ORIGINAL ARTICLE

Factors associated with the symptomatic status of carotid artery stenosis: identification in a cross-sectional study and development of a scoring system

Przemysław Puz[1], Tomasz Urbanek[2], Damian Ziaja[2], Aleksandra Cieślik[1], Arkadiusz Stęposz[1], Anetta Lasek-Bal[1]

1 Department of Neurology, School of Health Sciences, Medical University of Silesia, Katowice, Poland
2 Department of General Surgery, Vascular Surgery, Angiology and Phlebology, Medical University of Silesia, Katowice, Poland

KEY WORDS

internal carotid artery stenosis, stroke risk, ultrasound plaque morphology

EDITORIAL

by Podlasek, Grunwald, and Musiałek, see p. 5

ABSTRACT

INTRODUCTION The identification of asymptomatic patients at high risk of internal carotid artery (ICA) stenosis destabilization and symptom occurrence is crucial for prognosis estimation.

OBJECTIVES This study aimed to determine differences between patients with symptomatic and asymptomatic ICA stenosis and to develop a predictive model for the risk of symptomatic stenosis based on data collected in routine clinical practice.

PATIENTS AND METHODS The study included 163 patients with asymptomatic and 182 patients with symptomatic ICA stenosis greater than 70%. The study groups were compared in terms of stroke risk factors and comorbidities, coexisting ICA stenosis on the contralateral side, atherosclerosis in other arterial territories, and the morphology of atherosclerotic plaque assessed by transcervical ultrasound.

RESULTS Independent risk factors for symptomatic ICA stenosis included: male sex (odds ratio [OR], 2.94; 95% CI, 1.87–4.32; P <0.001), diabetes (OR, 2.86; 95% CI, 1.62–5.12; P <0.001), body mass index >25 kg/m^2 (OR, 1.81; 95% CI, 1.72–1.86; P <0.001), chronic kidney disease (OR, 3.34; 95% CI, 1.34–8.87; P = 0.007), increased-risk features of ultrasound plaque morphology (OR, 2.52; 95% CI, 1.29–3.72; P = 0.009), and coexisting atherosclerosis in 3 or 4 vascular areas (OR, 3.72; 95% CI, 1.77–7.23; P <0.001).The sensitivity and specificity of the scoring model designed to estimate the risk of symptomatic ICA stenosis reached 77.6% and 76.9%, respectively.

CONCLUSIONS This cross-sectional study indicated that the analysis of selected imaging and clinical parameters may enable clinicians to estimate the risk of symptomatic ICA stenosis. The proposed scoring system requires further prospective validation.

Correspondence to:
Przemysław Puz, MD, PhD, Department of Neurology, School of Health Sciences, Medical University of Silesia, ul. Ziołowa 45, 40-635 Katowice, Poland, phone: +48 32 359 83 06, email: ppuz@tlen.pl
Received: August 18, 2020.
Revision accepted: October 23, 2020.
Published online: November 4, 2020.
Pol Arch Intern Med. 2021; 131 (1): 17-25
doi:10.20452/pamw.15676

INTRODUCTION Atherosclerotic stenosis of carotid and / or cerebral arteries accounts for approximately 20% to 30% of ischemic stroke cases. It has been demonstrated that the risk of stroke rose proportionately to the increase in the degree of internal carotid artery (ICA) stenosis.[1]

As concluded by Puz and Lasek-Bal elsewhere,[2] the choice of therapy for patients with ICA stenosis, particularly those asymptomatic, remains a clinical issue that has not been explicitly resolved —diagnostic methods to allow for optimal patient selection criteria are still sought in relation with pharmacological and interventional treatment.

Recommendations for the evaluation of patients' eligibility for surgical treatment are based on the results of clinical trials performed more than 20 years ago.[3-7] As previously described,[2] the risk arising from interventional treatment should not be greater than the risk arising from the natural course of the disease and applied pharmacotherapy. In recent years, the effectiveness of

WHAT'S NEW?

Identifying patients at increased risk of internal carotid artery stenosis destabilization and symptom occurrence is critical for the management of asymptomatic patients, including decision making with regard to the point and time of intervention and, possibly, the type of intervention. In patients with symptomatic carotid stenosis, as compared with those asymptomatic, we found an increased prevalence of male sex, diabetes, elevated body mass index, chronic kidney disease, and multifocal atherosclerosis. "Unstable" plaque morphology assessed by a rough estimate on transcervical ultrasound was also more prevalent in symptomatic individuals. Using the potential risk factors we have identified, we created a model for estimating the risk of clinical symptom occurrence in patients with internal carotid artery stenosis. Our scoring model, with the proposed cutoff values, showed the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 77.6%, 76.9%, 75.2%, 79.4%, and 75.4%, respectively.

conservative, best medical treatment has significantly improved.[2] It is estimated that the annual risk of stroke in patients with asymptomatic stenosis has dropped below 1%.[8]

Classic risk factors for vascular diseases do not enable us to determine the actual risk of the occurrence of carotid artery stenosis symptoms manifested by a cerebral ischemia incident.[9,10] The onset of neurological symptoms resulting from ICA stenosis depends not only on the degree of stenosis and plaque morphology but also on the probability of thrombus formation at the site of stenosis, development of collateral circulation, and presence of other stroke risk factors.[2,11,12]

Routinely used imaging modalities such as duplex Doppler ultrasound, magnetic resonance imaging (MRI) angiography, and computed tomography (CT) angiography are usually of limited value in identifying patients at high risk of asymptomatic stenosis progression to symptomatic stenosis. Additional methods used to assess ICA plaque or stenosis instability and a potentially increased risk of ischemic incidents involving the central nervous system (CNS) include the assessment of atherosclerotic plaque morphology by ultrasound, virtual histology or intravascular ultrasound, as well as the assessment of microembolic signals on transcranial Doppler sonography.[13,14]

The identification of patients at high risk of stenosis destabilization in terms of symptom occurrence is crucial for prognosis estimation in asymptomatic patients and for risk stratification associated with interventional treatment. The continuous development of interventional treatment methods (carotid endarterectomy and / or stenting) contributes to further risk minimization. The use of intravascular ultrasound allows clinicians to optimize the use of procedural techniques at the time of intervention.[15]

Factors associated with poorer prognosis in patients with ICA stenosis include: coexisting atherosclerosis in other vascular territories, stenosis progression greater than 20% found at periodic ultrasound examinations, unstable atherosclerotic plaque morphology, changes in proinflammatory cytokine blood concentrations, areas of silent ischemia visualized on neuroimaging, microembolic signals on transcranial Doppler sonography, as well as an impaired reactivity of cerebral arteries on the side of stenosis.[5,10,12,16] The coexistence of other diseases and complex genetic and environmental relations represent factors that further modify the risk of stroke in that group of patients.[17]

The aim of this study was to determine differences between patients with symptomatic ICA stenosis and those with asymptomatic ICA stenosis, based on data accumulated in routine clinical practice, ie, risk factors for cerebral ischemic stroke, comorbidities including atherosclerosis in other vascular territories, and the ultrasound morphology of atherosclerotic plaque causing ICA stenosis. Our secondary objective was to develop a predictive model for the assessment of symptomatic stenosis risk based on the collected clinical data.

PATIENTS AND METHODS In this cross-sectional study, we compared various clinical and ultrasound factors in patients with symptomatic and asymptomatic ICA stenosis. Primarily, the study included 474 patients: 298 individuals with symptomatic atherosclerotic ICA stenosis greater than 50% and 176 individuals with asymptomatic ICA stenosis greater than 70%. After the verification of the stenosis degree, 163 patients with stenosis exceeding 70% were chosen to remain in the asymptomatic group. Eventually, in order to standardize the comparison and assess the study patients with ICA stenosis of similar degree, 182 patients from symptomatic group in whom the degree of the stenosis exceeded 70% were included (FIGURE 1).

In the group of symptomatic patients, neurological symptoms including stroke or transient ischemic attack (TIA) on the side ipsilateral to the stenotic artery were diagnosed within 6 months prior to inclusion into the study. The study patients were recruited among those hospitalized in the Department of Neurology and the Department of General Surgery, Vascular Surgery, Angiology and Phlebology of Medical University of Silesia in Katowice (in the years 2016 to 2018). Stroke and TIA were defined according to the 2013 American Heart Association / American Stroke Association statement.

The exclusion criteria were as follows: nonatherosclerotic stenosis, potential causes of cerebral embolism other than atherosclerotic lesions in the carotid artery (atrial fibrillation, mitral and / or aortic valve stenosis, mechanical heart valve, previous myocardial infarction, patent foramen ovale or another defect, interatrial septal aneurysm, hypokinesia or akinesia of the cardiac walls, cardiac cavity myxoma, and thrombus in the left ventricle or atrium), carotid artery

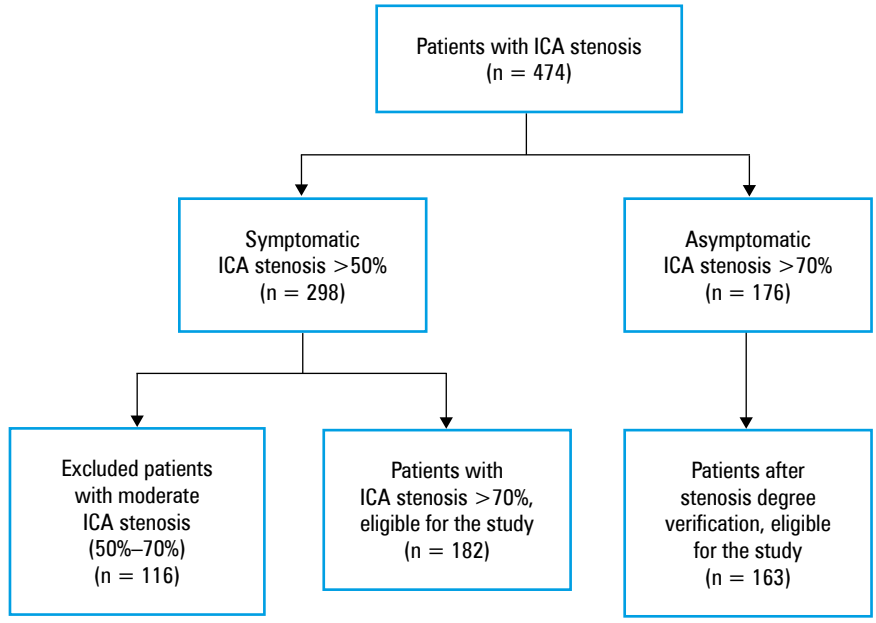

FIGURE 1 The flowchart of the patient selection process
Abbreviations: ICA, internal carotid artery

dissection, or intraluminal thrombosis—visible on ultrasound.

All study patients were also evaluated for the occurrence of stroke risk factors and comorbidities including arterial hypertension, coronary artery disease, diabetes, body mass index (BMI) greater than 25 kg/m^2, abdominal aorta atherosclerosis, lower extremity arterial disease, chronic kidney disease (CKD), lipid disorders, tobacco smoking, and a positive family history of stroke. Drug treatment for chronic diseases was analyzed in all patients (use of angiotensin-converting enzyme inhibitors, β-blockers, calcium-channel blockers, diuretics, statins, and antiplatelets—aspirin or clopidogrel).

Patients included into the study underwent duplex Doppler ultrasound of the carotid and vertebral arteries. The examination was performed using the 7.5-MHz linear array probe and the degree of stenosis and atherosclerotic plaque morphology were assessed. Carotid stenosis grading was based on morphological data (B-mode images, color flow imaging), velocity measurements (in the stenotic and poststenotic segments), and the assessment of collateral flow according to the combined criteria for ICA stenosis grading.[18,19] In patients with bilateral ICA stenosis, the symptomatic side, or the one with more advanced involvement in asymptomatic patients, was considered for comparison.

Plaque echogenicity was assessed using the Gray–Weale classification and the evaluation of the greyscale median (GSM) after the normalization of ultrasound images.[11,12] Based on ultrasound findings, 2 categories of plaque echogenicity were determined: hypoechogenic (GSM ≤25) and hyperechogenic (GSM >25).

The characteristic features of unstable atherosclerotic plaque included hypoechogenic plaque structure and / or the presence of ulcerations on the surface of atherosclerotic plaque and / or plaque area above 40 mm^2. We adopted the same definition of ulceration as used by Puz and Lasek-Bal.[2] Irregularities on the plaque surface, visible during the color-coded duplex examination and in the power Doppler mode, were regarded as ulceration. The plaque area was measured in a longitudinal view in the plane in which the plaque reached its maximal size. The image was frozen and magnified on the screen and the cursor was traced around the perimeter of the cross section. A microprocessor in the duplex scanner displayed the cross-sectional area of plaque.[11,18,19]

The velocity criteria for significant ICA stenosis (>70%) included: peak systolic velocity ≥330 cm/s, end-diastolic velocity ≥100 cm/s, and the ratio of the peak systolic velocity in the internal carotid artery to the peak systolic velocity in the common carotid artery ≥4. In all study patients, carotid duplex Doppler ultrasound was performed by an experienced vascular surgeon (TU) and a neurologist (PP), who agreed on the assessment of the stenosis degree.

Patients with symptomatic and asymptomatic stenosis were compared in terms of stroke risk factors, comorbidities, coexisting ICA stenosis on the contralateral side, atherosclerosis in other arterial areas (coronary artery disease, lower extremity arterial disease, abdominal aorta disease), and the ultrasound morphology of atherosclerotic plaque in the ICA. Data on the prevalence of atherosclerosis in other vascular areas were obtained from patients' physical examination, previous medical records, and diagnostic procedures carried out during hospitalizations in our institution (ultrasonography). Coronary artery disease, arterial hypertension, diabetes, lipid disorders, CKD, and abdominal aorta atherosclerosis were

TABLE 1 Clinical characteristics of the study patients

Characteristics	Asymptomatic stenosis (n = 163)	Symptomatic stenosis (n = 182)	*P* value
Stroke risk factors and comorbidities			
Male sex	51 (31.3)	106 (58.2)	<0.001
Age, y, median (range)	72 (46–87)	71 (49–95)	0.78
Arterial hypertension	144 (88.3)	157 (86.3)	0.56
CAD	76 (46.4)	102 (56.4)	0.08
LEAD	31 (19)	50 (27.5)	0.06
AAA	6 (3.7)	8 (4.4)	0.74
Lipid disorders	106 (65)	124 (68.1)	0.54
BMI >25 kg/m^2	36 (22.1)	90 (49.5)	<0.001
Diabetes	29 (17.8)	61 (33.5)	0.009
Smoking status	90 (55.2)	107 (58.8)	0.5
CKD	8 (4.9)	22 (12.1)	0.02
Positive family history of stroke	12 (7.4)	19 (10.4)	0.31
Treatment used for chronic diseases			
Angiotensin-converting enzyme inhibitors	91 (55.8)	105 (57.7)	0.72
β-Blockers	59 (35.2)	64 (6.4)	0.84
Calcium-channel blockers	54 (33.1)	67 (36.8)	0.47
Diuretics	88 (53.4)	95 (52.2)	0.74
Statins	111 (68.1)	118 (64.8)	0.52

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: AAA, abdominal aorta atherosclerosis; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; LEAD, lower extremity arterial disease

diagnosed according to the current guidelines of the European Society of Cardiology / American College of Cardiology / American Heart Association / World Heart Federation / American Association of Clinical Endocrinologists / Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group.

Statistical analysis Basic statistical parameters were calculated for interval-scale variables (mean, SD, minimum, maximum, median, and range). The normal distribution of these variables was verified using the Shapiro–Wilk test. Nominal variables were expressed as number and percentage. Mean or median values of interval-scale variables were compared using the *t* test (for variables with normal distribution) or the Mann–Whitney test (for variables whose distribution differed from normal distribution). Nominal variables were compared using the χ^2 test or the Fisher test, depending on the size of the groups.

In order to identify risk factors for symptomatic ICA stenosis, a series of univariable logistic regression analyses was conducted for all analyzed factors. To determine independent risk factors for symptomatic ICA stenosis, a multivariable regression model was constructed based on variables that demonstrated statistical significance (in univariable regression and comparative analyses).

Receiver operating characteristics curve analysis was performed and the area under the curve was calculated to assess the predictive value of the multivariable logistic regression model regarding the risk of symptomatic ICA stenosis occurrence. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the model were calculated for the cutoff value less than 0.5, established for the equation from logistic regression.

Based on regression coefficients in multivariable logistic regression analysis, a scoring system for the evaluation of the risk of stenosis symptoms occurrence was proposed. For every variable, 2 categories were allocated: Yes (indicating symptomatic patients) and No (indicating asymptomatic patients) and points were assigned to the individual categories of variables. Point assignment to each variable was based on the comparison of their regression coefficients derived from the multivariable logistic regression model equation and scaling transformations with the use of the STATISTICA scorecard tool (Tibco Software, Inc., Palo Alto, California, United States). Then, the calculated values were rounded to the nearest integer value. In the developed scoring system, a cutoff value established based on the Youden index was determined to differentiate patients with symptomatic ICA stenosis and those asymptomatic. For the obtained value, goodness-of-fit scoring was determined by calculating the sensitivity, specificity, PPV, NPV, and accuracy of the model. A *P* value less than 0.05 was considered significant.

Each study participant provided informed consent. The study was approved by the Ethics Committee of Medical University of Silesia in Katowice.

RESULTS In patients with symptomatic stenosis, compared with those asymptomatic, the following risk factors for stroke and comorbidities were more frequent: male sex (58.2% vs 31.3%; *P* <0.001), diabetes (33.5% vs 17.8%; *P* = 0.009), CKD (12.1% vs 4.9%; *P* = 0.02), and BMI >25 kg/m^2 (22.1% vs 49.5%; *P* <0.001) (**TABLE 1**). There were no differences in the use of angiotensin-converting enzyme inhibitors, β-blockers, calcium-channel blockers, diuretics, or statins (**TABLE 1**). No differences in antiplatelet agent administration were noted between the study groups.

The presence of internal carotid artery stenosis on the contralateral side was found in 16 patients (9.8%) with asymptomatic ICA stenosis and in 31 patients (17%) with symptomatic stenosis (*P* = 0.05).

Multifocal atherosclerosis (at least in 2 of 4 vascular territories: carotid artery, coronary artery, abdominal aorta, and lower extremity arteries) was found in 86 patients (52.8%) with asymptomatic ICA stenosis and in 114 patients (62.6%) with symptomatic ICA stenosis (*P* = 0.06). Atherosclerosis of 2 vascular territories was detected in 64 patients (39.3%) with asymptomatic stenosis and

TABLE 2 Risk factors for symptomatic carotid artery stenosis based on univariable logistic regression analyses

Risk factor	OR	95% CI	*P* value
Male sex	3.06	1.96–4.77	<0.001
Age (per 1 year)	1.02	0.98–1.06	0.61
Arterial hypertension	0.82	0.43–1.56	0.56
CAD	1.46	0.95–2.33	0.08
LEAD	1.61	0.96–2.68	0.06
AAA	1.2	0.4–3.54	0.74
Lipid disorders	1.15	0.74–1.8	0.54
BMI >25 kg/m^2	1.86	1.81–1.91	<0.001
Diabetes	2.33	1.41–3.86	0.001
Smoking status	1.16	0.75–1.77	0.5
CKD	2.66	1.15–6.16	0.02
Positive family history of stroke	1.23	0.77–1.98	0.37
Coexisting atherosclerosis in 2 vascular areas	1.5	0.97–2.31	0.06
Coexisting atherosclerosis in 3 or 4 vascular areas	2.26	1.23–4.15	0.008
Contralateral ICA stenosis	1.88	0.88–3.59	0.07
Unstable plaque morphology	2.54	1.63–3.9	<0.001

Abbreviations: OR, odds ratio; others, see **FIGURE 1** and **TABLE 1**

TABLE 3 Risk factors for symptomatic carotid artery stenosis based on multivariable logistic regression analysis

Risk factor	OR	95% CI	*P* value
Male sex	2.94	1.87–4.32	<0.001
Age (per 1 year)	1.03	0.97–1.07	0.64
Diabetes	2.86	1.62–5.12	<0.001
BMI >25 kg/m^2	1.81	1.72–1.86	<0.001
CKD	3.34	1.34–8.87	0.007
Unstable carotid plaque morphology	2.52	1.29–3.72	0.009
Coexisting atherosclerosis in 3 or 4 vascular areas	3.72	1.77–7.23	<0.001

Abbreviations: see **TABLES 1** and **2**

in 70 patients (38.5%) with symptomatic stenosis (P = 0.88). Atherosclerosis of 3 or 4 vascular territories was found in 22 patients (13.5%) with asymptomatic stenosis and in 40 patients (22%) with symptomatic stenosis (P = 0.04).

Unstable carotid plaque morphology was seen in 58 patients (35.6%) with asymptomatic ICA stenosis and in 106 patients (58.2%) with symptomatic ICA stenosis (P <0.001).

Univariable logistic regression analysis showed that factors associated with symptomatic ICA stenosis included: male sex (odds ratio [OR], 3.06; 95% CI, 1.96–4.77; P <0.001), diabetes (OR, 2.33; 95% CI, 1.41–3.86; P = 0.001), CKD (OR, 2.66; 95% CI, 1.15–6.16; P = 0.02), coexisting atherosclerosis in at least 3 vascular areas (OR, 2.26; 95% CI, 1.23–4.15; P = 0.008), unstable carotid plaque morphology (OR, 2.54; 95% CI, 1.63–3.9; P <0.001), and BMI greater than 25 kg/m^2 (OR, 1.86; 95% CI, 1.81–1.91; P <0.001) (**TABLE 2**).

In the multivariable logistic regression model accounting for sex, age, and risk factors for symptomatic stenosis, whose statistical significance was demonstrated in univariable regression analysis, independent risk factors for symptomatic stenosis were as follows: male sex (OR, 2.94; 95% CI, 1.87–4.32; P <0.001), diabetes (OR, 2.86; 95% CI, 1.62–5.12; P <0.001), BMI greater than 25 kg/m^2 (OR, 1.81; 95% CI, 1.72–1.86; P <0.001), CKD (OR, 3.34; 95% CI, 1.34–8.87; P = 0.007), unstable carotid plaque morphology (OR, 2.52; 95% CI, 1.29–3.72; P = 0.009) and coexisting atherosclerosis in 3 or 4 vascular areas (OR, 3.72; 95% CI, 1.77–7.23; P <0.001) (**TABLE 3**).

As presented in **FIGURE 2**, the receiver operating characteristics curve analysis indicated that the regression model was predictive of the risk of symptomatic ICA stenosis, with an area under the curve of 0.7864 (95% CI, 0.74–0.83), 70.8% sensitivity, 74% specificity, a PPV of 76.3%, a NPV of 69.4%, and 73.3% accuracy (**FIGURE 2**).

In the scoring model to estimate the risk of symptomatic ICA stenosis developed using independent variables obtained in multivariable regression analysis, the total sum of fewer than 46 points determined symptomatic stenosis (**FIGURE 3**). The sensitivity, specificity, PPV, NPV, and accuracy for the scoring value were 77.6%, 76.9%, 75.2%, 79.4%, and 75.4%, respectively.

DISCUSSION The principal findings of this study were as follows: 1) independent clinical risk factors for symptomatic stenosis included: male sex, diabetes, BMI greater than 25 kg/m^2, CKD, unstable plaque morphology, and atherosclerosis coexisting in at least 3 vascular areas; and 2) the scoring model for the estimation of the risk of symptomatic ICA stenosis considers various clinical data: sex, age, comorbidities (diabetes, CKD), BMI, the ultrasound morphology of atherosclerotic plaque, and multiple sites affected by atherosclerosis.

Studies on the effect of sex on the risk of ICA stenosis symptoms are dubious; most of them, similar to our study, indicate that men are at higher risk of developing symptoms than women.[10,20,21] According to other authors, which is in line with our study, diabetes, CKD, and a high BMI have been associated with the risk of onset of CNS ischemia symptoms in patients with asymptomatic ICA stenosis.[22,23] In a meta-analysis by Paraskevas and Gloviczki,[22] additional factors linked to poorer prognosis have been identified: advanced age (>80 years), other comorbidities (heart failure, chronic obstructive pulmonary disease), contralateral ICA stenosis, and no treatment with statins. Our study also showed that advanced age was a significant risk factor for the occurrence of ICA stenosis signs. In the scoring model, the age cutoff value of 77 years was one of the components that determined the score.

In the present study, contralateral stenosis was found in 17% of the patients with symptomatic stenosis and in 9.8% of the patients with

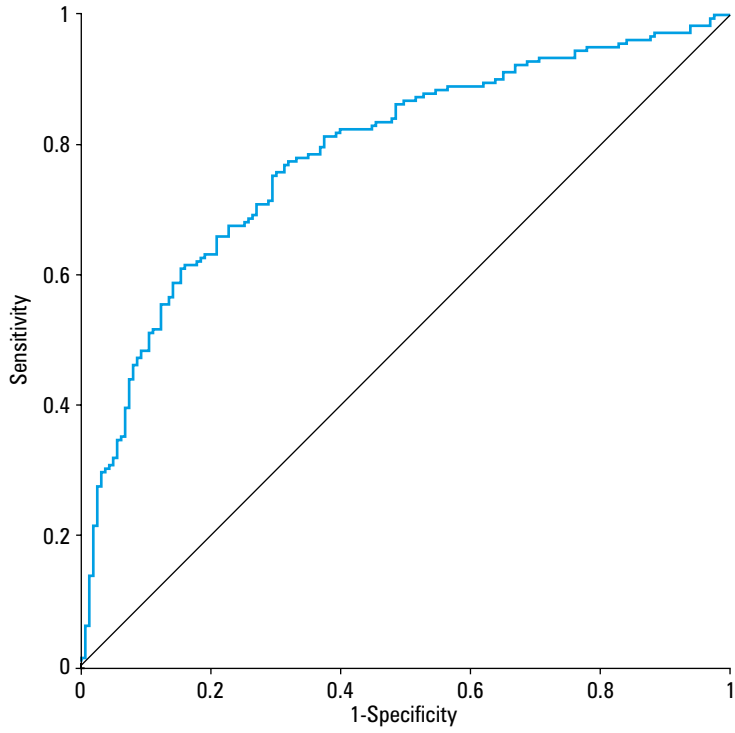

FIGURE 2 Receiver operating characteristics curve for the multivariable regression analysis model

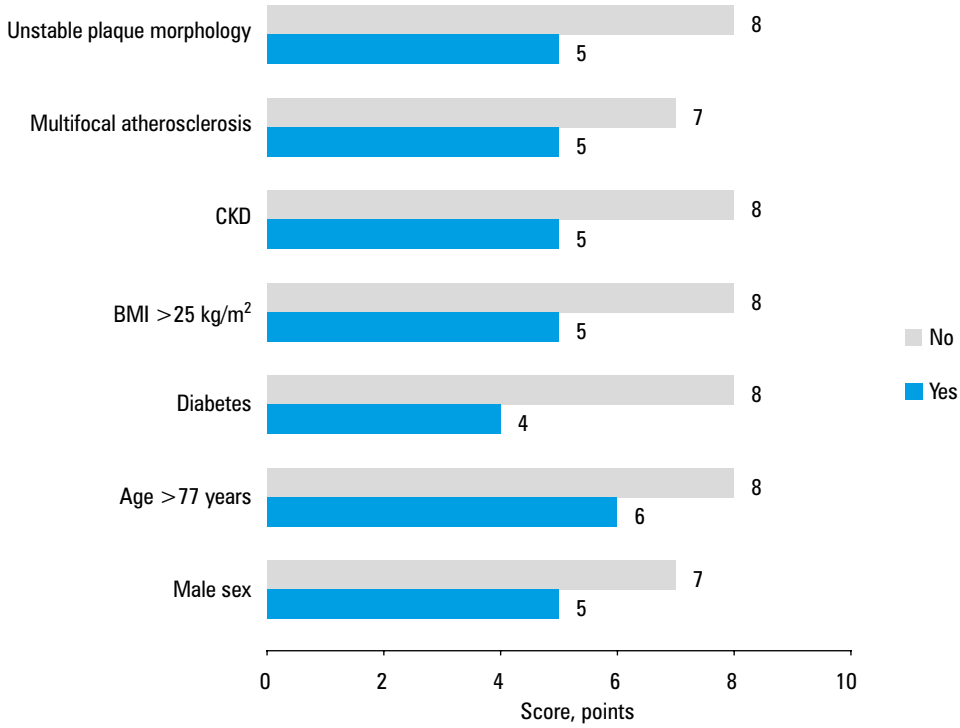

FIGURE 3 Scoring system for the assessment of the risk of developing symptomatic internal carotid artery stenosis
Abbreviations: see **TABLE 1**

asymptomatic stenosis; the difference was of borderline significance in the head-to-head comparison (P = 0.05) and irrelevant in univariable regression analysis. Lack of the statistical significance regarding the difference can be explained by a small number of patients with contralateral stenosis in both study groups: 47 patients in total (13.6% of the study cohort).

However, it was demonstrated that the coexistence of atherosclerosis in various vascular areas was relevant for the risk of symptomatic ICA stenosis (coronary arteries, the aorta, lower limb arteries) in the study group. Polyvascular atherosclerosis in patients with single or multifocal clinical manifestations has been associated with unfavorable clinical outcomes.[24-26]

Our study confirmed the usefulness of ultrasonography in the search for high-risk plaque. Ultrasonography of carotid plaques combined with the assessment of plaque stability may help to identify not only patients with asymptomatic stenosis at increased risk of progression to symptomatic disease but also those at increased stroke risk during and after interventional treatment. More advanced ultrasound modalities, such as intravascular ultrasound, together with virtual

histology assessment or GSM-derived plaque texture analysis, may be useful in identifying unstable plaques.[13,14] The development of low-risk carotid revascularization methods and adequate diagnostic procedures enable clinicians to choose the proper method for the treatment of different groups of patients, especially those with multifocal atherosclerosis, who can benefit from revascularization.[27,28]

The advancements in the conventional and interventional treatment of patients with ICA stenosis as well as the lack of randomized trials of the contemporary population prompt the search for risk stratification algorithms. The assessment of eligibility for interventional treatment in patients with symptomatic stenosis is based not only on the benefit in the secondary stroke prevention but also on data indicating the improvement of cerebral flow and perfusion and the functional outcome, as well as the potential positive impact on cognitive functions.[29] Treatment choice and the identification of patients at increased risk are much more difficult in asymptomatic individuals.

We developed a predictive scoring model based on significant differences between patients with symptomatic and asymptomatic stenosis, which enabled us to determine the risk of developing symptomatic stenosis. The model included diverse clinical data: age, sex, selected risk factors for atherosclerosis, comorbidities (BMI, diabetes, and CKD), information on the morphology of stenosis assessed by ultrasound, and comorbid multifocal atherosclerosis. The discriminatory sensitivity of the cutoff point of our model reached 77.6%, and its specificity—76.9%, which indicated its usefulness in estimating the risk of ICA stenosis symptom onset. Nevertheless, considering the cross-sectional design of our study, the proposed scoring system requires validation in a prospective study.

Clinical data obtained in daily practice were also used by other authors in order to estimate the risk of ICA stenosis symptom onset manifested by ischemic stroke. In a risk assessment model developed by Burke et al,[23] which was based on vascular stroke risk factors and comorbidities, factors associated with the risk of stroke in patients with ICA stenosis included elevated creatinine levels, a high BMI, and contralateral ICA stenosis. In a predictive model combining classic atherosclerosis risk factors and the assessment of ICA stenosis by ultrasound, the method combining risk factors and stenosis characteristics on ultrasound has been demonstrated to be superior to the model based only on the assessed risk factors for atherosclerosis.[30] The available models for estimating the risk of ICA stenosis symptom onset also involved the use of imaging findings (ultrasonography, head MRI, and perfusion MRI).[20] In other approaches to risk stratification in asymptomatic patients with ICA stenosis, circulating biomarkers have been used, which can also be applied in the construction of risk stratification models.[2,31]

From a clinical point of view, the data obtained in the present study can be useful in selecting the proper management of patients with ICA stenosis, as recommendations for the assessment of patient eligibility for surgical treatment have been based on the results of clinical trials carried out in populations different from patients currently treated. Of note, other potential factors contribute to progression to symptomatic disease in patients with asymptomatic ICA stenosis as well as to the occurrence of ischemic events in the periprocedural periods in patients undergoing interventional treatment. These include some serum biomarkers (eg, inflammatory ones) and cerebral circulation parameters (the state of collateral flow and vasomotor reactivity of cerebral arteries, microembolization), which can be investigated in transcranial Doppler studies. These factors were not examined in our study, because they are not included in a standard diagnostic procedure; however, they would be included in the symptomatic risk model construction in future studies.

Our study was based on data obtained in daily clinical practice and routinely collected from patients with ICA stenosis. The opportunity to use the data obtained in daily medical practice, without the need to apply additional diagnostic procedures or related workload, can certainly be helpful for clinicians. A potential application of the data obtained in the course of routine clinical practice is undoubtedly an advantage of our model for estimating the risk of developing clinical signs in patients with ICA stenosis. Combining clinical, demographic, and imaging parameters further raises the stratification value regarding the risk of brain ischemia in this group of patients.

Study limitations Admittedly, our study had several limitations. We did not compare patients with TIA and stroke—it did not affect the results of the study in terms of factors associated with the symptomatic status of ICA stenosis, but such an analysis could add to its value.

Only stroke and TIA were regarded as the symptoms of CNS ischemia and we did not investigate "silent" ischemic events detected in neuroimaging studies; of note, it is impossible to assess the onset time of silent strokes. On the other hand, due to ethical reasons, should not we regard silent infarct as a symptom or sign of stenosis before the occurrence of clinical symptoms? The development of new neuroimaging methods enabling the identification of early ischemic lesions together with the improvement of treatment strategies encourage us to redefine symptomatic or asymptomatic ICA stenosis.[32] Data on the areas of silent CNS ischemia visualized on neuroimaging can be used in a predictive model for the estimation of symptomatic stenosis could increase the accuracy of such model.

Furthermore, no other imaging methods were included in the assessment of atherosclerotic plaque instability in the ICA (CT angiography

and / or MRI angiography). The aim of the study was to assess the potential use of clinical data collected routinely from patients with ICA stenosis, and CT and / or MRI angiography are not routinely performed in all patients; these modalities are used only when ultrasonography is inconclusive for the assessment of the degree and morphology of ICA stenosis.

The ultrasound criteria for plaque instability adopted in our study lacked some possible features of unstable plaque: stenosis progression greater than 20%, neovascularization within the plaque, presence of mobile fragments of the plaque, detection of spontaneous embolization using transcranial Doppler monitoring, evaluation of an impaired cerebrovascular reserve. The adopted criteria are not of high accuracy, especially for the assessment of plaque ulceration and high-grade stenosis.[33]

The exclusion of patients with moderate symptomatic stenosis (50%–70%) might have caused a selection bias, but it helped us to unify the compared groups and did not affect the results of the study.

The retrospective design of the scoring model for the evaluation of the risk of symptomatic ICA stenosis development also limited our study, as the prospective long-term one would be more reliable to assess the actual risk of progression from asymptomatic to symptomatic ICA stenosis.

Conclusions Our cross-sectional study indicated that male sex, diabetes, an elevated BMI, CKD, the unstable ultrasound morphology of atherosclerotic plaque, and multifocal atherosclerosis are more frequently found in patients with symptomatic carotid artery stenosis than in those asymptomatic. We also showed that the analysis of selected imaging and clinical parameters may allow clinicians to estimate the risk of the symptomatic progression of ICA stenosis. However, the proposed scoring system requires further prospective validation.

ARTICLE INFORMATION

ACKNOWLEDGMENTS The project was financed by National Science Centre Poland (UMO-2012/07/B/NZ7/04207; to AL-B).

CONTRIBUTION STATEMENT PP collected data, performed analysis, and wrote the manuscript. TU was involved in study planning and manuscript drafting. DZ was involved in data collection and analysis. AC and AS contributed to data analysis and literature search. AL-B conceived and designed the analysis and supervised the study. All authors edited and approved the final version of the article.

CONFLICT OF INTEREST None declared.

HOW TO CITE Puz P, Urbanek T, Ziaja D, et al. Factors associated with the symptomatic status of carotid artery stenosis: identification in a cross-sectional study and development of a scoring system. Pol Arch Intern Med. 2021; 131: 17-25. doi:10.20452/pamw.15676

REFERENCES

1 Masoomi R, Shah Z, Dawn B, et al. Progression of external and internal carotid artery stenosis is associated with a higher risk of ischemic neurologic events in patients with asymptomatic carotid artery stenosis. Vasc Med. 2017; 22: 418-423.

2 Puz P, Lasek-Bal A. Repeated measurements of serum concentrations of TNF-alpha, interleukin-6 and interleukin-10 in the evaluation of internal carotid artery stenosis progression. Atherosclerosis. 2017; 263: 97-103.

3 Gaba K, Ringleb P, Halliday A. Asymptomatic carotid stenosis: intervention or best medical therapy? Curr Neurol Neurosci Rep. 2018; 18: 80.

4 Brott T, Calvet D, Howard G, et al. Long-term outcomes of stenting end endarterectomy for symptomatic carotid stenosis: a pre-planned pooled analysis of individual patient data. Lancet Neurol. 2019; 18: 348-356.

5 Meschia JF, Klaas JP, Brown RD Jr, Brott T. Evaluation and management of atherosclerotic carotid stenosis. Mayo Clin Proc. 2017; 92: 1144-1157.

6 Naylor AR, Ricco JB, de Borst GJ, et al. Editor's Choice – Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2018; 55: 3-81.

7 Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014; 45: 3754-3832.

8 Reiff T, Eckstein HH, Mansmann U, et al. Angioplasty in asymptomatic carotid artery stenosis vs. endarterectomy compared to best medical treatment: one-year interim results of SPACE-2. Int J Stroke. 2019 Mar 15. [Epub ahead of print].

9 Gacoń J, Przewłocki T, Podolec J, et al. Prospective study on the prognostic value of repeated carotid intima-media thickness assessment in patients with coronary and extra coronary steno-occlusive arterial disease. Pol Arch Intern Med. 2019; 129: 12-21.

10 Kakkos SK, Nicolaides AN, Charalambous I, et al. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. J Vasc Surg. 2014; 59: 956-967.

11 Gupta A, Kesavabhotla K, Baradaran H, et al. Plaque echolucency and stroke risk in asymptomatic carotid stenosis: a systematic review and meta-analysis. Stroke. 2015; 46: 91-97.

12 Aboyans V, Ricco J-B, Bartelink ML, et al. 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries endorsed by: The European Stroke Organization (ESO) The Task Force for the diagnosis and treatment of peripheral arterial diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018; 39: 763-816.

13 Sangiorgi G, Bedogni F, Sganzerla P, et al. The Virtual histology In Carotids Observational Registry (VICTORY) study: a European prospective registry to assess the feasibility and safety if intravascular ultrasound and virtual histology during carotid interventions. Int J Cardiol. 2013: 168: 2089-2093.

14 Madycki G, Staszkiewicz W, Gabrusiewicz A. Carotid plaque texture analysis can predict the incidence of silent brain infarcts among patients undergoing carotid endarterectomy. Eur J Vasc Endovasc Surg. 2006; 31: 373-380.

15 Musiałek P, Pieniążek P, Tracz W, et al. Safety of embolic protection device-assisted and unprotected intravascular ultrasound in evaluating carotid artery atherosclerotic lesions. Med Sci Monit. 2012; 18: 7-18.

16 Puz P, Lasek-Bal A, Urbanek T, Kazibutowska Z. Assessment of cerebral embolism and vascular reserve parameters in patients with carotid artery stenosis. Neurol Neurochir Pol. 2016; 50: 356-362.

17 Lasek-Bal A, Kula D, Urbanek T, et al. The Association of SNPs located in the CDKN2B-AS1 and LPA genes with carotid artery stenosis and atherogenic stroke. Front Neurol. 2019; 10: 1170.

18 Sprynger M, Rigo F, Moonen M, et al. Focus on echovascular imaging assessment of arterial disease: complement to the ESC guidelines (PARTIM 1) in collaboration with the Working Group on Aorta and Peripheral Vascular Diseases. Eur Heart J Cardiovasc Imaging. 2018; 19: 1195-1221.

19 von Reutern GM, Goertler MW, Bornstein NM, et al. Grading carotid stenosis using ultrasonic methods. Stroke. 2012; 43: 916-921.

20 Park MS, Kwon S, Lee MJ, et al. Identification of high risk carotid artery stenosis: a multimodal vascular and perfusion imaging study. Front Neurol. 2019; 10: 765.

21 Stoberock K, Debus ES, Atlihan G, et al. Gender differences in patients with carotid stenosis. Vasa. 2016; 45: 11-16.

22 Paraskevas KI, Gloviczki P. Prognostic factors of long-term survival to guide selection of asymptomatic patients for carotid endarterectomy. Int Angiol. 2020; 39: 29-36.

23 Burke JF, Morgenstern LB, Hayward RA. Can risk modelling improve treatment decisions in asymptomatic carotid stenosis? BMC Neurol. 2019; 19: 295.

24 Vlajinac HD, Marinković JM, Maksimović MZ, et al. The prevalence of polyvascular disease in patients with carotid artery disease and peripheral artery disease. Kardiol Pol. 2019; 77: 926-934.

25 Puz P, Lasek-Bal A, Warsz-Wianecka A, Kaźmierski R. Prevalence of atherosclerotic stenosis of carotid and cerebral arteries in patients with stable or unstable coronary artery disease. Pol Arch Intern Med. 2020; 130: 412-419.

26 Haberka M, Bałys M, Matla M, et al. Carotid artery stenosis and ultrasound vascular indexes predict the coronary revascularization in patients with high cardiovascular risk scheduled for coronary angiography. Kardiol Pol. 2019; 77: 1028-1033.

27 Musiałek P, Mazurek A, Trystuła M, et al. Novel PARADIGM in carotid revascularisation: Prospective evaluation of All-comer peRcutaneous cArotiD revascularisation in symptomatic and Increased-risk asymptomatic carotid artery stenosis using CGuard™ MicroNet-covered embolic prevention stent system. EuroIntervention. 2016; 12: 658-670.

28 Mazurek A, Boratyńska A, Malinowski KP, et al. MicroNET-covered stents for embolic prevention in patients undergoing carotid revascularisation: twelve-month outcomes from the PARADIGM study. EuroIntervention. 2020; 16: e950-e952.

29 Badacz R, Kabłak-Ziembicka A, Urbańczyk-Zawadzka M, et al. Magnetic resonance imaging and clinical outcome in patients with symptomatic carotid artery stenosis after carotid artery revascularization. Adv Interv Cardiol. 2017: 13: 225-232.

30 Jamthikar A, Gupta D, Khanna NN, et al. A low-cost machine learning-based cardiovascular/stroke risk assessment system: integration of conventional factors with image phenotypes. Cardiovasc Diagn Ther. 2019; 9: 420-430.

31 Musiałek P, Tracz W, Tekieli Ł, et al. Multimarker approach in discriminating patients with symptomatic and asymptomatic atherosclerotic carotid artery stenosis. J Clin Neurol. 2013; 9: 165-175.

32 Musiałek P, Grunwald IQ. How asymptomatic is "asymptomatic" carotid stenosis? Resolving fundamental confusion(s) – and confusions yet to be resolved. Pol Arch Inern Med. 2017; 127: 718-719.

33 Yuan J, Usman A, Das T, et al. Imaging carotid atherosclerosis plaque ulceration: comparison of advanced imaging modalities and recent developments. AJNR Am J Neuroradiol. 2017; 38: 664-671.