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DEPARTMENT OF CARDIOLOGY AND RHEUMATOLOGY
INTERVENTIONAL CARDIOLOGY CLINIC

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Concomitant Carotid Pathology in Invasive Cardiac Diagnostics

AUTHOR'S DISSERTATION SUMMARY

for the acquisition of the educational and scientific degree of '**doctor of philosophy'** in the field of higher education No 7. Public health and sports, professional trend No 7.1. Medicine and scientific speciality of cardiology

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Varna

2026

The present dissertation has been elaborated in the Department of Internal Medicine, Clinic of Interventional Cardiology at the Faculty of Medicine of the Medical University "Prof. Paraskev Stoyanov" of Varna.

The dissertation contains 118 type-written pages and is illustrated with 11 tables and 21 figures. The reference list includes 201 primary sources, of which seven by Bulgarian authors and 194 by foreign authors.

The dissertation has been discussed and forwarded to a public defence by the Departmental council of the Department of Internal Medicine of the Medical University "Prof. Paraskev Stoyanov" of Varna according to article No 24, paragraphs 6 and article 30, paragraph 3 of the Statute-book for the Application of the Law for development of the academic staff in the Republic of Bulgaria and article 68, paragraph 1 of the Statute-book for development of the academic staff in the Medical University of Varna based on report No ……/……. by Assoc. Prof. Atanas Angelov Atanasov, MD, PhD, Head of the Department of Internal Medicine of the Medical University of Varna, according to Decision of the Faculty Council of the Faculty of Medicine, protocol No …/ …….

The public defense of the dissertation will be held on 10.07.2026 starting at 12 p.m. at St. Marina University Hospital of Varna based on Order No. R-….. of ……2026 of Prof. Dimitar Ivanov Raykov, MD, PhD, DSc, Rector of the Medical University "Prof. Paraskev Stoyanov" of Varna in front of a scientific jury consisting of:

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Dissertation-related materials have been published on the Internet site of the Medical University "Prof. Paraskev Stoyanov" of Varna and are at the disposal in the Research Department of the Medical University "Prof. Paraskev Stoyanov" of Varna.

CONTENTS

Abbreviations used

IHD – ischemic heart disease

CAD – coronary artery disease

CAS – carotid artery stenosis

CT – computer tomography

CTA – computerized tomography angiography

SCAG – selective coronary angiography

MRI – nuclear magnetic resonance

CEA – carotid endarterectomy

CAS – carotid artery stenting

CABG - coronary artery bypass graft

CIMT – carotid intima-media index

ACS – acute coronary syndrome

3VD – three-vessel disease

PAD - peripheral arterial disease

IBS - ischemic heart disease

BMI – body mass index

LDL – low-density lipoproteins

ECAS - extracranial atherosclerosis

ICAS - intracranial atherosclerosis

TIA – transient ischemic attacks

ACA - anterior cerebral artery

MCA - middle cerebral artery

PCA – posterior cerebral artery

AF - atrial fibrillation

PFO – persistent foramen ovale

IS - ischemic stroke

DSA - digital subtraction angiography

AH – arterial hypertension

CEUS – contrast enhanced ultrasound

1. INTRODUCTION

1.1. Actuality of the problem - epidemiology, complications, disability, economic burden

The diagnosis of accompanying carotid pathology during cardiac invasive diagnostics is, usually, an additional incidental finding, except in cases where subaortic angiography is purposefully performed to establish carotid pathology. These are patients with a realized cerebrovascular accident or evidence of cerebrovascular pathology. Patients with a realized stroke and residual withdrawal symptoms have an acquired degree of disability and a changed lifestyle.

Ischemic stroke (IS) is the most common cause of death and disability in economically advanced countries. Over 25% of patients die within the first year and over 50% develop serious neurological deficits.

Stroke has become a clearly defined medical emergency, as it has been declared at least partially curable within the therapeutic window. If revascularization is not achieved, or if it occurs too late, the chances of recovery decrease and severe complications associated with devastating neurological effects become more likely.

Over the past teb years, Bulgaria has consistently been at the top of the list in terms of mortality from strokes - every fifth or sixth man and every fourth or fifth woman in the country dies from them, while in Europe - every tenth man and every seventh woman does. According to data from the National Center for Public Health and Analysis, in 2019, 58,128 people suffered from stroke, of which 52,891 (90%) were IS and 5,237 (10%) were hemorrhagic or unspecified strokes with an overall mortality rate of about 10%.

According to data from the Expert Club for Economics and Politics (ECIP), between 400-450 million leva per year go to stroke treatment, which is 5% of the NHIF budget. This includes hospital treatment and immediate care for patients after an acute stroke. This amount is a significant item in health spending in Bulgaria.

Bulgaria has among the lowest healthcare costs after a stroke among other countries in Central and Eastern Europe - an average of about 11 Euros per person per year spent on treatment and rehabilitation of patients after an acute stroke.

Over one-third of all strokes are due to atherosclerotic changes in the extracranial cerebral vessels (carotid and vertebral arteries). Carotid atherosclerosis is an independent predictor of increased mortality.

Patients with asymptomatic atherosclerotic carotid stenosis in 50% of cases die within five years from stroke, myocardial infarction, or vascular gangrene.

1.2. Risk factors for the development of coronary and carotid atherosclerosis

Commonly known risk factors for the development of atherosclerosis play a major role in the stenotic process of the carotid arteries. Of these, arterial hypertension (AH) is the main risk factor for stroke development. Advanced age, the presence of more risk factors, and the progression in the severity of carotid obstruction lead to a significant increase of stroke risk.

At the same time, carotid stenotic pathology is one of the strongest predictors of the presence of coronary artery disease and, in particular, stenosis of the left main coronary artery.

An inverse relationship has also been observed - multivessel coronary disease (3VD) is often combined with carotid artery stenoses.

Literature data indicate that coronary atherosclerosis is an independent predictor of carotid pathology and the severity of carotid pathology is related to the number and extent of coronary artery involvement.

When forming a risk profile of patients with ischemic heart disease (IHD), the following risk factors were analyzed: AH, total cholesterol, diabetes mellitus, weight, smoking, and age.

This gave us reason to conduct the present study with a view to improving the diagnostic protocol for establishing carotid atherosclerosis in patients hospitalized for cardiac symptoms, as well as to confirm the relationship described in the literature between the severity of carotid and coronary atherosclerosis. By analyzing the risk factors, we set ourselves the goal of forming a risk profile of a patient with a high degree of probability of coronary pathology.

1.3. Conclusions

The carotid and coronary arteries are the two systems most commonly affected by the atherosclerotic process. Literature data show that both arterial systems share similar characteristics, risk factors, and mechanisms for the formation of atherosclerotic plaque despite the different location. For this reason, the detection of carotid stenoses during cardiac invasive diagnostics is important for risk stratification in patients with coronary stenosis, especially in those with multivessel coronary disease.

Coronary atherosclerosis is an independent predictor of carotid atherosclerotic pathology and the severity of carotid atherosclerosis is related to the number and extent of coronary artery involvement.

Currently, there is no single diagnostic method that can reliably determine each plaque as stable or unstable (colour Doppler, computed tomography angiography (CTA), magnetic resonance imaging, MRI).

Invasive digital subtraction angiography (DSA) remains the golden standard for the diagnosis of vascular diseases. This is a method used to validate the results obtained from non-invasive examinations. With the improvement of diagnostic catheters and the methodology for carotid angiography, the incidence of neurological events after this examination has decreased according to Johnston *et al*. from 4%-5% to less than 0.5%. This in turn gives grounds for individual centres to assess the severity of carotid atherosclerosis based on the information obtained from carotid angiography, in combination with the data obtained from the preceding non-invasive duplex Doppler examination.

The decision to use a diagnostic technique depends on the training and qualifications of the specialists working with it. The combination of different imaging techniques is the prerogative of the team of specialists working in the respective vascular centre.

The combination of diagnostic instrumental studies can help us make a decision about intervention, especially in asymptomatic patients with multi-focal atherosclerosis.

2. GOAL, TASKS, HYPOTHESES

2.1. Purpose of the dissertation

To establish and validate how the severity of cardiovascular pathology correlates with the severity of carotid atherosclerosis, in order to optimize the preventive and diagnostic-therapeutic approach in patients with coronary heart disease.

2.2. Tasks

1. Analysis of risk characteristics in groups with cardiovascular and cerebrovascular atherosclerosis.
2. To verify the presence of exposure dependence between risk factors in groups with different degrees of cerebrovascular and cardiovascular atherosclerosis.
3. To test the presence of a correlation between cardiovascular and cerebrovascular pathology.

2.3. Hypotheses

1. There is a moderate degree of correlation between the severity of coronary and carotid atherosclerosis.

2. There is an exposure dependence between risk factors in patients with cardiovascular and cerebrovascular atherosclerosis.

3. MATERIAL AND METHODS

3.1. Nature and type of the study, location, observation period

A pre-planned study was conducted in 299 patients admitted to the Second Cardiology Clinic at St. Marina University Hospital of Varna during the period from 2016 to 2019 for diagnostic clarification. The present study was conducted on a selected hospital cohort, not on a representative population sample, and included 299 patients with data on ischemic heart disease (IHD) and cerebrovascular symptoms, established on the basis of anamnesis and/or medical documentation available. The study design is mainly prospective and retrospective, in some of the patients meeting the inclusion criteria.

The study was approved by the Research Ethics Committee of the Medical University of Varna, where it was registered as a diagnostic study.

Each patient participated voluntarily after completing written informed consent.

Indications for hospitalization were assessed by a prehospital cardiologist.

3.2. Selection of the subjects studied

3.2.1. Inclusion criteria

The study group included patients who met the following criteria:

1. Age over 18 years
2. Informed consent obtained for anesthesia, invasive and non-invasive imaging studies and surgical treatment after the patient has been properly informed about the planned diagnostic procedures and the potential risks associated with them
3. Presence of risk characteristics assessed by a pre-hospital or hospital cardiologist, giving grounds for conducting the invasive diagnostics. History of cerebrovascular symptoms and/or the presence of medical documentation in patients admitted for invasive evaluation due to suspected IHD are grounds for inclusion in the selected cohort

3.2.2. Exclusion criteria

Exclusion criteria for invasive diagnostic procedure:

1. Presence of diseases related to coagulopathies
2. Intolerance to heparin, aspirin, and clopidogrel

3. Acute coronary syndrome requiring immediate intervention
4. Peripheral vascular disease leading to inability to perform catheter studies.

3.3. Clinical protocol - general principles and stages

In all the patients, there is registration of:

- gender, age, anthropometric data (height and weight)
- body mass index (BMI) is also calculated (patients are grouped into three groups: normal BMI - at values between 18 and 24.9 kg/m^2; overweight - at values between 25 and 29.9 kg/m^2, and obesity at values above 30 kg/m^2 (according to the international standards of the World Health Organization from 2000)
- lipid profile: total cholesterol and LDL cholesterol levels; patients are classified as having hypercholesterolemia based on total cholesterol levels >5.18 mmol/L and LDL-C levels ≥2.6 mmol/L (>100 mg/dL) (according to European recommendations for the treatment of dyslipidemias
- indicators for assessing renal function: creatinine level; with serum creatinine values ≥97 (women)/115 (men) μmol/L, GFR <90 mL/min/1.73 m^2, patients are classified as having impaired renal function (according to international recommendations for the treatment of chronic renal failure)
- based on the complete hospital and prehospital medical documentation, the presence or absence of AH is determined. Patients are classified as having AH at values above 139/89 mm Hg (according to the European recommendations for the treatment of AH). The severity of AH is classified according to the number of medications needed to achieve adequate blood pressure control in each specific case
- smoking status at the time of the study: patients are classified as current smokers or non-smokers.
- presence or absence of diabetes mellitus (according to European recommendations for the treatment of cardiovascular diseases in patients with diabetes mellitus)
- data on the presence of supraventricular arrhythmia attacks or current atrial fibrillation (AF) are retrospectively collected and/or documented
- IS occurred.

Coronary and carotid angiography is performed in all the patients to determine carotid status and the presence of significant coronary pathology.

Echocardiography is performed in all the patients.

In 70 patients from the study cohort, an ultrasound examination of the carotid arteries is also performed.

3.4. Study endpoints

The endpoints of the current study are focused on examining the relationship between coronary and carotid atherosclerosis.

Primary endpoint: Assessment of the combined presence and extent of cardiovascular and cerebrovascular pathology in the studied patients

Secondary endpoint: Analysis of the distribution of cardiovascular risk factors and assessment of their impact on the severity and combination of coronary and carotid pathology

Objective: To optimize the preventive and diagnostic-therapeutic approach.

3.5. Methods

3.5.1. Diagnostic protocol - non-invasive methods

- 12-lead ECG (Schiller device) - in all patients
- Transthoracic echocardiography ("Philips Epiq" with cardiac transducer S5-1 and X-51)

In all the patients within the same hospital stay, usually, before the invasive diagnostic procedure, transthoracic echocardiography was performed to determine left ventricular muscle mass as an independent prognostic predictor. The Devereux formula (g) was used as a method to determine the presence of left ventricular (LV) hypertrophy by comparing the echocardiographically calculated LV muscle mass and the anatomical LV muscle mass.

The echocardiographic examination was performed according to established standards by positioning the transducer in the third intercostal space in the left parasternal position, with image acquisition along the long axis of the heart and acquisition of the above parameters at the maximum perpendicular position of the one-dimensional beam to the walls of the LV at the level of the chordae, immediately below the level of the mitral leaflets in the left lateral position.

Through two-dimensional (2D) echocardiography, single-plane (M-mode) echocardiography for each patient, the following were measured:

- LV end-diastolic diameter (LVEDD) (mm),
- LV end-systolic diameter (LVESD) (mm),
- interventricular septal thickness at end-diastole (IVSd) (mm),
- LV free wall thickness at end-diastole (LWPWd) (mm).

Based on the derived parameters, the following were calculated:

- LV ejection fraction (LVEF) (%) according to the Teicholz formula,

- left ventricular muscle mass according to the Devereux formula (g) (LVM = 1.04 (LVIDp+PWTP+IVSTp)3-(LVIDp)3) - 14 g), which is indexed to the patient's body surface area.

❖ Laboratory panel - venous blood testing in the University Clinical Laboratory using an OPTIMA device - Kone Lab 601 Finland. Blood samples were taken in the morning on an empty stomach and tested the same day without being subjected to prolonged storage by freezing. In case of suspected acute coronary syndrome (ACS), cardiac biomarkers were tested serially at the second, sixth, and twelfth hour.

❖ Hematology panel: erythrocytes (RBC), hematocrit (HCT), mean corpuscular volume (MCV), index (MCH), index (MCHC), erythrocyte distribution width (RDW), leukocytes (WBC), and platelets (PLT).

❖ Hemostasis panel: platelet count, activated partial thromboplastin time (APTT), fibrinogen (Fbg), prothrombin time (PT), and ratio (INR).

❖ Biochemical panel: glucose (GLUC), potassium (K), calcium (Ca), sodium (Na), chlorine (Cl), creatinine (CREA), urea (UREA), lactate dehydrogenase (LDH), total protein (TPROT), total bilirubin (T BIL), uric acid (UR AC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), creatine kinase (CK), MB-fraction of creatine kinase (CK-MB), total cholesterol (CHOL), triglycerides (TRIG), HDL-cholesterol (HDL), and troponin.

❖ Ultrasound examination of the carotid arteries.

In 70 of the patients with established significant carotid pathology, an ultrasound examination of the carotid arteries was also performed. For ultrasound diagnostics, a "Philips Epiq" ultrasound machine with a linear transducer L12–3 was used. Using pulse Doppler, the blood flow velocity in the area of stenosis was measured. This is the maximum peak systolic velocity (PSV). Depending on the PSV indicators, over 120 cm/s or over 250 cm/s are divided into low-grade and high-grade stenoses.

The diameter of the unchanged common carotid artery in the bulbar area (C) and the diameter of the maximally stenotic artery (A) were measured and the European ECCT methodology was used to determine the degree of stenosis.

%stenosis = CA/Cx100.

To determine the degree of carotid stenosis, a second, so-called distal NASCET method is also applicable, reflecting the ratio of the diameter of the residual lumen in the stenotic area to the diameter of the distal patency area of the internal carotid artery, which is constant to the base of the skull.

According to the results obtained, we divided the patients into four groups: group 1 - ≥50% (moderate stenosis), group 2 - ≥70% (high-grade stenosis), group 3 - ≥80% (critical stenosis) and group 4 - 100% (total occlusion).

3.5.2. Diagnostic protocol - invasive methods

- ***Coronary and carotid angiography***

The Siemens Artis angio system was used for invasive diagnostics.

All thee patients underwent diagnostic selective coronary arteriography (SCAG). The radial artery dextra (after Allen's test) with a 5 or 6 Fr arterial introducer was used for the main access. This makes the procedure much more tolerable for the patient and less risky compared to the femoral access. The radial access used has established itself as the preferred vascular access in the cardiac catheterization laboratory. It avoids forced immobilization of the patient, local vascular complications and hematomas in the puncture area. At the end of each procedure, a hemostatic device - radi-stop - is placed. Using a universal diagnostic catheter (Tiger 5F), the right and left coronary arteries are selectively cannulated. The assessment of coronary pathology was performed according to the internationally accepted classification for CAD: single-, double-, tri-vessel or multivessel, depending on the presence of angiographically documented stenosis ≥50% affecting a main coronary vessel (LM, LAD, LCA, and RCA). Reduction of the vascular lumen is angiographically assessed by the atherosclerotic plaque in seven grades: 0-24% - unevenness/insignificant plaque, 25-49% - lesion, >50% - intermediate stenosis, 75-89% - high-grade stenosis, 90-98% - critical stenosis, 99% - subtotal occlusion, and 100% - complete occlusion. Hemodynamically significant coronary stenosis = degree >50% of LM and LAD in the proximal segment and >75% of LCA, RCA, LAD in the medial and distal segments, and their large branches with a diameter >1.5mm.

Using the same or another diagnostic catheter appropriate for the specific anatomy, supraaortic angiography was also performed during the study to identify pathology along the course of the carotid arteries with selective injection of a minimal amount of additional contrast (between 5 and 8 mL for each carotid artery).

3.5.3. Statistical methods

Descriptive statistical methods were used, grouping the data for quantitative and qualitative variables. Quantitative variables were summarized with means and standard deviations or with median and interquartile range. Qualitative variables were presented in a summarized form with relative shares.

Parametric and nonparametric tests were used to test hypotheses.

Analysis of variance was applied to compare quantitative variables in more than two samples.

Spearman's correlation analysis was used to test the hypothesis of a correlation between the severity of CAD and carotid stenosis. A multiple logistic regression model was tested to determine the severity of CAS, controlling for the severity of CAD, gender, age, smoking, diabetes mellitus, AH, hyperlipidemia, CKD, and history of stroke. A two-tailed test was performed in all analyses, and statistical significance was assumed at $p<0.05$.

The statistical package IBM SPSS (SPSS Inc., Chicago, IL) vers. 19.0 was used.

The results are presented through tables and figures prepared with Microsoft Excel.

4. RESULTS AND DISCUSSION

4.1. General characteristics of the subjects studied

The total number of subjects who met the inclusion criteria in the study was 299, of whom 187 (62.5%) were men and 112 (37.5%) were women. A description of the baseline characteristics of the patients and a comparison by gender are presented in tables 1 and 2.

Table 1. General characteristics of the studied group of patients

Characteristics	Women (n=112)	Men (n=187)	Total (n=299)	p value
	mean (SD)	mean (SD)	mean (SD)	
Age [years]	64.8 (7.93)	62.9 (8.69)	63.6 (8.45)	**0.049**
BMI [kg/ ^{m2}]	29.7 (4.98)	28.7 (4.21)	29.1 (4.53)	0.062
BSA [^{m2}]	2.6 (0.22)	2.9 (0.26)	2.8 (0.31)	< **0.001**
Total cholesterol [mmol/L]	4.9 (1.33)	4.8 (1.28)	4.9 (1.29)	0.8
LDL-C [mmol/L]	2.7 (1.10)	2.8 (1.04)	2.8 (1.06)	0.272
Creatinine [mmol/L]	75.8 (20.14)	91.6 (32.2)	85.7 (29.3)	<**0.001**
LVEDD [mm]	47.9 (6.11)	52.2 (5.69)	50.6 (6.20)	<**0.001**
IVSd [mm]	12.5 (1.69)	12.9 (1.97)	12.7 (1.88)	0.145
LVPWd [mm]	12.6 (1.63)	13.0 (1.79)	12.8 (1.75)	**0.046**
LVEF% [%]	59.3 (7.81)	54.5 (10.1)	56.3 (9.58)	<**0.001**
Number of medications for hypertension	3.3 (0.9)	3.0 (1.0)	3.1 (0.97)	**0.012**

* BMI - body mass index; BSA - body surface area; LDL-C - low-density lipoprotein cholesterol; LVEDD - left ventricular end-diastolic diameter; IVSd - interventricular septal end diastole; LVPWd - left ventricular posterior wall end diastole; LVEF% - left ventricular ejection fraction percentage.

Table 2. Analysis of the studied group of patients depending on the presence of the main risk factors

Characteristics	Women (n=112)	Men (n=187)	Total (n=299)	p value
	n (%)	n (%)	n (%)	
AH	111 (99.1)	183 (97.9)	294 (98.3)	0.654
Diabetes mellitus	44 (39.3)	66 (35.3)	110 (36.8)	0.284
Smoking	24 (21.4)	80 (42.8)	104 (34.8)	< **0.001**
CKD Creatinine ≥97 (women)/115 (men) μmol/L	7 (6.3)	26 (13.9)	33 (11.0)	0.055
Atrial fibrillation	21 (18.8)	41 (21.9)	62 (20.7)	0.558
CAD	57 (50.9)	146 (78.1)	203 (67.9)	< **0.001**

In our cohort of 299 patients, there was no recorded incident related to the extension of the diagnostic coronary procedure into the extracranial vessel basin. No embolic incidents were recorded.

The attached data show that this is a high-risk group, with an average age of over 60 years, almost all (98.3%) with AH and a relatively large proportion of patients with diabetes mellitus (table 2). Men are older, have higher values of creatinine, LVEDD, LVEF%, a larger proportion of them are smokers and a significantly larger proportion have coronary disease. A larger proportion of men also have CKD, although the difference with women is not significant. A large proportion of patients in the studied group have coronary pathology and coronary atherosclerosis - a total of 203 (67.9%), of which mainly men - 146 (78.1%).

4.1.1. Distribution according to the presence of carotid stenotic pathology

In order to determine the peculiarities of the risk profile of patients with different accompanying carotid atherosclerosis, the following three groups are defined:

Group A - patients with at least one carotid stenosis ≥50% in the carotid basin;

Group B - patients without significant stenoses (≥50%) in the carotid basin, but with at least one insignificant (<50%) atherosclerotic plaque in the carotid arteries;

Group C - patients with no visible atherosclerotic changes in the carotid basin.

Of the 299 patients studied, 134 patients (44.8%) had significant carotid stenosis (≥50%) and, accordingly, fell into the defined group A.

Almost one third - 87 patients (29.1%) have atherosclerotic changes in the carotid vessels, narrowing <50% of their lumen, therefore, they are included in group B. Thus, a total of 221 patients (73.9%) have atherosclerosis of the carotid arteries (table 3). In 78 patients (26.1%) no changes in the inner lumen of the extracranial vessels were detected - they form group C.

4.1.2. Distribution according to the number of affected carotid arteries

Patients from groups A and B with carotid stenosis, regardless of its severity - above 50% or below 50%, a total of 221, are presented in table 3 according to whether one or both arteries are affected by atherosclerotic changes.

Table 3. Distribution of patients with carotid stenosis according to the number of affected arteries

Number of affected vessels	Group A (stenosis ≥50%)	Group B (stenosis <50%)	Total
	n (%)	n (%)	n (%)
One artery	106 (79.1)	62 (71.3)	168 (76.0)
Two arteries	28 (20.9)	25 (28.7)	53 (24.0)
Total	134 (100.0)	87 (100.0)	221 (100.0)

The results show that in the presence of high-grade stenosis, one of the carotid arteries is more often affected, although the differences are not statistically significant (p=0.182).

In patients with significant carotid stenosis (≥50%), unilateral involvement was found in 79.1% of the cases, while bilateral involvement was observed in 20.9%. Similarly, in patients with stenosis <50%, unilateral involvement was present in 71.3% and bilateral one in 28.7%.

The results obtained show that unilateral carotid involvement is the dominant pattern regardless of the severity of stenosis. There is no trend towards an increase of the frequency of bilateral involvement in the patients with significant carotid stenosis. On the contrary, the relative proportion of bilateral involvement is numerically higher in patients with stenoses below 50%, suggesting that the spread of the atherosclerotic process in terms of the number of affected vessels does not necessarily follow the severity of the stenosing lesion.

4.1.3. Risk profile of patients depending on the presence of carotid stenosis

Table 4 compares Group A (n=134) and Group B (n=78) depending on the presence of carotid atherosclerosis and the presence of the main risk factors. The comparative analysis of patients depending on the presence of carotid atherosclerosis revealed statistically significant differences in a number of demographic and clinical indicators (Table 4) .

Table 4. Comparison of patient groups depending on the presence of carotid atherosclerosis and the presence of the main risk factors

Characteristics	Group A (n=134) (stenosis ≥50%)	Group B (n=78) (without stenoses)	p-value
Age	65.8 (7.83)	61.2 (8.9)	< **0.001**
Gender Men Women	88 (65.7) 46 (34.3)	39 (50.0) 39 (50.0)	**0.026**
BMI	28.5 (4.07)	29.2 (4.41)	0.062
Total cholesterol	4.7 (1.29)	4.9 (1.29)	0.066
LDL cholesterol	2.6 (0.99)	2.9 (1.18)	**0.039**
Creatinine	92.2 (37.5)	78.4 (16.9)	**0.001**
Number of hypertension medications	3.5 (0.67)	2.5 (1.00)	**<0.001**
Smoking	25 (18.7)	31 (39.7)	**<0.001**
Diagnosed diabetes	62 (46.3)	17 (21.8)	**0.002**
Hypercholesterolemia	36 (26.9)	29 (37.2)	**0.045**
AH	134 (100.0)	75 (96.2)	**0.043**
AF	23 (17.2)	15 (19.2)	0.168
CKD	21 (15.7)	5 (6.4)	**0.032**
IS	35 (26.1)	7 (9.0)	**0.001**

1. Patients with hemodynamically significant carotid stenoses ≥50% (Group A) were statistically significantly older compared to patients without carotid stenoses (65.8±7.83 versus 61.2±8.9 years, p<0.001).

2. A statistically significant difference in gender distribution was found between the two groups, with males predominating in patients with significant carotid atherosclerosis (65.7% versus 50.0%, p=0.026).

3. In terms of laboratory parameters, patients with carotid atherosclerosis had statistically significantly lower LDL-cholesterol values (2.6±0.99 versus 2.9±1.18 mmol/L, p=0.039), as well as higher serum creatinine values (92.2±37.5 versus 78.4±16.9 μmol/L, p=0.001).

4. Patients with significant carotid stenosis used a greater number of antihypertensive medications needed to achieve blood pressure control compared to patients without stenosis (3.5±0.67 versus 2.5±1.00, p<0.001), which indirectly reflects more difficult control of arterial hypertension and higher cardiovascular risk.

5. Diabetes mellitus was significantly more common in patients with carotid atherosclerosis (46.3% versus 21.8%, p=0.002), as was CKD (15.7% versus 6.4%, p=0.032).

6. Patients with significant carotid stenosis had a higher incidence of IS (26.1% versus 9.0%, p=0.001).

7. Of interest is the higher prevalence of smoking in patients without significant carotid stenosis (39.7% versus 18.7%, p<0.001), as well as the higher relative share of hypercholesterolemia in the same group (37.2% versus 26.9%, p=0.045), which at first glance seems paradoxical given the known role of these factors in atherogenesis. This fact can, probably, be explained by the influence of additional factors such as drug therapy, selection effect, or differences in the duration of exposure to risk factors.

8. No statistically significant differences were found between the two groups in terms of BMI, total cholesterol, and AF (p>0.05).

The results obtained show that advanced age, male gender, diabetes mellitus, CKD, and more severe AH are associated with significant carotid atherosclerosis in the studied population.

P. Antova and M. Staneva (2023) found that males are more common among patients with peripheral atherosclerosis. The explanation for this fact is that men visit a doctor 2.9 times more often than women.

According to literature data from foreign authors, males are more often affected by carotid atherosclerosis. Data from the TROMSØ Study by E. B. Mathiesen *et al.* (2001) show that carotid stenosis occurs more often in men - in 3.8% (between 3.2% and 4.6% at 95% CI) compared to women - in 2.7% (between 2.2% and 3.3% at 95% CI; p=0.001).

Results where males are more often affected by carotid atherosclerosis were also found by M. P. da Rosa *et al*. (2013). In 455 patients referred for coronary bypass surgery, 65.6% were men. In preoperative screening, carotid stenosis was diagnosed in 18.7%. Carotid stenosis ≥50% in patients referred for coronary bypass was independently associated with higher in-hospital mortality (12%) and it is an independent predictor of increased mortality (p=0.005).

4.1.4. Distribution of the group with carotid pathology according to the presence of risk characteristics and coronary pathology

Arterial hypertension (blood pressure values above 139/89 mm Hg) is part of the risk profile of over 98% of the studied population, making it the most common risk factor in the studied patients (table 4).

We compared the three groups with different severity of carotid stenosis in terms of the number of medications needed to achieve blood pressure control.

Figure 1 demonstrates the clear relationship between the severity of AH defined as the number of medications required to achieve control, and the severity of atherosclerotic changes in the carotid arteries. The distribution in group A is particularly indicative, in which there are no patients achieving control without or with one medication only.

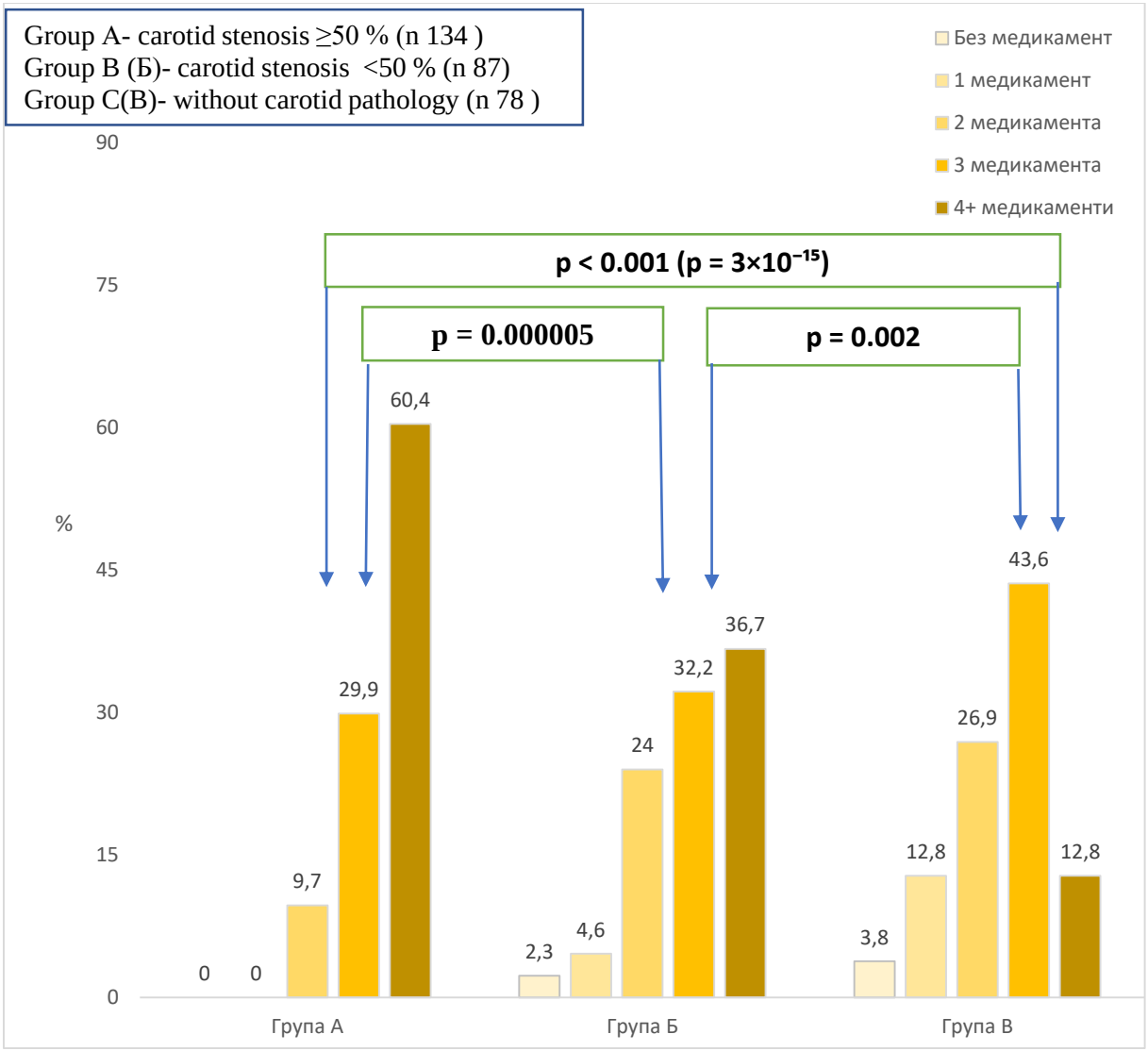

Figure 1. Distribution of different severity forms of AH according to the number of medications needed to control it in groups with different degrees of carotid atherosclerosis

1. A highly statistically significant difference (p=0.000005) was found between patients with significant carotid stenosis ≥50% (Group A) and patients with insignificant carotid pathology (Group B) indicating that patients with more severe carotid atherosclerosis require more intensive antihypertensive therapy.

2. A statistically significant difference (p=0.002) was observed between patients with carotid plaques <50% (Group B) and patients without carotid pathology (Group C) which suggests that even in the early stages of the atherosclerotic process, there is a need for more complex control of AH.

3. The most pronounced differences were observed between patients with significant carotid stenosis (Group A) and patients without carotid pathology (Group C) ($p<0.001$; actual $p=3\times10^{-15}$) thus confirming a strong relationship between the severity of carotid atherosclerosis and the need for multicomponent antihypertensive therapy.

4. There is a clear trend for the increased number of antihypertensive medications used with increasing severity of carotid atherosclerosis. The proportion of patients requiring combined antihypertensive therapy with two, three or more medications is increasing, which, indirectly, reflects more severe and more difficult to control AH.

5. In Group A (significant carotid stenosis ≥50%), no patients were identified in whom blood pressure control was achieved without drug therapy or with monotherapy.

The results obtained show a relationship between the severity of AH and more pronounced atherosclerotic changes in the carotid arteries, and support the literature data on the role of AH as one of the main risk factors for the development and progression of carotid atherosclerosis.

The comparison of the risk characteristics of the three defined subgroups (group A, group B, and group C) depending on the severity of carotid artery involvement, such as the degree of narrowing, shows reliable differences in the percentage distribution of the various risk factors in the individual groups, but without a logical connection with the degree of involvement of the carotid basin by the atherosclerotic process (table 5).

Table 5. Risk characteristics of the study group (n=299)

Groups	Known AH	Known diabetes	Current smokers	LDL-C ≥2.6 mmol/L	Creatinine ≥97-115 mol/L
Total group n=299	98.3%	36.8%	34.8%	68.9%	11.0%
Group A ≥50%	100.0%	46.3%	18.7%	73.9%	15.7%
Group B <50%	96.2%	21.8%	39.7%	60.3%	6.4%
Gr.C = 0%	97.7%	35.6%	55.2%	69.0%	8.0%
Gr.A vs Gr.B; p value	NS	NS	<0.00001	NS	NS
Gr.A vs Gr.B; p value	0.02	0.00033	0.0007	0.039	0.048
Gr.B vs Gr.C; p value	NS	NS	0.048	NS	NS

A certain, albeit paradoxical logic can be found in the percentage distribution of current smokers in the three defined groups. They are most numerous in the group without changes in

the carotid vessels (group C) and decrease with increasing severity of carotid pathology. Our explanation of this paradoxical fact is the following: considering the average age of the patients in the study and the known fact that smokers, usually, start with this disease at a young age, most likely, the stress associated with the appearance of symptoms caused by carotid pathology is the basis for making the decision to quit smoking.

Another explanation for the smoking paradox is that the study includes data on smoking at the time of the study only. The analysis does not include a pack of years before the study - the criterion was not initially included in the study design. As a risk factor for the development of carotid and coronary pathology, smoking shows moderate statistical significance (p=0.027, table 9).

Literature data from foreign studies show the relationship between smoking and carotid atherosclerosis.

According to G. S. Tell *et al*., the presence of hemodynamically significant ≥50% stenosis of the internal carotid artery increases from 4.4% in non-smokers to 7.3% in former smokers.

H. R. Müller *et al.* describe similar results with a statistically significant association between smoking and carotid atherosclerosis.

W. Li *et al*. (2024) establish that smokers have an increased risk of developing carotid atherosclerosis.

Given the set goal, we decided to compare the severity of the risk profile defined as the accumulation of the risk factors studied by us with the severity of carotid vessel involvement by the atherosclerotic process. In the study, we included AH and/or data on diabetes mellitus and/or LDL-C values ≥2.6 mmol/L at the time of the study and/or creatinine ≥97-115 mol/L at the time of the study. We excluded smoking from the analysis due to its paradoxical dynamics (explanation above), which could distort the results obtained.

Figure 2 presents the entire group with the percentage distribution of the cumulation of risk factors as a number in combination. The most common combination among the studied patients is the combination of two risk characteristics, and every fourth patient presents with at least three risk factors for the development of atherosclerosis.

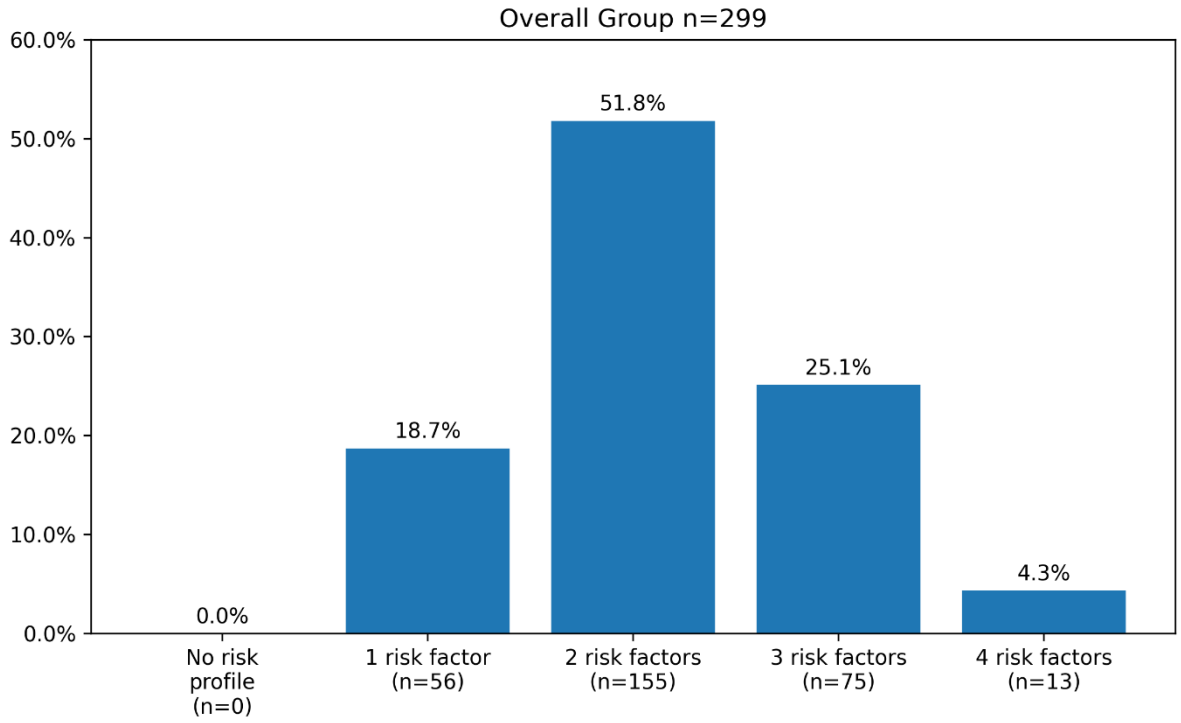

Figure 2. Cumulation of risk factors in the general group

Table 6. Cumulation of risk factors in the defined subgroups depending on the severity of carotid pathology (cumulation of AH; diabetes mellitus; CKD; LDL-C)

	Group C (without plaques) n=78	Group B (stenosis <50%) n=87	Group A (stenoses ≥50%) n=134
no risk factors (n=0)	0.0 %	0.0 %	0.0 %
with 1 risk factor (n=56)	29.5 %	19.5 %	11.9 %
with 2 risk factors (n=155)	57.7 %	54.0 %	47.0 %
with 3 risk factors (n=75)	11.5 %	23.0 %	34.3 %
with 4 risk factors (n=13)	1.3 %	3.4 %	6.7 %

The distribution of the cumulation of risk factors in the three defined subgroups according to the severity of involvement of the carotid basin is presented in table 6. From the data it can be concluded that the more severe the carotid stenotic pathology, the more severe the risk profile of the respective patients.

After the additional analysis, we found that patients in group C had an average of 1.8±0.8 risk factors, in group B they had 2.1±0.7 risk factors, and in the most severe group A, an average of 2.4±0.7 risk factors. The differences are significant when comparing all three defined subgroups to each other. The relationship between the severity of the risk profile and the degree of involvement of the carotid arteries is linear, with a high degree of reliability (figure 3).

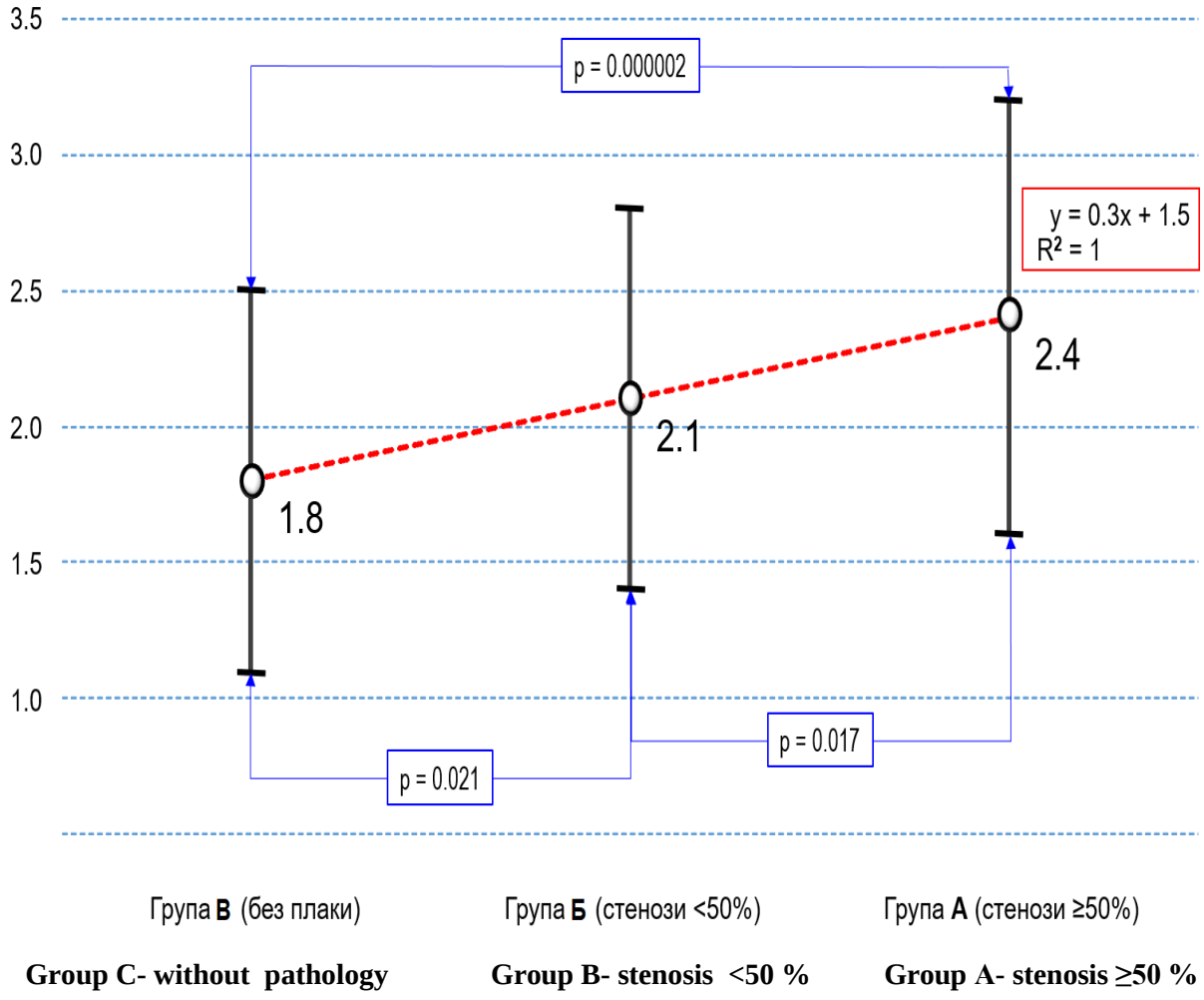

Figure 3. Average number of risk factor combinations depending on the severity of atherosclerotic changes in the carotid arteries

4.5.1. Distribution according to the presence of coronary stenotic pathology

4.5.1.1. Relationship between coronary and carotid atherosclerosis. Combination of carotid and coronary artery disease

Depending on the presence or absence of at least one coronary stenosis ≥50% of the diameter of the epicardial arteries, and to study the relationships between the presence or

absence of coronary and carotid pathology, all patients were grouped based on the results of the coronary vessel examination into two main groups:

Group D: with at least one coronary stenosis ≥50% of the diameter of the epicardial arteries

Group E: patients without stenoses ≥50% in the coronary arteries.

Significant coronary artery disease (stenosis ≥50% of the artery lumen) in at least one of the epicardial vessels was found in 203 of the patients (67.9%), or two-thirds of all 299 examined in the study, while carotid artery stenosis, regardless of severity, was found in 221 (73.9%) of the patients.

Table 7. Combination of coronary and carotid pathology

	Group A (n=134) (carotid stenosis ≥50%)	Group B (n=87) (carotid stenosis < 50%)	Group C (n=78) (without carotid stenosis)	Total
	n (%)	n (%)	n (%)	n (%)
Group D Significant coronary stenosis (n=203)	111 (82.8)	60 (69.0)	32 (41.0)	**203 (67.9)**
Group E No coronary stenosis (n=96)	23 (17.2)	27 (31.0)	46 (59.0)	96 (32.1)
Total	134 (100.0)	87 (100.0)	78 (100.0)	299 (100.0)

A significantly high incidence of combined carotid and coronary pathology was found - 171 out of all 299 patients studied (**57.1%**, between 51.4% and 62.9% at 95% CI) had simultaneous involvement of the coronary vessels of the heart and carotid arteries (table 7).

The group with significant coronary and severe (≥50%) carotid stenosis is larger - 111 out of all 299 (**37.1%**, between 31.6% and 42.9% at 95% CI) studied patients. The proportion of patients without damage to the coronary and carotid arterial vessels is only 46 (15.4%, between 11.5% and 19.9% at 95% CI). The relationship between the severity of carotid stenosis and the presence of coronary disease is statistically significant. Spearman correlation analysis demonstrated a statistically significant positive relationship between the severity of carotid stenosis and the presence of coronary disease ($p<0.001$) (table 8). These results confirm the conclusions drawn by I. Petrov *et al.* (2006) that 3VD is often combined with carotid artery stenoses.

When the identified cases of combined carotid and coronary stenosis are analyzed against the 203 patients with significant coronary disease, the relative proportions of patients with combined impairment are even greater. More than one half, 111 patients (54.7%) of the 203 coronary patients had significant carotid stenosis ≥50%. Sixty patients (29.6% of 203) had carotid plaques <50%. A total of 171 patients (84.2%) of all the patients with significant coronary pathology had atherosclerotic changes in the carotid arteries. The data from the analysis show a high percentage (84.2% of 203) of combined coronary and carotid pathology (figure 4).

According to data from a meta-analysis in 2021, the frequency of patients with carotid stenosis with established significant coronary artery disease is between 30% and 70%. The higher rate occurs in patients with multivessel coronary artery disease referred for bypass surgery.

Similar results showing a high rate of carotid atherosclerosis were reported by S. P. Jordanova and S. Kedev in Macedonia. Carotid pathology is established in 1009 out of 1031 patients with proved significant coronary disease (in 97.8% of the cases) identifying diabetes mellitus and carotid stenosis as predictors of future cardiovascular events.

Only 32 of the patients studied by us (15.8%) presented without visible atherosclerotic carotid pathology. In 23 out of 96 patients (24%) in the group without significant coronary disease, there is a high degree of carotid stenosis ≥50%. The absence of coronary stenotic pathology in patients in this group does not mean low cardiovascular risk. This was confirmed by A. Steinvil *et al*. in a study of 1391 patients referred for invasive coronary diagnostics and carotid ultrasound. The presence of carotid stenoses increased mortality and the risk of cardiovascular events not only in patients with coronary pathology but also in patients without coronary stenoses (hazard ratio=2.93; between 1.09 and 7.87; p=0.03).

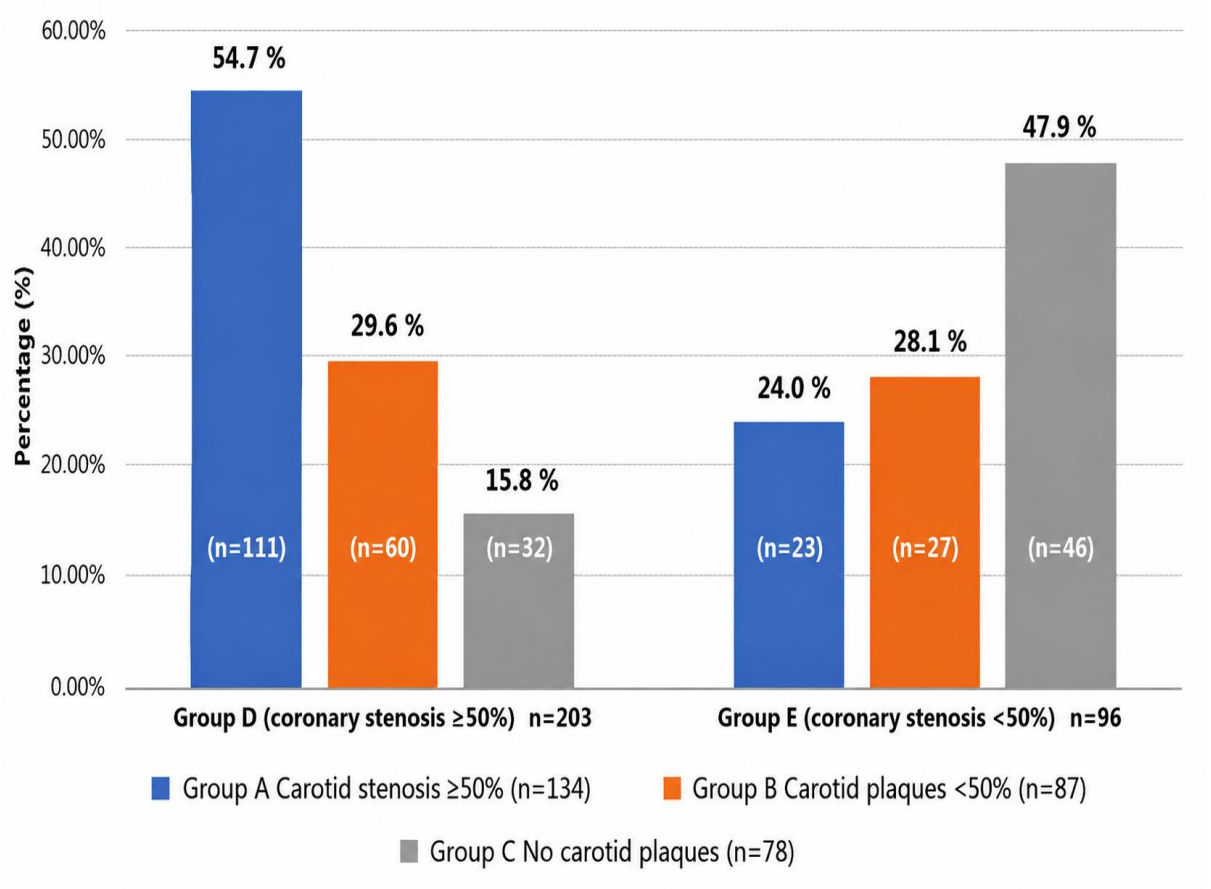

Figure 4. Distribution of patients with carotid pathology depending on the presence of coronary stenosis. Combined coronary and carotid pathology

Other 27 patients (28.1% of 96) have insignificant atherosclerotic plaques in the carotid arteries without coronary stenoses, or a total of 50 (52.1% of 96) patients with atherosclerotic changes in the carotid arteries, and 46 (47.9% of 96) do not have atherosclerotic changes in the carotid basin and do not have any carotid stenoses (figure 4).

As a summary of the analysis of the distribution of carotid pathology depending on the presence of coronary stenosis, we find that:

1. Among patients with hemodynamically significant coronary stenosis >50% (Group D, n=203), the highest relative proportion of patients with significant carotid stenosis ≥50% (Group A) was observed, representing 82.8% (n=111) of all patients in this group. Patients with carotid plaques <50% (Group B) were 69.0% (n=60), and patients without carotid plaques (Group C) were 41.0% (n=32).

2. In patients without significant coronary stenosis <50% (Group D, n=96), patients without carotid plaques (Group B) predominated, representing 59.0% (n=46) of the cases.

Patients with carotid plaques <50% (Group B) were 31.0% (n=27), while patients with significant carotid stenosis ≥50% (Group A) were 17.2% only (n=23).

3. The results obtained show a significantly higher incidence of significant carotid atherosclerosis in patients with accompanying significant coronary artery disease.

4. As the severity of coronary pathology increases, a higher incidence of significant carotid stenoses is observed. The presence of significant coronary stenosis is associated with a higher incidence of carotid atherosclerosis, while in patients without significant coronary pathology, the absence of carotid plaques or the presence of insignificant carotid atherosclerosis predominates (figure 4).

A correlation analysis was performed to test the hypotheses of combined unilateral left/right manifestation of carotid and coronary stenosis. The values of the Spearman correlation coefficients are presented in table 8.

Table 8. Spearman correlation coefficients between the presence of carotid and coronary artery stenosis

Coronary/Carotid artery disease severity	**Left carotid artery**	**Right carotid artery**	**Both carotid arteries**
Left coronary artery	0.036	0.041	0.070
Left anterior descending artery	0.107	0.277***	0.289***
Circumflex artery	0.101	0.196**	0.179**
Right coronary artery	0.183**	0.160**	0.326***
Three-vessel coronary disease	0.161**	0.268***	0.367***

***p<0.001; ** 0.05 < p<0.001

The Spearman correlation analysis comparing the severity of coronary tree involvement defined as the presence of significant stenoses with the severity of carotid artery involvement by the atherosclerotic process established a reliable, positive correlation (r=0.367; p<0.001). The results obtained show that with increasing severity of carotid atherosclerosis, the frequency of concomitant coronary pathology increases, too.

The presence of atherosclerotic changes in the coronary arteries correlated weakly but significantly with the presence of changes in the right carotid artery (table 8). Interestingly, the presence of changes in the right coronary artery correlated significantly with the presence of changes not only in the right but also in the left carotid artery.

Literature data also report a relatively weak, but statistically significant correlation between the degree of stenosis and the prevalence of atherosclerosis in the coronary and carotid vascular systems in patients with combined vascular involvement.

4.1.6. Risk profile of groups with and without carotid stenosis in accompanying coronary stenosis

The risk factors responsible for atherosclerotic changes in the coronary and carotid vascular systems are identical. Our research hypothesis assumes that the involvement of a larger number of carotid and coronary vessels could be explained by higher values of the risk factors for atherosclerosis. To test this hypothesis, we compared the average levels of the main risk factors between the groups with: hemodynamically significant coronary and accompanying carotid stenosis (n=111) (group ‚c'), and as a reference group, we used patients without atherosclerotic changes in the carotid and coronary vessels (n= 46) (group ‚a') (table 9).

Table 9. Distribution of patients with hemodynamically significant coronary and accompanying carotid stenosis and patients without atherosclerotic changes in the carotid and coronary vessels

Characteristics	Group (a) without coronary or carotid stenosis (n=46)	Group (b) with coronary without carotid stenosis (n=32)	Group (c) with significant coronary and carotid stenosis (n=111)	p value Group (a)/Group (c)
Age	59.7 (8.39)	63.3 (9.21)	66.2 (7.83)	**<0.001**
Gender Men	16 (34.8)	23 (71.9)	79 (71.2)	**<0.001**
Gender Women	30 (65.2)	9 (28.1)	32 (28.2)	
BMI	28.7 (4.04)	29.1 (3.87)	29.3 (4.79)	0.69
Total cholesterol	5.1 (1.24)	4.8 (1.36)	4.7 (1.35)	0.24
LDL cholesterol	3.0 (1.07)	2.7 (1.31)	2.6 (1.03)	0.181
Creatinine	75.7 (16.7)	82.4 (16.7)	94.8 (38.6)	**0.002**
Number of hypertension medications	2.4 (1.04)	2.7 (0.93)	3.5 (0.67)	**<0.001**
Smoking	18 (39.1)	13 (40.6)	24 (21.6)	**0.027**
Diagnosed diabetes mellitus	6 (13.0)	11 (34.4)	56 (50.5)	**<0.001**
Hypercholesterolemia	20 (43.5)	9 (28.1)	32 (28.8)	0.180
AH	44 (95.7)	31 (96.9)	111 (100.0)	**0.044**
AF	9 (19.6)	6 (18.8)	16 (14.4)	0.652
CKD	2 (4.3)	3 (9.4)	17 (15.3)	0.059
IS	4 (8.7)	3 (9.4)	27 (24.3)	**0.027**

In the comparative analysis between patients without coronary and carotid pathology and patients with combined significant coronary and carotid stenosis, statistically significant differences were found in terms of a number of demographic, clinical and laboratory indicators.

1. Patients with significant combined coronary and carotid atherosclerosis are statistically significantly older compared to patients without vascular pathology (66.2±7.83 versus 59.7±8.39 years, $p<0.001$).

2. A statistically significant difference in gender distribution was also found out, with males predominating in patients with combined coronary and carotid pathology (71.2% versus 34.8%, $p<0.001$).

3. In terms of renal function, patients with significant combined vascular pathology have statistically significantly higher serum creatinine values (94.8±38.6 versus 75.7±16.7 μmol/L, $p=0.002$).

4. A significant difference is also established in the number of antihypertensive medications used, with patients with significant coronary and carotid stenosis using a greater number of medications to control arterial hypertension (3.5±0.67 versus 2.4±1.04, $p<0.001$).

5. Diabetes mellitus is significantly more common in patients with combined coronary and carotid pathology (50.5% versus 13.0%, $p<0.001$), which confirms its importance as a major risk factor for the generalized atherosclerotic process.

6. Patients with significant combined vascular pathology have a higher incidence of ischemic stroke, too (24.3% versus 8.7%, $p=0.027$).

7. The lower prevalence of smoking in patients with significant combined coronary and carotid pathology compared to patients without vascular pathology (21.6% versus 39.1%, $p=0.027$) is of interest, which can, probably, be explained by older age or cessation of smoking after detection of the vascular disease.

8. No statistically significant differences are established between the groups in terms of BMI, total cholesterol, LDL-C, hypercholesterolemia, AF, and CKD ($p>0.05$).

The results obtained show that advanced age, male gender, diabetes mellitus, more severe AH and impaired renal function are factors associated with combined coronary and carotid atherosclerosis in the studied population.

The difference is statistically significant with respect to the studied risk factors: age ($p<0.001$), gender ($p<0.001$), the presence of AH ($p=0.044$), diagnosed diabetes mellitus ($p<0.001$), and number of medications necessary for its control ($p<0.001$).

By analyzing the risk factors, we formed the following risk profile of a patient with a high probability of carotid and coronary stenotic pathology:

A man over 55 years of age, with diabetes mellitus, with poorly controlled AH requiring treatment with at least four medications and with clinical manifestation of IHD.

In this direction are the results by F. Jashari *et al.* (2013), too, where age, diabetes mellitus, AH, smoking and dyslipidemia are analyzed as common risk factors for the development of coronary and carotid pathology. The severity of coronary pathology correlates with the frequency and severity of carotid stenosis. What is different in the present study is that we were able to establish a correlation between the severity of carotid pathology (expressed in stenosis percentage of the carotid artery lumen) and the severity of AH (expressed in the number of medications needed for its control). The more medications are needed to achieve normotonic cardiac activity, the more advanced the stenotic process is.

The analysis of the obtained results and the literature data raises the following clinically significant questions:

1. Is there a reason for the patients with significant coronary artery disease to be systematically evaluated for accompanying carotid atherosclerosis?
2. Should the patients with IS and hemodynamically significant carotid stenosis be considered a high-risk group for accompanying coronary artery disease?

According to the literature review, heart disease is the second most common cause of acute cerebrovascular events and it is found in approximately one third of IS patients. P. Amarenco *et al.* (2008) define IS as equivalent to the risk of IHD, leaving the topic open for future clinical trials in the secondary prevention of IS.

A. Sagatelyan *et al.* (2022) establish a significant correlation between the severity of carotid atherosclerosis and the degree of coronary involvement, and their data correspond to the results of the present study.

Our results are also consistent with the data of J. Donlan *et al.* (2020). In 121 patients with proven coronary pathology referred for PCI, 55.4% were also diagnosed with carotid artery stenosis by single-stage SCAG and selective carotid angiography. The researchers find out a significant correlation ($r=0.22$; $p=0.014$) between the severity of coronary pathology (multi-vessel coronary disease) and the severity of carotid pathology by using linear regression analysis. Coronary atherosclerosis is an independent predictor of carotid pathology and the severity of carotid pathology is related to the number and degree of coronary artery involvement.

The severity of coronary artery disease correlates with the degree and risk of carotid stenosis. According to our data, we establish a significantly high morbidity of combined carotid and coronary pathology - 171 of all 299 examined patients (57.1%, between 51.4% and 62.9% at 95% CI) have simultaneous involvement of the heart and carotid vessels.

The group with significant coronary and severe (≥50%) carotid stenosis is larger - in 111 out of all 299 patients studied (37.1%, between 31.6% and 42.9% at 95% CI). The relationship between the severity of carotid stenosis and the presence of coronary artery disease is statistically significant ($p<0.001$).

The results obtained by us are similar to the data of A. Steinvil *et al*. (2011). In the study which includes 1405 patients, the authors demonstrate a direct relationship between the degree of coronary atherosclerosis and the severity of carotid stenosis ($r=0.255$, $p<0.001$). The involvement of the left main coronary artery and three-vessel coronary disease are an independent predictor of severe carotid stenosis.

Within the analysis of the results from the present study and the literature review, we find out that predictors of carotid stenotic pathology are not only age, diabetes mellitus, smoking, IS, but also coronary artery disease.

4.2. Assessment of the severity of carotid stenosis by echographic and angiographic examination of the carotid arteries

The existing literature comparing non-invasive methods for assessing the severity of carotid stenosis with DSA, the golden standard, stimulated the present analysis comparing ultrasound with invasive examination in 70 patients with carotid stenosis as evaluated by ultrasound and DSA. For ultrasound diagnostics, a "Philips Epiq" ultrasound machine with a linear transducer L12–3 is used. For invasive diagnostics, a "Siemens Artis angio system" is made use of.

The frequency of agreement between the two methods in assessing the severity of carotid stenosis is presented in table 10.

Table 10. Comparison between angiographic and ultrasound assessment of the severity of carotid stenosis (n=70)

Degree of obstruction assessed by ultrasound	Degree of obstruction assessed by angiography				Total
	≥50%	≥70%	≥80%	100%	
≥50%	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (5.7)
≥70%	0 (0.0)	20 (100.0)	**35 (76.1)**	0 (0.0)	55 (78.6)
≥80%	0 (0.0)	0 (0.0)	10 (23.9)	0 (0.0)	10 (14.3)
100%	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (1.4)
Total	4 (100.0)	20 (100.0)	45 (100.0)	1 (100.0)	70 (100.0)

A discrepancy between both methods is found out in the group with more severe stenoses classified by the invasive method as ≥80%. Two thirds of the cases (76.1%) classified by angiography as stenosis ≥80% are underestimated by the ultrasound examination, which could, potentially, have an impact on the therapeutic strategy.

The correlation between the two methods is moderate and statistically significant with Spearman's correlation coefficient of r=0.519 (p<0.001).

The characteristics of the ultrasound examination for the "carotid stenosis severity category ≥80%" are as follows:

Sensitivity - 50%

Specificity - 100%

Full population totality - 100%

covered population totality - 100%

Accuracy - 50%

The present results are in line with those of other authors, in that high sensitivity of the ultrasound examination is found in patients with a lower degree of stenosis, as well as in complete 100% occlusion. The differences towards the data of R. Liu *et al.* (2020) are expressed in that in them, a lower sensitivity of about 85% in the group of intermediate stenoses over 50% is established. In the present study, lower sensitivity for the ultrasound method is found in more severe stenoses >80%, in which the ultrasound examination underestimates the severity of the stenosis (table 10).

The explanation for this result is likely to be the fact that in most cases it is a chronic, hemodynamically significant calcified stenosis, and as already mentioned in the literature review, severe calcification is the "blind" spot of the method used (colour Duplex scanning). In the presence of such pathology, it is not possible to accurately determine the degree of stenosis.

Other authors have also reported results similar to ours characterized by a discrepancy in the assessment of the degree of carotid stenosis comparing ultrasound diagnostics with invasive DSA.

J. William *et al.* investigate 34 symptomatic patients with significant carotid stenosis. In the study it is esablished that ultrasound and DSA have similar sensitivity for detecting carotid atherosclerosis - 84% versus 81%. The differences come in cases where the external carotid artery must be assessed, too. Visualization and diagnosis of the external carotid artery is difficult with ultrasound examination (in 12% of patients there is a discrepancy with DSA). When the common and internal carotid arteries are examined only, the results are similar in both groups - the sensitivity of ultrasound examination improves to 93% versus 86% for DSA. The authors conclude:

- image quality and visualization is better with DSA
- the surgical team prefers DSA as a diagnostic test before carotid endarterectomy
- similarity in the sensitivity of the two methods for diagnosing carotid pathology
- ultrasound examination can be used as a screening method.

4.3. Side/adverse effects and advantages associated with invasive testing

It is important to note that in all 299 patients who underwent invasive angiography, neither transient, nor permanent complications related to the examination were recorded. This result confirms the data of R. Thiex *et al*. (2010) in 1715 patients regarding the achievement of a high level of safety of invasive examination in a university environment characterized by high technological availability, good team work, high competence and extensive experience of multidisciplinary teams. These researchers do not observe neither IS, nor permanent neurological deficit in any of the patients undergoing diagnostic neuroangiography.

T. Huang *et al.* (2022) analyze in their investigation in China the ersults in 186 patients with carotid stenosis referred for surgical revascularization. The researchers conclude that preoperative colour Doppler combined with DSA can evaluate the condition of the extracranial carotid vessels as in this way they orient the physician concerning the choice of surgical method. These and other similar results explain the high frequency of diagnostic application of the method not only in validation studies as a standard method for evaluating the non-invasive methods, but also perioperatively for assessing the anatomy of the carotid bifurcation for the determination of the treatment approach.

In the present study, we decided to compare the advantages and disadvantages of additionally performing carotid angiography and DSA during invasive coronary diagnostics. We calculated the additional cost of the procedure, as well as analyzed the additional radiation exposure for the patient and medical staff. We compared it with the advantages and benefits for the patient.

Figure 5 presents a comparative analysis of the advantages and disadvantages of additionally performing carotid angiography during the invasive coronary diagnostics.

Disadvantages:

- Increased procedural cost**.** Each additional 1 mL of contrast medium increases procedural cost by approximately EUR 0.21. Therefore, the use of an additional 12 mL of contrast medium (approximately 5–8 mL for each carotid artery) increases the total cost of the examination by approximately EUR 2.58**.**
- Additional radiation exposure for the patient. Each angiographic acquisition (DSA) contributes an additional cumulative radiation dose of approximately **4%** (approximately 16–30 mGy**)** relative to the total radiation exposure of the procedure (approximately 300–700 mGy**).**
- Additional radiation exposure for medical staff. The additional exposure associated with DSA **(**16–30 mGy**)** is considered practically negligible when appropriate protective clothing and radiation-shielding equipment are used

Advantages:

- Potential for favourable changes in national healthcare economic indicators. Earlier detection and treatment of carotid pathology may contribute to reducing the substantial economic burden associated with stroke management. According to data from the Expert Club for Economics and Policy (EKIP), annual expenditures for stroke treatment in Bulgaria are estimated at approximately BGN 400–450 million**,** representing nearly 5% of the annual budget of the National Health Insurance Fund (NHIF)**.**
- Reduction of the individual economic burden through timely diagnosis of carotid pathology. Early identification and management of carotid disease may reduce healthcare costs associated with delayed diagnosis, complications, prolonged treatment, and long-term disability**.**
- Prevention of stroke-related morbidity. Improved detection of carotid atherosclerosis may contribute to reducing stroke incidence (affecting more than 50,000 individuals annually in Bulgaria**)** and decreasing the number of patients with persistent neurological deficits and acquired disability.
- Optimisation of diagnostic and therapeutic protocols in patients with carotид atherosclerosis. Earlier identification of carotid disease may improve diagnostic pathways, facilitate timely intervention, and enhance therapeutic decision-making in patients with carotid atherosclerosis.

Figure 5. Advantages and disadvantages of additionally performed carotid angiography and DSA during the invasive coronary diagnostics

- The main disadvantages are the increased cost of the examination due to the use of an additional amount of contrast agent, as well as the increased radiation exposure for the patient and medical staff. The use of approximately 12 mL of additional contrast leads to a

minimal raise of the cost of the procedure, and the additional radiation exposure in DSA represents about 4% of the total cumulative dose for the examination.

- Despite the limitations described, the significant potential benefits of single-stage diagnosis of carotid and coronary pathology are emphasized. This allows for early diagnosis of carotid atherosclerosis, which could lead to a reduction of IS incidence, limitation of residual neurological deficit and reduction of the degree of disability.
- The potential economic benefits associated with reducing the costs of treatment and rehabilitation of patients with cerebrovascular accidents, as well as with improving the diagnostic and therapeutic algorithm in patients with carotid atherosclerosis have also been noted.
- It can be summarized that despite minimal additional contrast and radiation exposure, additional carotid angiography during invasive coronary diagnostics may have significant diagnostic, prognostic, and socioeconomic benefits in patients at high cardiovascular risk.

DSA is in the recommendations for the diagnosis and treatment of the peripheral arterial disease (PAD) of the European Society of Cardiology (ESC), in collaboration with the European Society of Vascular Surgery (ESVS). DSA remains the golden standard and it is of crucial importance in patients referred for carotid stenting. It is the diagnostic method giving the final assessment when we have a discrepancy in the results of the non-invasive examinations.

DSA is also included in the recommendations for diagnosis, treatment and follow-up of the patients with extracranial carotid stenosis. Colour Doppler is recommended for routine use in patients with suspected carotid pathology. In case of unsatisfactory result, CTA or MRI are recommended. When the results from the non-invasive examinations do not provide a definitive result and clarity regarding the diagnosis and therapeutic behaviour, DSA should be performed. The incidence of complications should not exceed 0.5%.

5. CONCLUSION

5.1. Generalization

It can be generalized that the present study aimed at analyzing the frequency and clinical significance of the accompanying carotid pathology in patients referred for invasive cardiac diagnostics.

- The results of the study showed us that concomitant carotid pathology is common in patients with IHD, who often remain undiagnosed in the context of standard cardiac invasive diagnostics.
- We found out that the compared groups with different severity of carotid pathology had significant differences in terms of biological factors - gender and age.
- The proportion of men is higher in the groups with moderate and severe carotid stenosis while in the group without carotid stenosis, both sexes are represented with equal shares. We found out that the age of the patients in the group with severe carotid stenosis is the highest in both sexes because in this group, the proportion of patients over 65 years is the largest.
- We established a clear relationship between the severity of AH defined as the number of medications needed to achieve AH control, and the severity of atherosclerotic changes in the carotid vessels.
- We established a clear correlation between the accumulation of risk factors and the severity of carotid artery involvement. The more severe the carotid artery pathology, the more severe the risk profile of the respective patients.
- We found out a significantly high morbidity from combined carotid and coronary pathology.
- We established a reliable positive correlation between the severity of coronary tree involvement defined as the presence of significant stenoses and the severity of carotid artery involvement by the atherosclerotic process ($r=0.367$; $p<0.001$).
- By analyzing the risk factors, we formed the following risk profile of a patient with a high probability of carotid pathology:

A man over 55 years of age, with diabetes melluts, with poorly controlled AH requiring treatment with at least four medications, and with clinical manifestation of IHD.

- We have established differences in the assessment of the severity of carotid stenosis by echographic and angiographic examination of the carotid arteries.
- Based on the results obtained in this work, we confirmed the hypotheses about the existence of a statistically significant correlation between the severity of coronary and carotid pathology as well as the existence of an exposure dependence between risk factors in patients with cardiovascular and cerebrovascular pathology.

These findings highlight the importance of a holistic approach to the diagnosis of cardiovascular disease, including both coronary and cerebrovascular pathology.

- In all 299 patients who underwent invasive angiography, we recorded neither transient nor permanent complications related to the examination.

In this regard, we found out that our results are similar to those of R. Thiex *et al*. (2010) who reported neither cases of stroke, nor permanent neurological deficits. This showed that in interventional practice with a high volume and trained team, the risk of neurological complications can be brought close to zero.

5.2. Behaviour algorithm

Through an in-depth study of carotid atherosclerosis and its relationship with coronary artery disease, emphasis was placed on the need for early diagnosis of patients with carotid pathology in this population referred for invasive diagnostics while considering the possibilities for improving the existing diagnostic protocols.

We recommend the following diagnostic protocol for patients referred for admission to a cardiology clinic:

❖ Ultrasound screening for carotid pathology

1. In all the patients meeting the risk profile: "A man over 55 years of age, with diabetes melluts, with poorly controlled AH requiring treatment with at least four medications, and with clinical manifestation of IHD".

2. Patients with established significant or insignificant coronary atherosclerosis.

3. Patients with a realized IMI.

4. Patients with TIA and transitory disturbance of the cerebral circulation.

The screening is non-invasive, widely available, and does not involve any financial commitment to the treatment process. A linear transducer and a physician who has completed the relevant training course are required.

❖ If stenotic carotid atherosclerosis is detected during screening, we recommend performing the invasive coronary angiography as the diagnostic process including the supraaortic vessels (supraaortic angiography), too.

❖ Patients with a realized IS/TIA and established stenotic carotid atherosclerosis should also be referred for coronary diagnostics when:

1. They have clinical manifestations of coronary artery disease.

2. They meet the risk profile: "A man over 55 years of age, with diabetes melluts, with poorly controlled AH requiring treatment with at least four medications, and with clinical manifestation of IHD".

3. Upon additional clarification or verification of the results obtained from non-invasive tests.

Coronary diagnostics can be performed as CTA or SCAG. Both methods have their advantages and disadvantages. We recommend in these cases a single-stage SCAG and subaortic angiography.

In order to facilitate the diagnostic process and its visualization, **a behaviour algorithm** was developed aiming at optimizing the workflow, increasing the diagnostic efficiency, limiting the diagnostic gaps, and reducing the costs of diagnosis and treatment (figure 6).

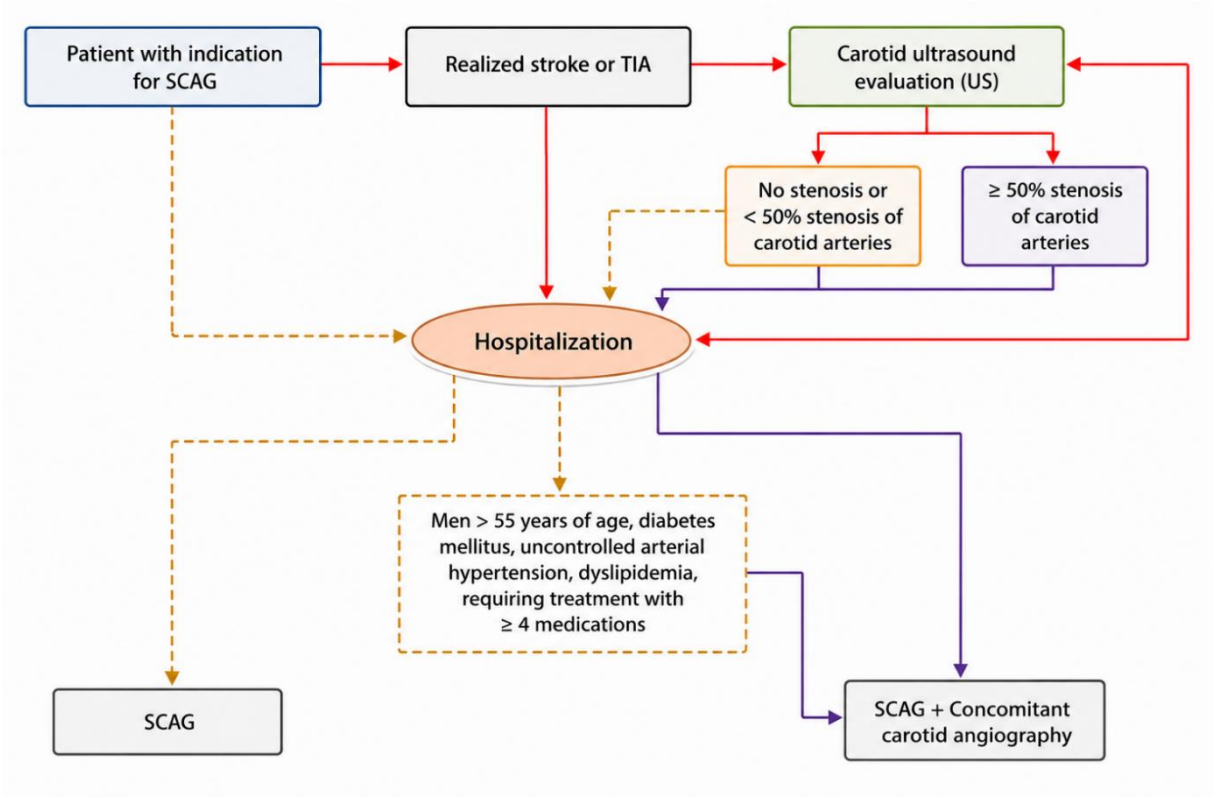

Figure 6. Diagnostic algorithm for identifying the accompanying carotid atherosclerosis in patients with IHD smptoms

The algorithm presents the diagnostic and clinical approach for identifying the accompanying carotid atherosclerosis in patients examined for IHD.

1. Patients requiring SCAG or patients with realized IS/TIA are subject to hospital admission and vascular risk assessment.
2. In patients with a IS or TIA, a Doppler ultrasound examination of the carotid arteries is performed.
3. In the absence of hemodynamically significant carotid stenosis (<50%), patients are subject to conservative follow-up and evaluation for coronary pathology if clinically indicated.

4. When carotid stenosis ≥50% is detected, combined invasive evaluation by SCAG and supraaortic angiography is recommended.

5. High-risk patients are males, aged >55 years, with diabetes mellitus and difficult-to-control AH requiring ≥4 medications.

6. For the patients referred for invasive evaluation for IHD and establishment of a risk profile (A man over 55 years of age, with diabetes melluts, with poorly controlled AH requiring treatment with at least four medications, and with clinical manifestation of IHD), combined invasive evaluation by SCAG and supraaortic angiography is recommended.

In high-risk patients, early combined vascular testing to simultaneously detect coronary and carotid pathology should be considered.

5.3. Limitations

Limitations of the present study include:

1. The single-centre nature of the study and the relatively small sample of patients.

2. The present study used a selected hospital cohort of patients with suspected cardiovascular and cerebrovascular atherosclerosis, rather than a representative population sample.

3. We can not correctly analyze the impact of smoking on the atherosclerotic process in the carotid basin because we have current data at the time of the study only, without information about the previous history related to the problem.

4. We do not have any real data on the duration and adherence to statin prophylaxis in the study group.

5. We do not have any details concerning the history of diabetes mellitus and the type and duration of treatment.

6. In the present study, no data are available regarding low birth weight as a potential risk factor for IHD and carotid atherosclerosis in spite of existing literature data on such an association.

5.4. Recommendations

1. Future studies should also examine the long-term prognosis in patients with combined carotid and coronary atherosclerosis to assess the effectiveness of different therapeutic strategies.

2. In future studies, it is appropriate to analyze in more depth the influence of smoking on the atherosclerotic process, given the paradoxical results found out in the present study, in which the frequency of smoking is higher in patients without carotid pathology and decreases with increasing severity of carotid stenosis.

3. It is recommended that future research focus on the development of new diagnostic and therapeutic protocols for the diagnosis of patients with combined carotid and coronary pathology, as well as on the assessment of long-term effects of treatment.

6. CONTRIBUTIONS

The contributions of the scientific wotk of **original nature** are:

1. We formed a risk profile of a patient with a high probability of carotid and coronary stenotic pathology. When establishing the described risk profile, we recommend performing carotid angiography during diagnostic coronary arteriography to prove or rule out significant carotid pathology.

2. We elaborated an applicable diagnostic algorithm for the diagnosis of carotid atherosclerosis in patients referred for admission to a cardiology clinic.

3. We established a statistically significant gradient relationship between the severity of AH assessed by the number of antihypertensive medications required and the degree of atherosclerotic involvement of the carotid arteries as the need for more intensive therapy increases along with carotid pathology progression.

4. We found out that the combination of AH requiring at least four medications for adequate blood pressure control with at least two additional risk factors (presence of diabetes mellitus and/or LDL-C ≥ 2.6 mmol/L and/or creatinine ≥ 97-115 mol/L) in individuals referred for diagnostic coronary arteriography means:

- 63.7% probability of having significant stenosis(es) in the carotid basin
- 90.6% probability of atherosclerotic changes in the carotid basin
- less than 10% probability of no atherosclerotic changes in the carotid arteries.

The results obtained require special attention to AH patients requiring at least four medications for its control. In a similar situation with at least two additional risk factors (presence of diabetes mellitus and/or LDL-C ≥ 2.6 mmol/L and/or creatinine ≥ 97–115 mol/L), we recommend a single-stage SCAG and supraaortic carotid angiography during diagnostic coronary arteriography to prove or rule out stenotic pathology. This is associated with the use of a minimal additional amount of contrast, significantly lower X-ray exposure of the patient

and the operator compared to the separation of the two diagnostic procedures and is significantly more economically advantageous.

The scientific contributions of the dissertation of **confirmatory nature** are expressed in supplementing the existing literature concerning the frequency and clinical significance of the accompnying carotid pathology in the patients with cardiac diseases.

1. We confirmed the presence of a clear relationship between the accumulation of risk characteristics in a given individual and the severity of carotid artery involvement.
2. We confirmed that as risk characteristics accumulate in a given individual, the severity and spread of the atherosclerotic process increases.
3. We confirmed the presence of a statistically significant relationship between the severity of carotid stenosis and the presence of coronary stenotic atherosclerosis ($p<0.001$).
4. We confirmed the presence of a high morbidity percentage from combined carotid and coronary pathology (54.7% of 203 coronary patients had significant carotid stenosis ≥50%).
5. We confirmed the presence of a positive correlation between the severity of coronary tree involvement defined as the presence of significant stenoses and the severity of carotid artery involvement by the atherosclerotic process ($r=0.367$; $p<0.001$)
6. We confirmed the need for routine use of ultrasound carotid diagnostics in cardiology clinics. This is a cheaper, safer for the patient and more accessible diagnostic method - an alternative to invasive carotid angiography. The goal is a higher success rate of diagnosed patients with carotid pathology who have passed through the cardiology wards.
7. We have confirmed that during invasive diagnostics, the risk of neurological complications can be brought close to zero in the interventional practice with a high volume and trained team.
8. We confirmed the data described in the literature on the presence of a discrepancy in the assessment of the degree of carotid stenosis when comparing ultrasound examination and invasive DSA.
9. We confirmed existing literature data that the male gender is more often affected by the atherosclerotic process.

In conclusion, the results from this study emphasize the necessity of an integrated and multidisciplinary approach to the diagnosis and treatment of patients with cardiovascular diseases, which includes not only the assessment of the coronary vessels, but also the condition of the carotid arteries. The work shows the importance of early diagnosis in the patients with combined pathology, which could lead to an improvement in the overall prognosis of these patients and a reduction in the risk of cerebrovascular accidents and disability.

The results may be useful for clinicians in making decisions about the prevention and treatment of the patients with cardiovascular and cerebrovascular atherosclerosis. The presence of carotid stenotic pathology is associated with a higher risk of IS and may worsen the prognosis of the patients undergoing invasive cardiovascular diagnosis and therapy. Many patients with carotid pathology still remain undiagnosed, which leads to their inadequate treatment.

7. LIST OF PUBLICATIONS RELATED TO THE DISSERTATION

1. Zhelev Ts. Carotid pathology in patients referred for diagnostic catheterization due to ischemic heart disease, MD Journal, Interventional Cardiology, 2021;18(6;126):… (in Bulgarian).
2. Zhelev Ts. Differences between invasive (digital subtraction angiography) and non-invasive (Doppler) examination in patients with cardiovascular and cerebrovascular atherosclerosis. Nauka kardiologiya, 2026; … (1):… (in Bulgarian).