

# Risk factors for ischemic stroke in Bulgaria

Mihael Emilov Tsalta-Mladenov<sup>1,2</sup>, Silva Peteva Andonova<sup>1,2</sup>

<sup>1</sup>Department of Neurology and Neuroscience, Faculty of Medicine,  
"Prof. Paraskev Stoyanov" Medical University, Varna, Bulgaria

<sup>2</sup>Second Clinic of Neurology with ICU and Stroke unit,  
"St. Marina" University Hospital, Varna, Bulgaria

## ABSTRACT

**Background.** Stroke is a multifactorial disease with various clinical presentations ruled out by modifiable and non-modifiable risk factors (RF). Multiple vascular and behavioural factors lead to an increased risk of ischemic stroke, as they can differ in various countries. Understanding those factors may result in the implementation of strategies for screening, prevention, and reducing the overall risk of stroke. There is a lack of contemporary information regarding the RF for ischemic stroke (IS) in Bulgaria.

**Objective.** We aimed to determine the major potential RF for ischemic stroke in the Bulgarian population.

**Material and methods.** A prospective hospital-based case-control study was conducted between July 1, 2019, and June 30, 2020, at a tertiary care referral center for neurological disorders. We included cases with first-ever and recurrent stroke and stroke-free controls. Association between RF and IS was expressed in odds ratio (OR) through a 95% confidence interval (CI). Statistical significance was defined as a p-value of 0.05 or less.

**Results.** Overall 150 cases and 100 stroke-free participants were included. All risk factors were more prevalent in the case-group, except for dyslipidemia which had an inverse association with IS risk. The most significant RF for IS consisted of hypertension (OR, 28.78; 95% CI, 6.67 – 124.15) heart failure (OR, 15.25; 95% CI, 6.29-36.97), atrial fibrillation (OR, 11.29; 95% CI, 3.92-32.51), ischemic heart disease (OR, 5.83; 95% CI, 2.81-12.12), diabetes mellitus (OR, 2.65; 95% CI, 1.28-5.49), daily alcohol abuse with concentrate (OR, 9.39; 95% CI, 1.21-73.00) and current smoking (OR, 1.82; 95% CI, 1.00-3.32).

**Conclusions.** The results of this study confirm the significant contribution of modifiable RF, both behavioral and related to medical conditions. Early detection and management of the major stroke RF may result in lower stroke incidence. Therefore, implementations of strategies for screening and prevention are needed to reduce the overall risk of stroke.

**Keywords:** ischemic stroke, stroke, risk factors, case-control study, relative risk, odds ratio, Bulgaria

## INTRODUCTION

Stroke is a socially significant disease, ranked as the second most common cause of death and chronic disability in patients who survived the acute stage. Therefore, stroke is a disease of high public health importance with serious socio-economic consequences. The burden of stroke is expected to rise over the next decades because of demographic characteristics especially in developing countries (1).

Bulgaria is in one of the forefront places of stroke mortality in Europe, as the average mortality

rates are three times higher than in other European countries (2). According to The Global Burden of Diseases Study from 2016, about 38,000 people get a stroke in Bulgaria every year, and about 206,000 people live in the country with the consequences of a stroke (3).

Stroke is a multifactorial disease with various clinical presentations ruled out by modifiable and non-modifiable risk factors (4).

In 2010 the international study INTERSTROKE denoted 10 modifiable risk factors that account for up to 90% of all strokes (5). The most influential of them are hypertension, diabetes mellitus, atrial fi-

brillation, dyslipidemia, smoking, abnormal alcohol intake (6). The presence of one or a combination of these risk factors is associated with an increased risk and incidence of ischemic stroke. The strict control of these risk factors is associated with a reduced risk of cerebral infarction, as well as milder symptoms in the case of such (7). Non-modifiable factors include age, sex and race. Additionally, genetic factors can be found in 40% of idiopathic thromboembolic events. The most common causes for inherited thrombophilia are antithrombin III, protein C, protein S deficiency or a mutation in factor V Leiden (F V), factor II prothrombin (F II), plasminogen activator inhibitor (PAI) and methylenetetrahydrofolate reductase (MTHFR) genes (8). Other less-well documented risk factors include geographic location, socioeconomic status, air pollution and passive smoking. They are part of local and national campaigns related to promotion of higher physical activity, non-smoking in public places, reducing the amount of sugars in food and drinks and others (9).

We can prevent up to 80% of all stroke events by early detection of risk factors, treatment of diseases linked with increased cerebrovascular risk and lifestyle modifications (10).

The present study aims to identify, in a hospital-based case-control study, the prevalence and the relative importance of various major modifiable risk factors contributing to ischemic stroke in the Bulgarian population.

## MATERIAL AND METHODS

### Study design and participants

Participants in the present study are part of a wider prospective study of quality of life after ischemic stroke in which participants were recruited from July 1, 2019, to June 30, 2020. The study was done at Second Clinic of Neurology with ICU and stroke unit at “Sveta Marina” University Multiprofile Hospital for Active Treatment, which is the largest center for stroke treatment in Eastern Bulgaria. All of the participants signed informed consent before the analysis and the study was approved by the ethics committee of Medical University Varna.

### Inclusion and exclusion criteria

In this study were included patients with acute ischemic stroke – cases, and non-stroke patients –

controls. Our study is based on consecutive cases of ischemic stroke patients hospitalized in our department. We used the American Heart Association/American Stroke Association (AHA/ASA) definition of stroke (11). Patients with first-ever and recurrent stroke were included in the study.

Additional inclusion criteria for the cases – patients with ischemic stroke were the age of 18 years or more, acute onset of neurological symptoms lasting more than 24 hours, conducted neuroimaging examination of the head – computed tomography (CT) or magnetic resonance imaging (MRI) and signed informed consent. Exclusion criteria for cases were age under 18 years, lack of neurological symptoms or the presence of such was less than 24 hours, and refusal to sign an informed consent. Patients with a transient ischemic attack (TIA) were not included in the present study.

Controls were non-stroke patients and they were included if they were 18 years of age or older, who had no anamnestic or clinical data for a previous stroke, who had at least one modifiable risk factor for ischemic stroke and signed informed consent. Controls we excluded from the study when they were younger than 18 years of age, when they had neuroimaging data for acute stroke (ischemic or hemorrhagic), when anamnestic or clinical data for a previous stroke was available and when there was a refusal to sign an informed consent.

### Measurement of risk factors

All participants were interviewed by a neurologist in an as similar as possible manner to get information for comorbidities and behavioral risk factors for stroke. Demographic data, social history, and past medical records were also checked and collected. To obtain detailed information for the cases, relatives and care-givers were also interviewed. All participants underwent a medical assessment and examination including blood tests.

To accept the presence or absence of a certain risk factor, we used the following criteria:

- Hypertension – Patients enrolled in the study were diagnosed with hypertension if they were using regularly antihypertensive medications prior the enrolling in this survey, or if persistent values of systolic blood pressure > 140 and/or diastolic > 90 mmHg were reported during the hospital stay.

- Diabetes mellitus was considered when the participant was taking oral hypoglycemic drugs or insulin prior the enrolling in this survey or when the blood glucose levels were higher than 11.1 mmol/l in a random blood sample followed by a blood glucose profile.
- Atrial fibrillation was considered as a risk factor when an arrhythmia was present before the enrollment in the study or it was detected during the hospital stay by standard ECG, ECG monitoring, or Holter-ECG.
- Dyslipidemia has been reported in patients who were receiving statin or fibrate therapy before the enrollment in the study or when one or more of the following founding were detected in the lipid profile of the patient:
  - Total cholesterol values above 5.2 mmol/l;
  - LDL cholesterol above 2.6 mmol/l;
  - Triglycerides above 1.7 mmol/l;
  - HDL cholesterol less than 1.04 mmol/l;
- Smoking status – Smokers were categorized as non-smoker, current, and former smokers. Patients who had smoked tobacco in the past 3 months, including those who had quit in that period were classified as current smokers. These patients who had smoked in the past, but not in the last 3 months formed the group of former smokers. Smokers were further divided into groups according to the number of cigarettes smoked per day:
  - I group (light) – 1 to 5 cigarettes a day;
  - II group (moderate) – 6 to 14 cigarettes a day;
  - III group (heavy) – over 15 cigarettes a day;
- Alcohol consumption – Drinkers were categorized as never and currently drinking. Patients who we consuming alcohol were further divided into groups according to the UK alcohol guidelines (12):
  - Group I (Low alcohol consumption) – light alcohol (e.g. beer, wine) up to 3 glasses per week; concentrate (e.g. whiskey) daily intake up to 25 ml or 175ml per week;
  - Group II (Moderate alcohol consumption) – light alcohol between 4-6 glasses a week with at least 1 day weekly free of

alcohol; concentrate daily intake between 25 and 50 ml or 350 ml per week;

- Group III (Alcohol abuse) – light alcohol over 7 glasses a week without free of alcohol day; concentrate daily intake over 50 ml or 350 ml per week;

Additional comorbidities associated with higher cerebrovascular risk were also included in this research based on the medical documentation and the conducted consultations with relevant specialists.

### Statistical analysis

We analyzed data for an unmatched case-control study. The data were quantitative and obtained at a nominal, ordinal, interval, and ratio level. The statistical analysis was performed using the software programs SPSS, version 23.00 (IBM Statistics, USA) and GraphPad Prism, version 5.00 (GraphPad Software, San Diego California, USA). Regression analysis was performed to study the functional dependence between two or more variables (dependent and independent). The odds ratio was used to quantify the strength of the association between different factors and events. Confidence intervals (CIs) were calculated for odds ratios (OR; categorical data) and differences between means (continuous, normally distributed data). Statistical significance was defined as a p-value of 0.05 or less.

## RESULTS

### Baseline characteristics

This study included 150 cases of ischemic stroke and 100 unmatched stroke-free controls. In the group with an ischemic stroke, there were 116 (77.3%) with first-ever stroke and 34 (22.7%) patients who had a previous stroke. The mean age of stroke patients was  $68.8 \pm 11.4$ , as for the control group-  $57.2 \pm 13.0$ . The gender distribution showed no significant difference in the control group, but in the stroke group the male: female ratio was 0.6. Detailed socio-demographic characteristics for the participants are shown in Table 1.

### Main results

The distribution of the main cerebrovascular risk factors in the two groups shows noteworthy

**TABLE 1.** Sociodemographic characteristics of case and control patients

Sociodemographic characteristics				
	Cases (n=150)		Controls (n=100)	
	N	%	N	%
Age				
• Mean (years)	68.8 ± 11.4		57.2 ± 13.0	
Sex				
• Male	90	60.0	48	48.0
• Female	60	40.0	52	52.0
Residence				
• Town	121	80.7	81	81.0
• Village	29	19.3	19	19.0
Education level				
• Primary	45	30.0	12	12.0
• Secondary	63	42.0	50	50.0
• Tertiary	42	28.0	38	38.0
Profession				
• Currently working	40	26.7	61	61.0
• Not working	110	73.3	39	39.0
Marital status				
• Living with someone	133	88.7	94	94.0
• Living alone	17	11.3	6	6.0
Ischemic stroke				
• First-ever stroke	116	77.3	N/A	N/A
• Recurrent stroke	34	22.7	N/A	N/A

differences. In the stroke-group, there are higher frequencies of the traditional vascular risk factors except for dyslipidemia.

The most constant risk factor for ischemic stroke was hypertension, observed in 148 (98.7%) of the cases and 72 (72.0%) of the stroke-free patients. This risk factor was significantly more widespread in the case-group ( $p < 0.001$ ).

In the second place is dyslipidemia reported as in 112 (74.7%) stroke patients and 84 (84.0%) of the controls, with no significant difference between groups ( $p = 0.081$ ). The higher frequency of this risk factor in the control group is evident, which is probably a consequence of various interacting populational, socio-economic, and genetic factors.

In the third place is the atrial fibrillation observed in 48 (32.0%) of the cases and only 4 (4.0%) of the stroke-free patients with a significant intergroup difference ( $p < 0.001$ ). A subsequent risk factor is diabetes mellitus found in 37 (24.7%) stroke patients and only 11 (11.0%) of the controls ( $p = 0.008$ ).

There is also a statistically significant higher incidence of other cardiovascular diseases in patients with stroke. The foremost of them is heart failure, present in 74 (49.3%) of the cases, and 6 (6.0%) of the stroke-free participants ( $p < 0.001$ ). Further-

more ischemic heart disease ( $p < 0.001$ ) and Coronary artery disease ( $p = 0.032$ ) are also more common in the stroke population. Regarding the data for previous myocardial infarction, a higher frequency was observed in the group of patients, but without statistical significance ( $p = 0.054$ ).

The detailed distribution of modifiable cerebrovascular risk factors in patients with stroke (cases) and stroke-free participants (controls) in the present study are summarized in Table 2.

**TABLE 2.** Distribution of the main modifiable cerebrovascular risk factors of case and control patients

Cerebrovascular risk factors distribution					
	Cases (n=150)		Controls (n=100)		P-value
	N	%	N	%	
Hypertension	148	98.7	72	72.0	<b>&lt;0.001</b>
Atrial fibrillation	48	32.0	4	4.0	<b>&lt;0.001</b>
Myocardial infarction	9	6.0	1	1.0	0.054
Ischemic heart disease	59	39.3	10	10.0	<b>&lt;0.001</b>
Heart failure	74	49.3	6	6.0	<b>&lt;0.001</b>
Coronary artery disease	14	9.3	2	2.0	0.032
Right-to-left cardiac shunt	1	0.7	1	1.0	1.000
Cardiac valve disorder	4	2.7	1	1.0	0.651
Diabetes mellitus	37	24.7	11	11.0	<b>0.008</b>
Dyslipidemia	112	74.7	84	84.0	0.081
Systemic embolism	10	6.7	2	2.0	0.131
Cancer	10	6.7	11	11.0	0.250

From the lifestyle risk factors, smoking was more common among the stroke patients than in the controls, as there was no difference in the smoking status – former ( $p = 0.005$ ) or current smoker ( $p = 0.048$ ). In the case-group 47 (31.3%) were currently smoking and 48 (32.0%) were former smokers. Whereas in the control group the smoking status was respectively 20 (20.0%) currently smoking and 16 (16.0%) were former smokers. Non-smokers were only 55 (36.7%) of the participants with ischemic stroke and 64 (64.0%) of the controls and ( $p < 0.001$ ). In the case-group dominating part of the participants were heavy smokers. This trend is evident both for the current and former smokers ( $p < 0.001$ ).

Additional information concerning passive smoking (at work or home) was also obtained in this study. Higher levels of passive smoking were rendered in account in both groups, with a predominance in the case-group with a statistically significant difference ( $p < 0.001$ ).

The second most important lifestyle risk factor is alcohol consumption. The results for this risk factor are not as definite as for smoking, but there are some differences. There is no significant difference in the rate of participants who drink alcohol, but still, there is prevalence in the case-group – 102 (68.0%) as for the control-group it is 59 (59.0%) ( $p=0.146$ ). More interesting are the findings regarding the severity of alcohol intake. The most significant differences are found in groups with alcohol abuse. As for the weekly abuse with light alcohol, there were 31 (20.7%) patients with ischemic stroke and 9 (19.0%) of the control-group ( $p = 0.014$ ). The same trend is observed for the daily abuse with concentrate – 13 (8.7%) of the stroke patients and only 1 (1.0%) of the stroke-free participants ( $p = 0.010$ ).

Detailed information regarding the lifestyle modifiable risk factors in patients with stroke (cases) and stroke-free participants (controls) in the present study are summarized in Table 3.

**TABLE 3.** Distribution of modifiable lifestyle risk factors of case and control patients

Lifestyle risk factors distribution					
	Cases (n = 150)		Controls (n = 100)		P-value
	N	%	N	%	
Smoker (current and former)	95	63.3	36	36.0	<b>&lt;0.001</b>
Non-Smoker	55	36.7	64	64.0	<b>&lt;0.001</b>
Current smoker	47	31.3	20	20.0	<b>0.048</b>
• Light smoking	1	0.7	2	2.0	0.360
• Moderate smoking	19	12.7	15	15.0	0.604
• Heavy smoking	26	17.3	3	3.0	<b>&lt;0.001</b>
Former smoker	48	32.0	16	16.0	<b>0.005</b>
• Light smoking	6	4.0	7	7.0	0.296
• Moderate smoking	13	8.7	5	5.0	0.269
• Heavy smoking	30	20.0	4	4.0	<b>&lt;0.001</b>
Passive smoking	104	69.3	45	45.0	<b>&lt;0.001</b>
Alcohol consumption	102	68.0	59	59.0	0.146
No alcohol intake	48	32.0	41	41.0	0.146
Light alcohol (Weekly)					
• Low consumption	20	13.3	18	18.0	0.311
• Moderate consumption	22	14.7	20	20.0	0.273
• Abuse	31	20.7	9	9.0	<b>0.014</b>
Concentrate (Daily)					
• Low consumption	1	0.7	2	2.0	0.360
• Moderate consumption	14	9.3	3	3.0	0.052
• Abuse	13	8.7	1	1.0	<b>0.010</b>
Concentrate (Weekly)					
• Low consumption	28	18.7	18	18.0	0.890
• Moderate consumption	15	10.0	6	6.0	0.265
• Abuse	5	3.3	1	1.0	0.243

To analyze the risk for ischemic stroke, we compared the data from the risk profiles in patients with ischemic stroke and those in the control group. Statistically significant differences were observed concerning hypertension, atrial fibrillation, ischemic heart disease, heart failure, diabetes mellitus, and to a lesser extent, Coronary artery disease ( $p < 0.05$ ).

From all the factors we studied, hypertension is associated with the highest risk of ischemic stroke - 28.78 (95% CI 6.67 – 124.15) times. Presence of heart failure and atrial fibrillation are associated with 15.25 (95% CI 6.29-36.97) and respectively 11.29 (95% CI 3.92-32.51) times higher risk for ischemic stroke. The presence of diabetes mellitus is associated with 2.65 (95% CI 1.28-5.49) times increased risk, while ischemic heart disease and Coronary artery disease are associated with respectively 5.83 (95% CI 2.81-12.12) and 5.04 (95% CI 1.12-22.70) times higher risk.

In this study dyslipidemia, as a risk factor for cerebrovascular disease, did not show a statistically significant increase in the overall risk for ischemic stroke ( $p = 0.086$ ).

The study also showed a statistically significant higher risk in the presence of behavioral risk factors ( $p < 0.05$ ). The data for smoking (both current and former) has the greatest importance – 3.07 (95% CI 1.81 – 5.18) times increased risk of ischemic stroke. There is also evidence of higher risk in the subgroup of former smokers compared to current ones. Regarding passive smoking, there is a relatively high risk for ischemic cerebrovascular events, comparable to active smoking- 2.76 (95% CI 1.63-4.67).

The risk from weekly abuse with light alcohol is 2.63 (95% CI 1.19-5.81) times higher, and for concentrate- 3.41 (95% CI 0.39-29.67) times. Daily alcohol abuse with concentrate is associated with more than 9 times higher risk of cerebral infarction- 9.39 (95% CI 1.21-73.00).

All investigated factors predicting the risk of ischemic stroke are presented in Table 4.

## DISCUSSION

In this study, we demonstrated the most common modifiable risk factors for ischemic stroke in the Bulgarian population.

The most widespread traditional risk factors were hypertension (98.7%), followed by dyslipi-

**TABLE 4.** Factors predicting ischemic stroke risk

Factors predicting ischemic stroke risk in the Bulgarian population					
Risk factor	Odds ratio (OR)		P-Value	Relative risk (RR)	
	OR	95% CI		RR	95% CI
Hypertension	28.78	6.67 - 124.15	<0.001	1.37	1.21 – 1.55
Atrial fibrillation	11.29	3.92 - 32.51	<0.001	1.41	1.26 - 1.59
Myocardial infarction	6.32	0.79 - 50.68	0.054	1.05	1.01 - 1.10
Ischemic heart disease	5.83	2.81 - 12.12	<0.001	1.48	1.28 - 1.71
Heart failure	15.25	6.29 - 36.97	<0.001	1.85	1.57 - 2.19
Coronary artery disease	5.04	1.12 - 22.70	<b>0.032</b>	1.08	1.02 - 1.15
Right-to-left cardiac shunt	0.66	0.04 - 10.75	1.000	1.00	0.97 - 1.02
Cardiac valve disorder	2.71	0.30 - 24.63	0.651	1.02	0.98 - 1.05
Diabetes mellitus	2.65	1.28 - 5.49	<b>0.008</b>	1.18	1.05 - 1.32
Dyslipidemia	0.56	0.29 - 1.07	0.086	0.63	0.37 - 1.07
Systemic embolism	3.50	0.75 - 16.33	0.131	1.05	1.00 - 1.10
Cancer	0.58	0.24 - 1.42	0.250	0.95	0.88 - 1.03
Smoker (current and former)	3.07	1.81 – 5.18	<0.001	1.76	1.32 – 2.35
Current smoker	1.82	1.00 - 3.32	<b>0.049</b>	1.57	0.991 - 2.48
Former smoker	2.47	1.31 - 4.66	<b>0.005</b>	2.00	1.205 - 3.32
Passive smoking	2.76	1.63 – 4.67	<0.001	1.54	1.210 - 1.96
Alcohol abuse – light alcohol (weekly)	2.63	1.19 - 5.81	<b>0.016</b>	2.30	1.143 - 4.61
Alcohol abuse – concentrate (weekly)	3.41	0.39 - 29.67	0.266	3.33	0.395 - 28.11
Alcohol abuse – concentrate (daily)	9.39	1.21 – 73.00	<b>0.032</b>	8.67	1.151 - 65.21

demia (74.7%), heart failure (49.3%), ischemic heart disease (39.3%), atrial fibrillation (32.0%) and diabetes mellitus (24.7%). Regarding the lifestyle risk factors it is notable that 63.3% of the stroke patients were smokers at some point in their lives – 31.3% current smokers and 32.0% former. The portion of passive smokers was also notably high – 69.3%. Alcohol consumption was reported in more than two-thirds of the patients with is-

chemic stroke (68.0%). The results are consistent with previous reports for our population (13,14). Besides this, there are some differences in comparison with other European countries shown in Table 5 (15-23).

In our population, there is a much higher prevalence of hypertension, dyslipidemia, and lifestyle risk factors such as smoking and abnormal alcohol intake. Both hypertension and dyslipidemia, tend

**TABLE 5.** Stroke risk factors in other European countries

Comparison of frequencies of major vascular risk factors in different European countries										
Author	Year	Country	Age mean	HTN (%)	AF (%)	DM (%)	DL (%)	CAD (%)	CS (%)	AA (%)
Grau A. (15)	2001	Germany	65.9	66.6	26.1	28.5	35.3	24.0	27.8	10.3
Béjot Y. (16)	2008	France	74.2	62.1	N/A	17.2	45.5	N/A	23.8	N/A
Vega T. (17)	2009	Spain	61.2	58.2	N/A	26.0	29.8	29.8	14.4	10.9
Malmivaara A. (18)	2015	Finland	72.6	70.9	9.1	20.0	N/A	13.3	N/A	N/A
		Hungary	69.5	76.5	4.5	21.7	N/A	6.9	N/A	N/A
		Italy	73.8	65.4	3.7	23.2	N/A	3.6	N/A	N/A
		The Netherlands	71.6	77.2	2.7	19.6	N/A	N/A	N/A	N/A
		Sweden	76.2	70.3	9.0	16.8	N/A	N/A	N/A	N/A
Correia M. (19)	2016	Portugal	75.4	72.8	18.5	24.9	45.2	N/A	19.3	N/A
Tsivgoulis G. (20)	2017	Greece	75.0	81.1	34.3	26.3	67.0	16.9	22.5	17.3
Köseoğlu Toksoy C. (21)	2018	Turkey	63.3	85.5	N/A	33.7	48.2	N/A	26.5	N/A
Rostohar-Bijelić B. (22)	2019	Croatia	71.6	81.6	19.5	24.1	66.9	N/A	15.5	11.5
Clery A. (23)	2019	England	75.3	66.1	13.8	22.3	N/A	N/A	28.8	54.4

HTN – hypertension; AF – atrial fibrillation; DM – diabetes mellitus; DL – dyslipidemia; CAD – coronary artery disease; CS – current smoker; AA – alcohol abuse

to be with higher prevalence in the Balkan countries in comparison to other European countries.

This study also provides estimates of the relative risk for ischemic stroke concerning different modifiable risk factors. Our data represent hypertension, atrial fibrillation, ischemic heart disease, heart failure, coronary artery disease diabetes mellitus, the status of current, former and passive smoker, and abnormal alcohol intake, as significantly associated with ischemic stroke risk factors.

Hypertension is the most important modifiable risk factor associated with the highest risk for ischemic stroke among our population (OR 28.78, 95% CI 6.67 – 124.15). Meta-analyses of randomized-control trials (RCTs) have reported a decrease of the total risk for first-ever and recurrent stroke in 30-40% only by administering adequate blood pressure (BP) lowering therapy (24). It is widely known that blood pressure reduction of 10 mmHg systolic and 5 mmHg diastolic is linked with a 40% reduction in the stroke risk. Besides this, every 10 mmHg increase in the systolic blood pressure is linked to an increased risk of 4.2% (25). Furthermore, stroke risk in hypertensives is associated with co-existence with other risk factors, which tends to follow an additive model (26). This is the reason why we should address not the single factor but the whole risk profile of the patient.

Dyslipidemia is found in 74.7% of all participants with ischemic stroke, but there was also a high prevalence in the stroke-free population. Therefore it was found that this risk factor was not a significant predictor for ischemic stroke in this study (OR, 0.56; 95% CI, 0.29-1.07) ( $p = 0.086$ ). In previous studies in our country was found a prevalence of dyslipidemia in up to 66.7% of the female and 69.0% of the male population (27). According to the EUROASPIRE IV study, this risk factor is found in more than 86% of the population with high vascular risk in our country (28). Nevertheless, cholesterol levels are determined by multiple genetic, environmental, and dietary factors. This might be one of the possible reasons for the higher prevalence of dyslipidemia in our population. Despite the variations in the lipid profile, this risk factor is still associated with negative health-related outcomes. Therefore early detection of dyslipidemia and normalization of the lipid levels are advisable for the general population (29).

Atrial fibrillation is associated with a 10 times higher risk for ischemic stroke in our population

(OR, 11.29; 95% CI, 3.92-32.51). One-third of all ischemic strokes due to cardio-embolism have a history of atrial fibrillation (30). The proportion of cardio-embolic associated with atrial fibrillation increases progressively with age as it accounts for up to 36% of the cases who are aged 80-89 years (31). Due to the aging population in our country, the percentage of patients with atrial fibrillation is increasing. In previous studies, a high risk for embolism and low levels of anticoagulation were reported in patients of 75 years of age or more (32). Another possible reason might be a higher prevalence of thrombosis of the left atrium (33). Because of all these facts, it is required early screening, detection, and initiation of therapy that aims to reduce the risk of AF-associated stroke (34).

Diabetes mellitus is responsible for 2.65 times higher risk of ischemic stroke (OR, 2.65; 95% CI, 1.28-5.49). Hyperglycemia and diabetes mellitus are both risk factors for stroke and predictors of poor prognosis in stroke patients (OR = 1.87; 95% CI 1.43–2.45) (35). They are also associated with an increased risk of fatal outcome (36). Therefore strict control of the glucose levels in all patients is advisable. Optimal antidiabetic treatment in combination with lifestyle changes such as weight control, diet, and increasing physical activities can be beneficial in high-risk individuals (37).

Current smokers are at 1.82 times greater risk for ischemic stroke (OR, 1.82; 95% CI, 1.00-3.32). With even higher risk are those who are passive smokers (OR, 2.76; 95% CI, 1.63-4.67). In current smokers, there is 2-4 times increased risk for stroke in comparison with non-smokers (38). Another study reports 6 times increased risk of ischemic stroke in the group of smokers (39). There is a growing interest in passive smoking as a risk factor in the last decades. There are reports of 1.5 times increased stroke risk in passive smokers (OR, 1.51; 95% CI, 1.14-1.99) (40). The more cigarettes being smoked, the higher risk of stroke is estimated. For example, the use of 1-10 cigarettes/day is associated with 2.2 times increased risk, 11-20 – 2.5 times, 21-39 – 4.3 times, and for 40 or more cigarettes/day – 9.1 times increased stroke risk (41). Cigarette smoking is a well-established risk factor for stroke and many other vascular diseases. There is the utmost need for reinforcement of the awareness of healthcare organizations and the population for the reduction of tobacco use in

order to reduce the burden of related diseases (38).

The association between alcohol intake and risk of ischemic stroke was addressed in numerous studies and it remains controversial (42). We found that daily alcohol abuse with concentrate (OR, 9.39; 95% CI, 1.21-73.00) and weekly abuse with light alcohol (OR, 2.63; 95% CI, 1.19-5.81) are associated with a statistically significant increase in the stroke risk. Previous case-control studies demonstrated the U-shaped relationship between alcohol consumption and stroke. Low and moderate alcohol intake has a protective effect, while alcohol abuse is associated with a higher risk of stroke (43). However, due to the well-described harmful effects of heavy alcohol consumption on vascular and non-vascular conditions, all patients should be encouraged to control this lifestyle risk factor. Care should be taken on a populational level when making general recommendations about safe levels of alcohol intake because it would do substantially more harm than good (44).

We acknowledge some limitations in our study. First, the study was conducted in a tertiary care referral center for neurological diseases, and may, therefore, be biased toward more disabling stroke cases with more severe comorbidities. We studied a relatively small population divided into an unequal ratio of patients with ischemic stroke (cases)

and stroke-free controls. Furthermore, we did not include all lifestyle risk factors like physical activity, diet, body mass index (BMI), and there were no risk factors related to women's reproductive health such as anti-contraceptive intake. A larger prospective study might be of interest to address the association between ischemic stroke and other well-described risk factors, which did not reach statistical significance or were not analyzed in our study.

## CONCLUSIONS

The results of this study are in coherence with others focusing on the risk profile for ischemic stroke. Our investigation is in confirmation of the significant contribution of hypertension, atrial fibrillation, diabetes mellitus, ischemic heart disease, heart failure, coronary artery disease, cigarette smoking, and alcohol abuse for the significant increase of the total ischemic stroke risk in the Bulgarian population. The high prevalence and importance of all the investigated risk factors also suggest the need for a multidisciplinary approach to ischemic stroke patients. It is of utmost importance to implement strategies for prevention on these pathologies and conditions to reduce the overall risk of ischemic stroke.

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