor for atherosclerosis of the coronary and periph-

eral arteries was examined in 5,000 people. The risk of ischemic stroke is 2.5 times higher in people with diabetes<sup>19</sup>.

The assessment of the risk of carotid atherosclerosis by examining the influence of individual risk factors in some studies has given way to the strategy of examining the combined and long-term effect of several risk factors on the prevalence of this disease. The study showed that an increase in systolic blood pressure, an increase in cholesterol levels, and cigarette smoking correlated with an increased risk of carotid atherosclerosis in adults<sup>20</sup>. Also, in persons who are prone to consuming alcoholic beverages and in smokers, elevated values of interleukins and other inflammatory compounds can be registered in the serum<sup>21</sup>.

Women who smoke and use oral contraceptives have a 13-fold increased risk of fatal cardiovascular disease than users of oral contraceptives who do not smoke<sup>22</sup>.

Available evidence suggests that inflammatory mediators play an important role not only in plaque formation but also in its progression toward changes responsible for neurological complications. A significantly higher presence of intercellular adhesive molecules in the zone of high - grade compared to lower-grade carotid stenoses has been proven<sup>23</sup>.

Subclinical changes are a syndrome in which three main forms are mentioned: the formation of carotid plaque at predestination sites, the appearance of thickening of the IMT and the disturbance of elasticity in the blood vessels of the brain. Recently, after the discovery of the sequence of the human genome, intensive re-

search has been done on which genes cause the diversity of IMT<sup>24</sup>. According to the latest data from the same authors, it has been considered that one of the groups of genes that determines variability is located on the short arm of chromosome<sup>12</sup>.

Among the protective risk factors for the development of atherosclerosis are physical activity, alcohol, high density lipoprotein (HDL) and its main apolipoprotein apo-A1<sup>25</sup>.

However, despite the knowledge about risk factors and factors that have a protective effect on the process of atherosclerosis, it is still not possible to predict with certainty the speed of atherosclerosis development and its clinical course.

Arterial hypertension - It is now known that arterial hypertension (HTA) is the most important risk factor for all CAD, and that its existence increases the probability of stroke being five-fold indicated in the multi-center Framingham study<sup>26</sup>.

Analysis of the obtained data shows that arterial hypertension, both systolic and diastolic, is one of the most important risk factors for the development of quantitatively significant arteriosclerosis, which is followed by cerebral infarction.

Arterial hypertension is known to increase the risk of stroke, with a strong association between blood pressure and stroke<sup>27</sup>. With each 10 mmHg increase, the risk of stroke increases by 30% to 45%. On the other hand, anti-hypertensive therapy reduces the risk of stroke, as has been shown in a meta-analysis that included more than 40 studies and more than 188,000 patients; lowering blood pressure by 10 mmHg reduced the risk of stroke by

33%<sup>28</sup>. Also, antihypertensive therapy reduces the risk of recurrent stroke by 24%<sup>29</sup>. Taking these facts into account, antihypertensive therapy is recommended for all patients who have had an ischemic stroke or TIA<sup>30</sup>.

Several epidemiological studies: the ARIC study<sup>31</sup>, the Framingham Heart study<sup>32</sup>, and the MESA (Multi-Ethnic Study of Atherosclerosis)<sup>33</sup> found a link between arterial hypertension and the risk of developing carotid atherosclerotic disease.

The SHEP study (Systolic Hypertension in the Elderly Program) found that systolic blood pressure equal to or greater than 160 mmHg was one of the most important independent predictors of carotid stenosis<sup>34</sup>. Also, the PROGRESS study (Preventing Strokes by Lowering Blood Pressure in Patients with Cerebral Ischemia) showed that treatment with ACE inhibitors and diuretics significantly reduces the risk of recurrent stroke<sup>35</sup>.

A very interesting question arises as to whether antihypertensive therapy is useful or leads to additional ischemia due to decreased cerebral perfusion in symptomatic patients with a significant carotid artery stenosis. On the other hand, if arterial hypertension lasts long enough, it can lead to changes in small blood vessels, leading to changes in brain mass that are described on magnetic resonance imaging as white mass "hyperintensities." These white mass hyperintensities are crucial because they are associated with poorer response to treatment, consequent cognitive impairment, as well as an increased rate of deterioration and progression to chronic forms of depression.

Diabetes mellitus - The risk of ischemic stroke in patients with diabetes

mellitus (DM) is increased 2-5 times compared to patients who do not have diabetes<sup>36</sup>. Similar has been reported in various studies; the results of the IRAS (Insulin Resistance Atherosclerosis Study) study<sup>37</sup> showed a significantly faster progression of intima medial thickening and the occurrence of heart and brain infarction.

The EDIC (Epidemiology of Diabetes Interventions and Complications) study, in addition to the same finding as in the previous one, found that the progression of atherosclerotic lesions in the carotid arteries was slower in patients treated with invasive insulin therapy than in patients treated conventionally<sup>38</sup>.

Evidence has been obtained in most European and North American countries that diabetes is a risk factor for all types of cerebrovascular disease, but especially subcortical infarction when associated with hypertension<sup>39</sup>.

A large number of statistical studies by our and world authors show a higher number of diabetics among patients with manifestations of ischemic brain disease, which ranges from 18 to 43%, while the percentage of this disease in the general population is around 6%.

Interestingly, in Fischer's initial work, only 11% of his subjects with subcortical infarctions suffered from diabetes, so he felt that cerebrovascular disease was not associated with diabetes.

Contrary to this opinion, the already mentioned study (Framingham Heart Study) indicates a significant prevalence of diabetes in 34% of cases and that, in fact, it is an important risk factor for the occur-

rence of infarction, especially subcortical localization.

**Hyperlipoproteinemia** - Hyperlipoproteinemia (HLP) is the most responsible risk factor for the accelerated process of atherosclerosis. HLP occurs due to disorders of lipid transmission due to accelerated synthesis or slowed degradation of lipoproteins, particles that carry cholesterol or triglycerides in plasma.

Hyperlipidemia is generally known as the main risk factor for arteriosclerosis, with the main emphasis on hypercholesterolemia and low-density lipoprotein (LDL), while high-density lipoprotein (HDL) enables the elimination of cholesterol from the cell. Today it is certainly clear that dyslipidemias are an important risk factor for cerebrovascular diseases, especially for ischemic stroke, and that the administration of drugs for dyslipidemias, especially statins, with appropriate treatment of arterial hypertension, diabetes, cessation smoking and weight maintenance, is crucial in the secondary prevention of ischemic stroke<sup>40</sup>.

This research is also confirmed by the European Guidelines for the Prevention of Cardiovascular Diseases, which were jointly developed by ten relevant European societies, including the European Stroke Initiative<sup>41</sup>.

Epidemiological studies show a strong association between cholesterol and atherosclerosis of the carotid artery determined by measuring the thickness of the intima-medial complex<sup>42</sup>.

Almost all large, randomized, double-blind, and placebo-controlled clinical trials with statins, based on results published in the last fifteen years, have clearly shown that statins can

prevent or reduce non-hemorrhagic strokes, or stroke, and mortality.

**Heart disease** - People who have any symptomatic or asymptomatic heart disease, regardless of blood pressure values, have twice higher risk to develop an ischemic stroke than people who do not have heart problems.

Cardiovascular diseases are, logically, connected with cerebral ischemia, considering that it is the same pathological process - atherosclerosis, which affects all blood vessels in the body, and is most often manifested in the coronary and cerebral arteries<sup>43</sup>.

There is a clear association between an increased risk of ischemic stroke and the following heart disease: atrial fibrillation, valvular heart disease, heart attack, coronary artery disease, congestive heart failure, electrocardiographically proven left ventricular hypertrophy, and possibly mitral valve prolapse.

Analysis of the database from the Johns Hopkins Hospital for Cardiac Surgery<sup>44</sup>, in which all patients were followed prospectively, provided very informative evidence related to the occurrence of stroke in this milieu<sup>45</sup>. In a total of 74% of patients, a stroke was registered on the day of the operation and in 91% within the first 3 days after the operation, which speaks in favor of the fact that the stroke is directly related to the operative procedure. Stroke in this group was found in 214 patients (3.6%), and neuroimaging findings showed acute infarction in 72%. As many as a quarter of these strokes were in the border cortical fields of the middle cerebral artery. Survival of stroke patients in this study was 67% in the first and 47% after 5 years, which is less than in the stroke group of the second



etiology. In addition, the results of a study by Lee et al. clearly established the understanding that severe systemic hypotension associated with a significant carotid stenosis can cause not only unilateral but also bilateral infarcts in the border cortical zones of the cerebral media artery<sup>46</sup>.

Bad life habits and association of risk factors - When risk factors for CAD or arteriosclerosis are observed, smoking, alcohol consumption, obesity and physical inactivity are classified as bad habits, but they are also risk factors that can be influenced.

The obtained data agree with the data from the literature on the harmful effects of cigarette smoking on the development and progression of atherosclerosis. First of all, the results of the Framingham study, which included 4255 male and female respondents, aged 36 to 68, who were followed for 26 years, indicate that smoking significantly contributes to stroke, and that the risk of stroke increases with the number of strokes per day smoked cigarettes.

Progression of atherosclerosis of the carotid arteries was found not only in active smokers but progression of atherosclerotic changes of the carotid arteries was also found in non-smokers who were exposed to passive smoking<sup>47</sup>.

Similar results were published in the Cardiovascular Health Study; the degree of carotid artery stenosis was higher in current than in former smokers, with a significant correlation between the degree of stenosis and the number of cigarettes smoked per day and years of smoking<sup>48</sup>. The obtained results speak in favor of the fact that the effect of smoking is reversible and should be an incentive for smokers to stop this bad habit.

In recent years, the connection between obesity and neurological diseases has been increasingly researched. Obesity is recognized as a clear risk factor for cardiovascular disease, however, the link between obesity and stroke is still not completely clear. A published guide by the Stroke Council of the American Heart Association characterizes obesity as a potential risk factor for stroke that can be influenced<sup>49</sup>.

In our study, obesity was slightly more common in the group of patients with subcortical infarction - 20 (50%) than in the group of patients with cortical cerebral infarction - 14 (35%).

The influence of arrogance on arteriosclerosis is indirect. The dominant site is a disproportionately large influence on the development of DM by increasing insulin resistance, which is almost proportional to the patient's body weight. This is understandable because obesity directly affects risk factors for cerebrovascular diseases, primarily hypertension, elevated cholesterol levels and glucose intolerance.

Research conducted in recent years has shown that heredity plays a significant role in the etiology of cerebrovascular diseases, and that many risk factors for stroke are genetically determined<sup>50</sup>.

Several studies have shown a clear role of genetic factors for all types of cerebrovascular disease, both ischemic and hemorrhagic.

Studies that have tried to bring the answer to the question of whether stroke is a genetic disease in itself have yielded controversial results. Analysis of our results has shown that more patients with a positive

family history were in the group with subcortical cerebral infarction - 24 (60%) than in the group of patients with cortical cerebral infarction - 17 (42.5%).

By analyzing the data from the inevitable Framingham study, a general risk profile for cerebrovascular diseases was defined, with the help of which it is possible to isolate those 10% of the members of the population who will later develop a stroke. This profile consists of five risk factors: elevated systolic blood pressure, elevated serum cholesterol, glucose intolerance, smoking, and electrocardiographically proven left ventricular hypertrophy.

This finding is important because according to data from the Framingham study, in patients who did not have any or had one of the valid risk factors, the risk of getting a stroke in five years is 22%, compared to the risk of 42% in individuals with three or four pronounced risk factors.

Therefore, it should be emphasized that the existence of several risk factors, their duration, as well as the expression of each factor separately, are positively correlated with the appearance of CAD.

## Conclusion

The results of this study can be used to define carotid artery disease in a population with risk factors. In our study group, prevalent patients were smokers, those with HLP and diabetes. Increased IMT is linearly correlated with smoking, HLP and HTA and carotid stenosis is correlated with HTA, HLP, DM and smoking. Our study has established that conventional risk factors such as hyperten-

sion, diabetes, smoking, and dyslipidemia are independently associated with a significant extracranial carotid artery stenosis (CAS). Prevalence of moderate stenosis increases with age in both men and women, but men at all ages have the higher prevalence estimates.

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