The present study in Bulgarian volunteers aged 45-55 years focuses on the type and frequency of some vascular risk factors (VRF); it analyzes physical data and results of instrumental investigations (ophthalmoscopy, electrocardiography, Doppler sonography) as well as magnetic resonance imaging (MRI). The study participants have neither subjective memory complaints nor previous cerebrovascular and cardiovascular incidents. The neurological examination and the mental status is normal and VRF are not considered to affect their normal daily living. The arterial hypertension (I degree), dyslipidemia and increased LDL-cholesterol correlate with the pathological findings from Doppler/MRI. The regression model explains 35% of the dispersion in statistics and correctly classifies 76.8% of the observations as independent prognostic factors for the presence of abnormal findings from Doppler/MRI at the age from 45 to 55 years, which corresponds to subclinical cerebrovascular disease.

INTRODUCTION

There is an increasing number of epidemiological and clinical cohort studies of complications as well as of mortality, due to a stroke in the middle-aged population. A stroke is a frequent cause of urgent hospitalization, motor disability (44 million individuals with permanent disability) and vascular dementia. It is ranked as the third cause of death (5.5 million per year).1,2 The incidence of arterial hypertension in Bulgaria at the age 25-64 is 40.1%; at the age over 45 – 50.3%, and many of the hypertensive patients have also other VRF.3 The incidence of diabetes mellitus in Bulgarians is 9.6% (56.7% in males and 43.3% in females).4 The presence of metabolic syndrome is more common in males - both overweight (55.29%) and with a normal body weight (21.2%).5 Following a study of 2040 hospitalized patients having a stroke 32.03% were under the age of 60.6 Another study highlights that in the age from 45 to 55 the percentage of patients suffering a stroke increases significantly by 37.8% to 50 years of age and 62.2% to 55 years, the mortality for the entire decade being 3.5%.7 In order to predict the hidden cerebrovascular risk in middle adulthood, we have performed this study of the factors related to the vascular risk status (VRS) abnormalities and we have analyzed their relationships with Doppler sonography and brain magnetic resonance imaging (DSG/MRI) findings, corresponding to functional and structural disorders in cerebrovascular disease.

AIM

To study the vascular risk factors and to determine their significance in regard to the hidden cerebro-
vascular risk in Bulgarian volunteers aged 45-55 without neurological and psychiatric disorders and with normal daily living.

MATERIALS AND METHODS
The study includes 98 consecutive persons from the 45-55 age group. The inclusion criteria were: (1) normal neurological examination and mental status; (2) medical records from general practitioner, concerning the health condition; (3) signed written informed consent. Exclusion criteria were: (1) previous cerebrovascular and/or cardiovascular accident; (2) neuro-infection sequelae or previous traumatic brain injury; (3) epilepsy, migraine; (4) current psychotic or affective disorder; (5) subjective memory complaints; (6) subjects dropped out of the study before its end.

Methods: 1. Clinical interview collecting data about physical and demographic characteristics of all participants, presence of family history of vascular diseases and bad habits - smoking, alcohol abuse, non-prescribed medications; 2. Document analysis for VRF; 3. Physical and neurological examination; 4. Laboratory tests: complete blood count; biochemistry – blood glucose, urea, creatinine, fibrinogen, ASAT, ALAT, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (TGL); Vitamin B12 serum levels, thyroid stimulating hormone (TSH) 5. Instrumental studies: standard 12-channel ECG - conducted with Schiller AT-2 plus, evaluated by a cardiologist; ophthalmoscopy – performed using YZ11D ophthalmoscope by a certified specialist; Extra- and transcranial DSG, performed with cerebrovascular Doppler with several neurosonographic parameters of the severity of arterial stenosis, according to accepted criteria for vascular pathology (low or non-significant - less than 50% and high-grade stenosis - 55-90% and occlusions); Neuro-imaging – MRI of the brain with MAGNETOM Aera magnetic resonance tomograph from Siemens (1.5 teslas). The reading of the tomograms using Software syngo MR D 13A software is performed according to accepted criteria for classification of brain structure parenchymal injuries as per the European Task Force on Age-Related White Matter Changes (ARWMC) rating scale. All participants are divided into two groups according to the MRI results – subjects with pathological changes and subjects with normal findings.

STATISTICAL ANALYSIS
We used descriptive statistics, alternative analysis, Mann-Whitney test, regression analysis, graphic analysis. For null hypothesis significance level we have assumed p<0.05. The findings from the Doppler

Table 1. Comparison of demographic data, physical, laboratory and instrumental findings

| Indices                      | Presence  | Absence  | U    | p     |
|------------------------------|-----------|----------|------|-------|
| Age 47 (under 50 yrs)        | 47 (48.0±5.05) | 51 (52.6±2.0) | 0.56 | >0.05 |
| Arterial hypertension 29     | 29 (29.5±4.61) | 69 (70.6±4.61) | 6.89 | <0.001|
| Dyslipidemia 28              | 28 (28.5±4.56) | 70 (71.5±4.56) | 6.65 | <0.001|
| Dysglycemia 20               | 20 (20.4±4.1)  | 78 (79.6±4.1)  | 10.2 | <0.001|
| Hypercholesterolemia 45      | 45 (46.8±5.09) | 51 (53.1±5.09) | 0.87 | >0.05 |
| Increased TGL 33             | 33 (34.3±4.85) | 63 (65.6±4.85) | 4.55 | <0.001|
| Decreased vit. B12 23        | 23 (38.9±6.35) | 36 (61.0±6.35) | 2.45 | <0.05 |
| Increased TSH 9              | 9 (14.0±4.35)  | 55 (85.9±4.35) | 11.54 | <0.001|
| Family history of CVD 59     | 59 (60.2±4.9)  | 39 (39.8±4.9)  | 2.94 | <0.01 |
| Obesity 68                   | 68 (69.4±4.66) | 30 (30.6±4.66) | 5.84 | <0.001|
| Increased waist circumference| 74 (77.9±4.26) | 21 (21.1±4.26) | 9.34 | <0.001|
| Smoking 54                   | 54 (55.1±5.02) | 44 (44.9±5.02) | 1.44 | >0.05 |
| Alcohol intake 50            | 50 (51.0±5.05) | 48 (48.9±5.05) | 0.28 | >0.05 |
| Abnormal ECG 11              | 11 (11.7±3.32) | 83 (88.3±3.32) | 16.31 | <0.001|
| Abnormal ophthalmoscopy 17   | 17 (26.9±5.59) | 46 (73.0±5.59) | 5.82 | <0.001|
| Abnormal DSG/MRI 24          | 24 (27.4±4.78) | 63 (72.4±4.7)  | 6.66 | <0.001|
sonography and MRI have been combined into one composite indicator, showing the presence of structural and/or functional brain changes (DSG/MRT).

RESULTS

DEMOGRAPHIC CHARACTERISTICS

The male participants are 38 (38.8%) with mean age 50.37±3.24 years, the women are 60 (61.2%), mean age 50.07±3.28 years. 27 (27.6%) of the subjects studied have secondary education and 71 (72.4%) - higher education.

VASCULAR RISK FACTORS

Table 1 shows the distribution of the main VRF in the studied group.

Doppler sonography of extracranial and intracranial brain vessels is performed in 66 participants. In 11 (7 males and 4 females) (16.7%) there are atherosclerotic changes of the cerebral vessels. In 1 male and 1 female, 50% stenosis of the M1 segment of the middle cerebral artery is detected. In 5 males and 3 females, single atheromatous plaques are found in the carotid arteries, and 1 has discreetly increased hypertensive-type resistance indices of the two internal carotid arteries.

Seventy-one participants have gone through a magnetic resonance (MRI) study. In 17 of them (23.94%) lacunar infarcts in deep brain structures are found; 4 (5.64%) have mild brain atrophy. No leukoaraiosis has been detected in our study.

Table 1 shows that arterial hypertension (1st degree), dyslipidemia, dysglycemia, increased TGL, decreased vitamin B₁₂ level, increased TSH and pathological findings from instrumental and MRI studies are found in a significantly smaller group of studied participants. Only the positive family history of CVD, the obesity and the increased waist circumference are present in a larger group of participants. The established dependencies are presented in Table 2.

The likelihood to find pathological results from DSG/MRI in VRF carriers is 2.416 times greater than in the subjects without VRF; in participants with hypertension, this probability is 2.722 times higher than in subjects with normal blood pressure; in diabetics there are pathological findings of DSG/MRI 4.229 times more frequently than in those with normal blood sugar; in volunteers with dyslipidemia the probability is 4.347 times higher than in those with normal blood lipids; in subjects with increased LDL-cholesterol this likelihood is 4.349 times higher than in those with normal LDL-values and in those with abnormally increased TGL levels the probability is 2.678 times greater than

Table 2. Relationship (Odds Ratio) between the VRF and the abnormal findings from DSG/MRI

| Characteristics / VRF          | Relative share of established (+) findings from DSG/MRI | Odds Ratio (95% CI) | P     |
|-------------------------------|--------------------------------------------------------|---------------------|-------|
| Gender (males/females)        | 34.3% / 32.8%                                          | 0.934 (0.384-2.268) | 0.880 |
| Age (under and over 50 yrs)   | 26.1% / 40.4%                                          | 1.923 (0.798-4.630) | 0.145 |
| *VRF                          | -                                                      | 2.416 (1.538-3.795) | 0.001 |
| *Arterial hypertension (no/yes)| 26.9% / 50.0%                                          | 2.722 (1.064-6.966) | 0.037 |
| *Diabetes mellitus type 2 (no/yes) | 29.8 % / 63.6%                                    | 4.229 (1.133-15.790) | 0.032 |
| *Dyslipidemia (%) [no/yes]    | 23.9% / 57.7%                                          | 4.347 (1.665-11.347) | 0.003 |
| *TGL (no/yes)                 | 26.2% / 45.2%                                          | 2.678 (1.248-5.747) | 0.011 |
| Increased waist circumference (no/yes) | 19.0% / 36.2%                                      | 2.415 (0.731-7.975) | 0.148 |
| Ophthalmoscopy (no/yes)       | 31.8% / 37.5%                                          | 1.286 (0.389-4.245) | 0.680 |
| Family history (no/yes)       | 29.7% / 35.7%                                          | 1.313 (0.538-3.209) | 0.549 |
| Obesity (no/yes)              | 30.0% / 34.9%                                          | 1.252 (0.491-3.196) | 0.638 |
| Smoking (no/yes)              | 32.5% / 32.1%                                          | 1.091 (0.662-1.798) | 0.733 |
| Decreased Vit. B₁₂ (no/yes)   | 5.55% / 15.38%                                         | 0.520 (0.173-1.567) | 0.245 |
| Increased LDL-cholesterol (no/yes) | 43.5% / 28.6%                                      | 4.349 (1.447-13.074) | .009 |

OR=odds ratio with a 95% confidence interval.
in participants with normal TGL levels (Table 2).

The strongest prognostic factors for pathological findings from DSG/MRI are the arterial hypertension (AH), dyslipidemia and the levels of LDL-cholesterol. The regression model explains 35% (Nagelkerke R Square) of the statistical dispersion and correctly classifies 76.8% of the observations (Table 3) as independent prognostic factors for the presence of abnormal findings from DSG/MRT.

**DISCUSSION**

CVD is most common in adults over 65 years of age. The risk is also present in younger individuals antihypertensive therapy, thus maintaining the AH in the age limits. However, in our hypertensive patients the likelihood of finding abnormal DSG/MRI results is 2.962 higher than that in non-AH (1.101-8.040), p<0.033. Such a positive correlation between AH and findings from brain’s MRI (silent brain infarcts [SBI], and cortical atrophy) has been reported by other authors who accept the presence of subclinical CVD in “young adults” (under 63 years of age).

The established dyslipidaemia in 28 (28.57%) of the examined patients also correlates positively and significantly with abnormal findings from DSG and/or MRI.

**Table 3. Independent prognostic factors for the presence of abnormal DSG/MRI findings**

| Independent variable (prognostic factor) | Accuracy 76.8% | OR (95% CI) | p |
|-----------------------------------------|----------------|-------------|---|
| Arterial hypertension                    | 7.129 [1.447-35.108] | 0.016 |
| Dyslipidemia                             | 4.409 [1.229-15.820] | 0.023 |
| LDL-cholesterol                          | 6.965 [1.863-26.045] | 0.004 |

Positive findings from DSG and/or MRI (n = 93 cases) are the binary code variable (positive = 1; negative = 0) where “positive” means “pathological” and “negative” means normal result.

in the previous decades (40-60 years), especially in presence of VRF - arterial hypertension, heart disease, smoking, dyslipidemia, impaired glucose tolerance, alcohol abuse and metabolic syndrome. This is the basis of our study. We have studied the vascular risk status in a middle adulthood group of Bulgarians trying to determine the risk of CVD. Our results concerning VRF (AH-I degree, dyslipidemia, dysglycemia), as well as abnormal findings from instrumental examinations, show that VRF are present in significantly fewer participants compared with data reported by other authors, but they have similar characteristics to those described by them.

Positive family history for cardiovascular and CVD have been found in 59 (60.2%) participants. The difference in the frequency of abnormal DSG/MRI findings in participants with a family history of CVD and those without such a history is very low.

Over one third (29.6%) of the individuals tested are with documented AH (1st degree), 10 (34.48%) have isolated systolic hypertension. This percentage is lower than the frequency reported for AH in Bulgaria for the age of 25-64 years – 40.1%. We explain this by the fact that our study participants actively go through regular and adequate according to population studies, the frequency of the metabolic syndrome (MetS) worldwide ranges from 20% to 30.8%. Metabolic syndrome with three components has been found in 28 (28.57%) participants. The three-component MetS has been established by Bulgarian authors in 26.8% and the four-component MetS in 6% of the population. In our study, 68 (69.4%) have abnormally increased BMI and 74 (77.89%) have increased waist circumference (the main components of MetS). In
31.8% of these MetS carriers there are abnormal asymptomatic findings of DSG/MRI responding to ischemic brain disturbances.

Ophthalmoscopy has revealed that in 17 individuals there are abnormal changes in ocular fundi and 37.5% of them were found to have abnormal results from DSG/MRI.

From the reported dependencies between the investigated VRF and the abnormal DSG/MRI findings only AH, dyslipidemia and increased LDL-cholesterol are independent prognostic factors for the presence of abnormal DSG/MRI findings and respectively subclinical CVD.

CONCLUSION

The study of 98 Bulgarian volunteers in the age range from 45 to 55 years, without neurological and mental disturbances and preceding cerebrovascular or cardiovascular incidents has revealed different types, frequencies as well as the significance of the VRF, which increase the risk for development of CVD. Only 27.6% of those surveyed have not been registered with VRF.

Vascular risk factors: AH, dyslipidemia, dysglycemia, increased triglycerides, LDL-cholesterol, abnormal BMI, increased waist circumference, alcohol intake, low vit. B12 levels and the presence of a family history of CVD have been shown to be significant for subjects studied in 45-55 years age range.

Of all significant VRF that correlate positively with abnormal DSG/MRI findings in a regression model only AH, dyslipidemia and LDL-cholesterol have been classified as 78.2% independent prognostic factors for abnormal DSG/MRI findings, respectively for subclinical CVD.

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Факторы риска сосудистых заболеваний среди добровольцев среднего возраста из Болгарии

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Настоящее исследование среди добровольцев в возрасте 45-55 лет из Болгарии посвящено типу и частоте некоторых факторов риска сосудистых заболеваний (ФРСЗ); оно анализирует физические данные и результаты как инструментальных исследований (офтальмоскопия, электрокардиография, допплеровская сонография), так и магнитно-резонансной томографии (МРТ). У участников исследования не было ни субъективных жалоб, ни предыдущих цереброваскулярных и сердечно-сосудистых событий. Неврологическое обследование и психический статус являются нормальными, а ФРСЗ не влияют на их повседневную жизнь. Артериальная гипертензия (первой степени), дислипидемия и повышенный LDL-холестерин коррелируют с патологическими допплеровскими / МРТ находками. Модель регрессии объясняет 35% распределения в статистике и правильно классифицирует 76,8% наблюдений в качестве независимых прогностических факторов наличия допплеровских / МРТ аномальных результатов в возрасте от 45 до 55 лет, что соотносится с субклиническим цереброваскулярным заболеванием.

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