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Prognostic Significance of Carotid and Lower Extremity Artery Stenosis in Patients With High and Very High Cardiovascular Risk

Aim To study prognostic significance of the degree of stenosis of carotid and lower-extremity arteries (LEA) in patients at high and very high risk of cardiovascular complications (CVC).

Material and methods The study included men and women aged 40–67 years at high and very high risk of CVC. Duplex ultrasound scanning of carotid arteries and LEA was performed for all patients. Laboratory tests included measurements of glucose, glycated hemoglobin, total cholesterol, low-density lipoprotein cholesterol (LDL–C), high-density lipoprotein cholesterol (HDL–C), triglycerides, uric acid, creatinine with estimation of glomerular filtration rate (GFR) using the CKD-EPI Creatinine Equation formula, and high-sensitivity C-reactive protein (hsCRP). Composite endpoint was death from CVC, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization.

Results The study included 214 patients from groups of high and very high risk of CVC. Median age of patients was 59.0 [53.2; 64.0] years. A very high risk was identified in 141 (65.8%) patients and a high risk of CVC in 73 (34.1%). Atherosclerotic plaques in at least one vascular bed were found in 191 (89.3%) patients. Duration of the follow-up period was 32.0 [13.7; 49.1] months. Outcomes comprising the composite endpoint were observed in 36 (16.8%) patients. Presence of carotid stenosis ≥35% was not statistically significantly associated with the occurrence of outcomes comprising the composite endpoint (relative risk, RR: 1.22; 95% confidence interval, CI: 0.56–2.66; p=0.607). In contrast, the presence of LEA stenosis ≥35% was associated with a 2.51 times increased RR of CVC (95% CI: 1.02–6.23; p=0.044).

Conclusion In patients from the groups of high risk and very high risk of CVC, the presence of LEA stenosis ≥35% predicted the development of severe CVC with a 69.4% sensitivity and a 61.8% specificity. The presence of LEA stenosis ≥35%, but not of carotid arteries, was an independent predictor of severe CVC (RR, 2.51; 95% CI: 1.02–6.23; p=0.044) after adjustments for sex, age, presence of arterial hypertension, diabetes mellitus, ischemic heart disease, obesity, smoking, LDL–C, GFR, and drug therapy.

Keywords Risk of cardiovascular complications; atherosclerotic plaque; carotid arteries; lower-extremity arteries; cardiovascular complications

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Introduction

The 2019 ESC/EAS Guidelines for the management of dyslipidemias for the first time included a recommendation to classify patients with atherosclerotic plaques not only in the carotid arteries but also in the femoral arteries as at least at high risk of cardiovascular complications (class of recommendation IIa, level of evidence B) [1, 2]. At the same time, imaging of atherosclerosis by duplex ultrasound scanning of the carotid arteries or lower limb arteries can contribute to improving the evaluation of prognosis for patients at high and very high risk of cardiovascular complications [3]. At the same time, the prognostic significance of atherosclerosis of the two vascular beds may differ significantly. Traditional risk factors (RFs) for cardiovascular diseases (CVDs) and complications are more associated with femoral artery atherosclerosis, rather than carotid atherosclerosis [4]. Moreover, the prevalence and severity of lower limb atherosclerosis is a stronger predictor of the presence of obstructive coronary atherosclerosis than the prevalence and severity of carotid atherosclerosis [5]. These could all be an indication that quantitative indicators characterizing the severity of lower limb artery lesions may be independent predictors of severe cardiovascular complications, and their prognostic value may correspond to or even exceed that of ultrasound markers of carotid atherosclerosis. There are limited results of prospective

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studies on this issue, which necessitates conducting corresponding clinical studies with solid endpoints [6].

We have previously found in a small sample of patients that lower limb artery stenosis ≥ 40% is an independent predictor of cardiovascular complications (cardiovascular death, non-fatal myocardial infarction (MI), or unstable angina, non-fatal stroke, coronary revascularization) in patients at high and very high risk of cardiovascular complications [3]. At the same time, a comparative study of the prognostic significance of the degree of stenosis of carotid and lower limb arteries is of immediate practical relevance due to the lack of instructions in the current clinical guidelines on the selection of a vascular bed (carotid or lower limb arteries) for the screening of atherosclerotic lesions in a given clinical situation [2].

Objective

Evaluate the prognostic significance of the degree of carotid and lower limb stenosis in patients at high and very high risk of cardiovascular complications.

Material and Methods

The study included male and female patient aged 40–67 years at high and very high risk of cardiovascular complications. The risk of cardiovascular complications was assessed following the 2019 ESC/EAS guidelines for the management of dyslipidemia [2]. The study protocol was approved by the ethics committee of South Ural State Medical University (Minutes No. 10 dated 27/10/2018). All patients signed the informed consent to participate in the study. The exclusion criteria were the following clinical conditions: acute period of cerebral and coronary circulation disorders; severe liver and renal dysfunction (decreased glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2); cancer; mental illness; alcohol and substance abuse.

All patients received relevant recommendations for lifestyle changes, lipid-lowering therapy was recommended (if there were indications) until the achievement of the target low-density lipoprotein (LDL) cholesterol levels, and antithrombotic therapy [2]. If atherosclerotic plaques were detected that narrowed the vessel lumen by more than 50%, it was recommended that the patient should consult a vascular surgeon.

All patients underwent duplex ultrasound of the carotid and lower limb arteries. The examination was conducted in the B mode, color-coded flow mapping, and pulse Doppler mode. The following vessels were examined along the entire length on both sides in longitudinal and cross-sectional views: common carotid artery and carotid bifurcation, internal and external carotid arteries, common femoral arteries, superficial femoral arteries, popliteal arteries, tibial peroneal trunk artery, anterior and posterior tibial arteries.

A focal intima-media thickness (IMT) of more than 1.5 mm or IMT greater than the surrounding IMT by 0.5 mm or IMT greater than IMT of the adjacent areas by 50% was considered a plaque [7]. The percentage of stenosis was measured planimetrically in the B mode by the cross-sectional diameter of the vessel. The percentage of stenosis was determined using the ECST (European Carotid Surgery Trial) method. When a plaque that narrowed the blood vessel lumen was detected, the maximum carotid stenosis (CSmax) and lower limb stenosis (LLSmax) were determined for a particular patient. The examination was conducted using a 10 MHz linear probe on an expert-grade multifunction digital ultrasound diagnostic scanner Samsung Medison EKO7 (Republic of Korea).

Blood samples were collected from all patients on an empty stomach in the morning. The following indicators were determined: glucose (venous blood), glycated hemoglobin, total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, uric acid, creatinine (with GFR calculation using the CKD-EPI formula), high-sensitivity C-reactive protein (hs-CRP).

The composite endpoint included cardiovascular death, nonfatal MI, nonfatal stroke, and coronary revascularization.

The statistical analysis of the data obtained was performed using SPSS Statistics version 18. The qualitative variables were expressed using the absolute and relative frequencies (n (%)), quantitative variables were presented using the medians (Me) and the interquartile ranges [25th percentile; 75th percentile] if the distribution was non-normal, and the means (M) and the standard deviations (SD), if the distribution was normal. ROC analysis was carried out to determine the thresholds of the indicators of interest, sensitivity and specificity were estimated, and the area under the characteristic curve (AUC) was calculated a 95% confidence interval (CI). Survival analysis was conducted in the groups using the Kaplan-Meier method, two curves were compared using a log-rank test. Observations, in which the outcome of interest occurred, were marked as complete. Observations, in which the outcome did not occur by the end of the study, were considered censored. Cox stepwise regression analysis was used to identify RFs. Time to the outcome was a dependent (predictable) variable, and the factors of interest were independent variables. The critical significance value was p=0.05 for all the statistical data analysis procedures used.

Results

The study included 214 patients at high and very high cardiovascular risk, the median age was 59.0 [53.2; 64.0] years. Very high risk was established in 141 (65.8%) patients: 134 (62.6%) subjects had atherosclerotic CVD at the time of inclusion, 5 (2.33%) patients had type 2 diabetes mellitus (DM) and major RFs for cardiovascular complications; 2 (0.93%) patients had the risk of cardiovascular complications SCORE ≥ 10%. High risk of cardiovascular complications was registered in 73 (34.1%) patients: 17 (7.94%) patients had a significantly increased level of one of the RFs, 17 (7.94%) patients had GFR <60 mL/min/1.73 m^2, and 39 (27.6%) subjects had the risk of cardiovascular complications of SCORE 5–9%. Clinical characteristics of patients are presented in Table 1.

Table 2 provides the results of duplex ultrasound of the carotid and lower limb arteries.

Table 1. Clinical characteristics of the subjects

Parameter	Value
Age, years	59.0 [53.2; 64.0]
Male / female patients, n (%)	108 (50.5)/106 (49.5)
BMI, kg/m^2	28.4 [25.0; 31.3]
Obesity, n (%)	80 (37.4)
Abdominal obesity, n (%)	144 (67.3)
Smoking, n (%)	55 (25.7)
Coronary artery disease, n (%)	128 (59.8)
Postinfarction cardiosclerosis, n (%)	57 (26.6)
Myocardial revascularization, n (%)	47 (21.9)
History of stroke, n (%)	10 (4.67)
Intermittent claudication, n (%)	35 (16.3)
Chronic lower limb ischemia (Pokrovsky classification), n (%)	
Stage IIa	16 (7.47)
Stage IIb	19 (8.87)
DM type 2, n (%)	75 (35.0)
Arterial hypertension, n (%)	176 (80.8)
Chronic heart failure, n (%)	104 (48.6)
Antiplatelet drugs, n (%)	133 (62.1)
Beta blockers, n (%)	108 (50.5)
RAAS inhibitors, n (%)	146 (68.2)
Diuretics, n (%)	38 (17.7)
Statins, n (%)	127 (59.3)
Oral hypoglycemic drugs, n (%)	50 (23.3)
Insulin therapy, n (%)	27 (12.6)
TC, mmol/L	5.08 [4.01; 6.21]
LDL cholesterol, mmol/L	3.05 [1.98; 4.05]
HDL cholesterol, mmol/L	1.24 [1.04; 1.52]
TG, mmol/L	1.52 [1.10; 1.98]
hs-CRP, mg/L	2.28 [1.06; 3.97]
Uric acid, µmol/L	325 [257; 407]
Glucose, mmol/L	5.80 [5.13; 6.89]
Glycated hemoglobin, %	5.40 [4.83; 6.12]
GFR, mL/min/1.73 m^2	62.0 [52.0; 73.5]

The data is presented as the medians and interquartile ranges (Me [25th percentile; 75th percentile] if not otherwise specified. RAAS, renin-angiotensin-aldosterone system; hs-CRP, high sensitivity C-reactive protein; GFR, glomerular filtration rate.

191 (89.3%) patients had plaques in at least one vascular bed, and in 136 (63.5%) patients had plaques in two vascular beds. Carotid plaques were relatively more common than plaques in the lower limb arteries.

The duration of the follow-up was 32.0 [13.7; 49.1] months. Outcomes constituting the composite endpoint occurred in 36 (16.8%) patients: cardiovascular death in 4 (1.86%) cases, non-fatal MI, or stroke in 13 (6.07%) patients, myocardial revascularization in 19 (8.87%) cases with coronary artery bypass grafting in 6 (2.80%) patients and endovascular intervention in 13 (6.07%) patients. ROC analysis was performed to determine the optimal thresholds for maximum carotid and lower limb stenosis to predict the onset of outcomes constituting the composite endpoint (Figure 1).

The following cut-off values were obtained: maximum carotid stenosis ≥ 35% (sensitivity 58.3%, specificity 60.0%); maximum lower limb stenosis ≥35% (sensitivity 69.4%, specificity 61.8%). Kaplan-Meier curves showing patient survival depending on the presence of carotid or lower limb stenosis ≥ 35% are provided in Figure 2.

To clarify the independent prognostic value of maximum carotid and lower limb stenosis for cardiovascular complications, Cox regression analysis was performed with the adjustment for sex, age, presence of arterial hypertension (AH), DM, coronary artery disease (CAD), obesity, smoking, LDL cholesterol, GFR, the use of angiotensin-converting enzyme inhibitors, antiplatelet drugs, statins, and beta-blockers. The presence

Table 2. Duplex ultrasound of carotid arteries and lower limb arteries

Parameter	Value
Carotid artery plaque, n (%)	170 (79.4)
Maximum carotid stenosis, %	35.0 [25.0; 43.0]
Carotid stenosis, n (%)	
≥ 35%	90 (42.0)
≥ 50%	37 (17.3)
lower limb artery plaque, n (%)	152 (71.0)
Maximum lower limb artery stenosis, %	35.0 [20.0; 50.0]
lower limb artery stenosis, n (%)	
≥ 35%	92 (42.9)
≥ 50%	57 (26.6)
Intact carotid arteries and lower limb arteries, n (%)	23 (10.7)
Carotid artery and lower limb artery plaques, n (%)	136 (63.5)

The data is presented as the medians and interquartile ranges (Me [25th percentile; 75th percentile] if not otherwise specified.

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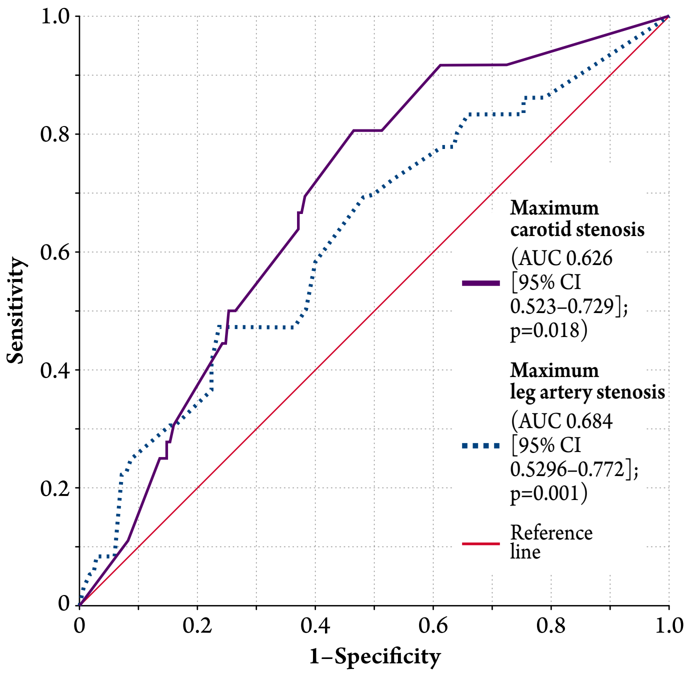
Figure 1. ROC curves showing the diagnostic value of maximum carotid artery stenosis and maximum lower limb artery stenosis for the development of cardiovascular complications



of carotid stenosis ≥ 35% was not statistically significantly associated with the outcomes constituting the composite endpoint (hazard ratio (HR) 1.22; 95% CI 0.56–2.66; p=0.607). In contrast, the presence of lower limb stenosis ≥35% was associated with a 2.51-fold increase in the HR for cardiovascular complications (95% CI 1.02–6.23; p=0.044) after adjustment for the specified factors.

Discussion

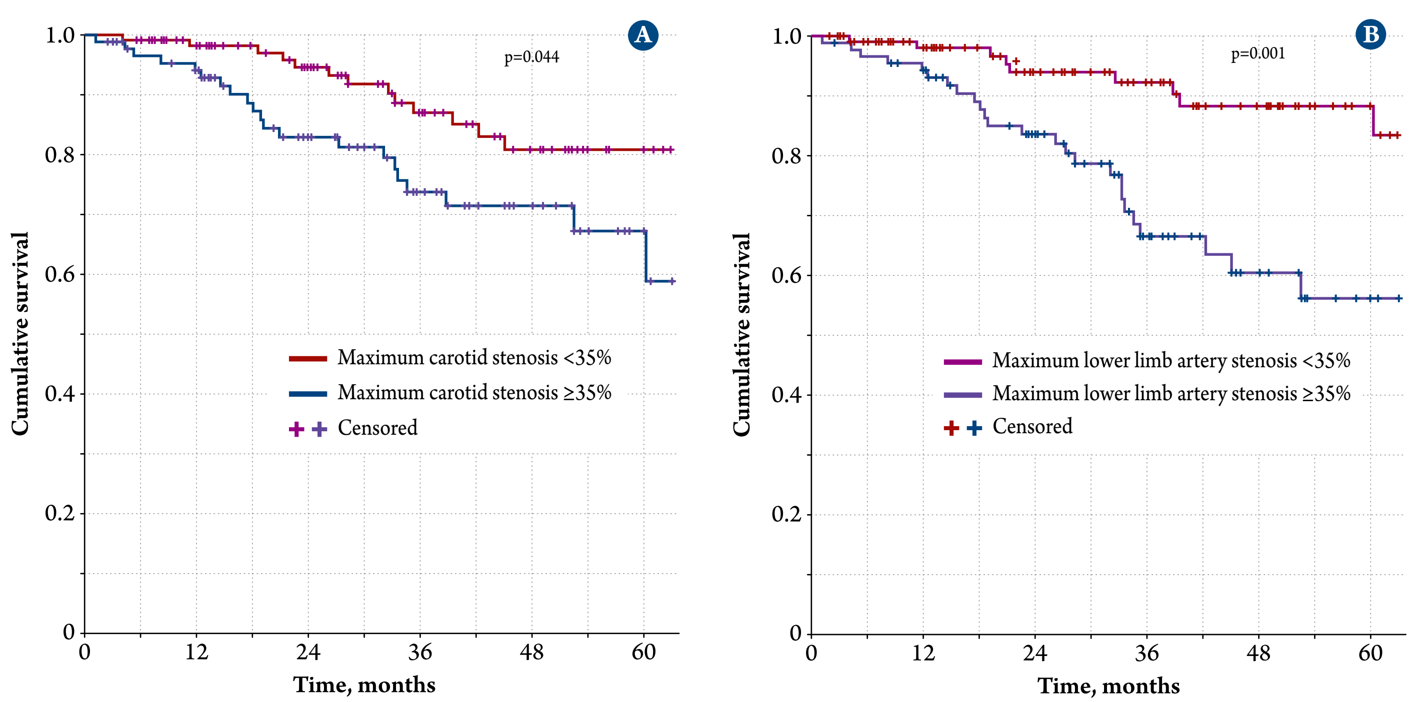
Patients at high and very high risk of cardiovascular complications represent an extremely heterogeneous group and differ significantly in the risk of cardiovascular complications [8, 9]. Non-invasive atherosclerosis imaging techniques used to re-stratify the risk in patients at low and moderate risk of cardiovascular complications can also be used to personalize the prognosis for patients at high and very high risk, including to identify patients at extremely high risk of cardiovascular complications [10].

The main results of the study are as follows:

1) For patients at high and very high risk of cardiovascular complications, the presence of carotid or lower limb stenosis ≥35% made it possible to predict severe cardiovascular complications with a sensitivity of 58.3% and 69.4% and a specificity of 60.0% and 61.8% respectively;
2) The presence of lower limb stenosis ≥35%, but not carotid stenosis, was an independent predictor of severe cardiovascular complications after adjustment for sex, age, AH, DM, CAD, obesity, smoking, LDL cholesterol, GFR, and drug therapy.

Several clinical studies have previously demonstrated the prognostic significance of lower limb atherosclerosis. Davidsson et al. [11] showed that the presence of plaques in both carotid arteries (HR 2.09; 95% CI 1.05–4.16; p=0.037) and femoral arteries (HR 1.99; 95% CI 1.01–3.91; p=0.047) was an independent predictor of cardiovascular complications in middle-aged male patients according to a 10 year follow-up period. In the study by

Figure 2. Kaplan-Meier curves depending on the presence of carotid artery stenosis (A) and lower limb artery stenosis (B)



Kocyigit et al. [12], among the markers of carotid, femoral, and coronary atherosclerosis, only coronary artery calcification and plaques with surface irregularities and ulceration in femoral arteries demonstrated independent prognostic value for severe CVDs. We found previously that the presence of lower limb stenosis > 40% (HR 3.17; 95% CI 1.27–7.92; p=0.013) and plaques in popliteal arteries (HR 2.49; 95% CI 1.27–7.92; p=0.013) is independently associated with an increased risk of cardiovascular complications in patients at high and very high risk of cardiovascular complications [3]. The degree of peripheral artery stenosis is directly related to the risk of cardiovascular complications. In the study by Barbarash et al. [13], the incidence of cardiovascular complications in patients with the history of coronary artery bypass grafting was highest in the group with peripheral arterial stenosis ≥ 50%, however, a statistically significant increase in the incidence of cardiovascular complications was observed in stenosis ≥ 30%.

It should be noted that, according to the literature, the assessment of atherosclerotic lesions of the lower limb arteries performed to clarify the risk of cardiovascular complications is most often limited to the examination of femoral arteries [1, 4, 5]. However, atherosclerotic lesions in other segments of the lower limb arteries also have independent prognostic significance. Tern et al. [14] showed that the severity of atherosclerosis (Bollinger score) of femoropopliteal (HR 1.34; 95% CI 1.11–1.08; p=0.05) and tibial (HR 1.03; 95% CI 1.01–1.03; p=0.03) segments of the lower limb arteries was independently associated with increased HR for all-cause death. The independent prognostic significance of tibial arterial atherosclerosis for cardiovascular and all-cause death was demonstrated earlier in a Finnish study including 887 patients with lower limb peripheral arterial disease [15, 16]. Our previous findings on the prognostic significance of plaques in the popliteal arteries also show that the assessment of atherosclerotic lesions of the lower limb arteries throughout the entire length can be used to predict the risk of cardiovascular complications [3, 17].

This work is a continuation of our previous research and significantly expands and supplements earlier results. The reproducibility and reliability of the data obtained are largely due to a 2-fold increase of the patient sample, longer follow-up, and modification of the composite endpoint in favor of more severe outcomes. As far as we know, this is the first study to demonstrate that the degree of lower limb stenosis can be superior to the degree of carotid stenosis as a predictor of cardiovascular complications in patients at high and very high risk. This may be due to the fact that the presence of plaques in the lower limb arteries more accurately reflects generalized atherosclerosis, including severe coronary atherosclerosis, responsible for the development of most outcomes that constitute the composite endpoint [18, 19].

This study has several limitations:

1) Lack of analysis of treatment adherence during the follow-up period;
2) Lack of analysis of the effect of achieving the target levels of LDL cholesterol on the risk of outcomes that constitute the composite endpoint.

Conclusion

In patients at high and very high risk of cardiovascular complications, the presence of the lower limb artery stenosis ≥ 35% made it possible to predict the development of severe cardiovascular complications with a sensitivity of 69.4% and a specificity of 61.8%. The presence of lower limb artery stenosis ≥ 35%, rather than stenosis of the carotid arteries, was an independent predictor of severe cardiovascular complications (hazard ratio 2.51; 95% confidence interval 1.02–6.23; p = 0.044) after adjustment for sex, age, presence of arterial hypertension, diabetes mellitus, coronary artery disease, obesity, smoking, low-density lipoprotein cholesterol, glomerular filtration rate, drug therapy.

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