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Prognostic significance of atherosclerosis of one or two vascular systems in patients with high and very high cardiovascular risk

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Aim. To study the prognostic significance of atherosclerosis of one and several vascular systems in patients with high and very high cardiovascular risk (CVR).

Material and methods. The study included 171 patients with high (26,9%) and very high (73,1%) CVR. All patients underwent duplex ultrasound of the carotid and lower limb arteries. The composite endpoint (CE) was cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization.

Results. The follow-up period lasted 31,1 (17,8; 47,9) months. CE events occurred in 29 (16,9%) patients: cardiovascular death — 3 (1,75%) patients; nonfatal myocardial infarction — 7 (4,09%) patients; nonfatal stroke — 6 (3,51%) patients; coronary revascularization — 13 (7,60%) patients. Cumulative survival of patients with high and very high CVR with atherosclerotic plaques in the same vascular system did not significantly differ from that in patients with intact peripheral arteries (p=0,977). The event-free survival of patients with combined lesions of the carotid and lower limb arteries was significantly lower in comparison with patients with one vascular system involvement (p=0,011). The combined lesion of the carotid and lower limb arteries was associated with an increase in the relative risk (RR) of adverse cardiovascular events (RR, 3,15 (95% CI, 1,02-9,74; p=0,046), adjusted for sex, age, and peripheral arterial disease symptoms.

Conclusion. In patients with high and very high CVR, atherosclerotic lesion of two vascular systems of peripheral arteries is associated with an increase in the RR of adverse cardiovascular events, adjusted for sex, age, and peripheral arterial disease symptoms. The presence of atherosclerotic plaques in one vascular bed was not associated with an increase in the risk of CE events.

Keywords: atherosclerosis, multifocal atherosclerosis, diabetes, adverse cardiovascular events.

Relationships and Activities: none.

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Introduction

Precise stratification of cardiovascular risk (CVR) is one of the most important and difficult problems of modern cardiology. The urgency of this problem remains both within primary and secondary prevention of cardiovascular diseases (CVD) [1, 2]. The need to improve the algorithms for classifying the risk of cardiovascular accidents in high and very high-risk patients, among other things, is associated with the introduction of new expensive drugs into clinical practice, the use of which across national health systems is most effective in terms of cost-benefit analysis in patients with the highest risk of adverse cardiovascular events [3, 4]. This contributed to the appearance of the extreme CVR category in clinical guidelines and the search for phenotypes associated with it [5]. For example, it was found that among patients without diagnosed CVD, but with severe calcification of the coronary arteries (Agatston index ⩾1000), the risk of cardiovascular events was higher than that for patients with established CVD [6]. The use of various non-invasive methods of cardiovascular imaging, serum and molecular genetic markers is a leading approach in the modernization of CVR classification systems.

Multifocal atherosclerosis (MFA), defined as a symptomatic or clinically significant lesion of two or more vascular territories, has been considered in the last few years as a separate prognostically unfavorable phenotype of atherosclerosis [7, 8]. At the same time, even asymptomatic atherosclerotic lesions of several vascular territories are associated with an increase in the relative risk (RR) of adverse cardiovascular events and overall mortality [9]. The need for systematic screening to detect MFA in high and very high-risk patients is

currently being debated [10]. However, current clinical guidelines do not support this strategy due to the limited available data demonstrating the effectiveness of this approach in terms of clinical benefits and costs [11]. The study of the prognostic significance of various variants of peripheral arterial lesions in patients with different CVR status is a prerequisite for introducing routine screening into clinical practice to detect MFA.

The aim is to study the prognostic significance of atherosclerotic lesions of one and several vascular territories in patients with high and very high CVR.

Material and methods

The study included men and women aged 35-70 years of high and very high CVR, directed by the attending physician for duplex ultrasound scanning (DUS) of the carotid arteries and/or lower limb arteries in order to clarify CVR. The assessment of CVR was carried out in accordance with the recommendations of the European Society of Cardiology for the correction of dyslipidemia 2019 [12]. The study protocol was approved by the Ethics Committee (meeting protocol No. 1 dated January 14, 2017). All patients signed informed consent to participate in the study. The withdrawal criteria for the study were the following clinical conditions: acute period of cerebral and coronary circulation disorders; severe impairment of liver and kidney function (decreased glomerular filtration rate (GFR) <30 ml/min/1,73 m^2); malignant neoplasms; mental illness; alcohol and substance abuse.

All patients underwent blood sampling in the morning on an empty stomach. The following parameters were determined: total cholesterol (C), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glycated hemoglobin, highly sensitive C-reactive protein (hsCRP), creatinine (with subsequent calculation of GFR according to the formula CKD- EPI).

All patients underwent DUS of the carotid arteries and lower limb arteries. The study was carried out in B-mode, color mapping mode, pulsed and power doppler ultrasonography. The following vessels were examined from both sides in longitudinal and cross sections along the entire length: common carotid arteries (CA) with bifurcation of common CA, internal CA, external CA, common femoral arteries, superficial femoral arteries, popliteal arteries, tibioperoneal trunk, anterior tibial arteries, posterior tibial arteries.

Atheroma was considered a focal thickening of the intima-media complex (IMC) >1,5 mm or 0,5 mm more than the surrounding IMC thickness, or 50% more than the IMC thickness of the adjacent parts of the vessel [13]. The percentage of stenosis was measured planimetrically in B-mode over the diameter in the cross-section of the vessel. The percentage of stenosis was determined according to the ECST method (The European Carotid Surgery Trial). When atheromas were detected, stenosing the vascular lumen, the maximum stenosis in a particular patient was determined. The study was carried out with a linear transducer with a frequency of 10 MHz on a digital ultrasonic multifunctional diagnostic scanner of an expert class "Samsung Medison EKO7" (Republic of Korea).

The composite endpoint (CE) was cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization.

Statistical analysis of the obtained data was carried out on a personal computer using Micrososft Excel software and the package for statistical data analysis IBM SPSS Statistics, version 18. Qualitative variables were described by absolute and relative frequencies (percentages). Quantitative variables were described by the median (Me) indicating the interquartile range (Q_1-Q_3) in the case of a discrepancy between the distribution of the value to the normal, mean (M) and standard deviation (SD) — in the case of a normal distribution of the indicator. Survival analysis in groups was performed using the Kaplan-Meier method; the log-rank test was used to compare the two curves. Observations in which the studied outcome occurred were designated as completed. Observations were considered censored if they did not have an outcome at the end of the study. Cox regression stepwise analysis was used to identify risk factors for survival. The time before the outcome was considered a dependent (predicted) feature, and the factors under study were considered independent. The critical level of significance for all statistical data analysis procedures used was taken equal to $p<0,05$.

Results

202 patients were examined according to a single protocol. 31 patients were excluded from the study due to loss to follow-up. The study included 171 patients with high and very high CVR (response rate was 84,6%). A very high risk was found in 125 (73,1%) patients: 123 (71,9%) participants had established atherosclerotic CVD at the time of enrollment in the study, 2 (1,17%) — CVR on the SCORE scale (Systematic Coronary Risk Evaluation) was ⩾10%. High CVR was registered in 46 (26,9%) patients: 12 (7,02%) patients had a significantly increased level of one of the risk factors, 17 (9,94%) patients showed a decrease in GFR <60 ml/min/1,73 m^2, in 4 (2,34%) — type 2 diabetes (D) without damage to target organs and CVR factors, in 13 (7,60%) — CVR on the SCORE scale was 5-9%. The clinical characteristics of the patients are presented in Table 1.

Table 2 shows the results of DUS of the carotid arteries and the lower limb arteries.

Thus, >66% of patients had concomitant atherosclerotic lesions of the CA and lower limb arteries. Atheromas in one of the studied vascular territories were detected in 24,5% of patients. In 8,77% of patients, atheroma was not found in the carotid arteries and lower limb arteries.

In comparison with patients with lesions of one vascular territory, patients with atheroma in two vascular territories were statistically significantly more likely to suffer from type 2 diabetes (43,6 vs 17,1%, $p<0,0001$), stable coronary artery disease (41,4 vs 80,0%, $p=0,001$), and also significantly more often received disaggregant (78,3 vs 53,5%, $p=0,019$) and beta-blockers (61,7 vs 41,4%, $p=0,020$) therapy. It should also be noted that only 64,9% of patients at the time of enrollment in the study received statin therapy. At the same time, the proportion of patients who achieved the corresponding target levels of LDL cholesterol among patients with

Table 1

Clinical characteristics of patients included in the study

Indicator	Patients (n=171)
Age, years, Me (Q_1-Q_3)	61,0 (55,0-66,0)
Male/female, n (%)	92 (53,8)/79 (46,2)
Body mass index, kg/m^2, Me (Q_1-Q_3)	28,7 (25,0-31,9)
Obesity, n (%)	68 (39,7)
Abdominal obesity, n (%)	115 (67,2)
Smoking, n (%)	49 (28,6)
Coronary artery disease, n (%)	118 (69,0)
Postinfarction cardiosclerosis, n (%)	53 (31,0)
Myocardial revascularization, n (%)	44 (25,7)
History of stroke, n (%)	10 (5,84)
Intermittent claudication, n (%)	37 (21,6)
Type 2 diabetes, n (%)	69 (40,3)
Arterial hypertension, n (%)	149 (87,1)
Chronic heart failure, n (%)	99 (57,9)
Disaggregants, n (%)	119 (69,6)
Beta-blockers, n (%)	96 (56,1)
Inhibitors of the RAAS, n (%)	121 (70,7)
Diuretics, n (%)	27 (15,8)
Statins, n (%)	111 (64,9)
Oral hypoglycemic drugs, n (%)	48 (28,0)
Insulin therapy, n (%)	26 (15,2)
Total cholesterol, mmol/l, Me (Q_1-Q_3)	4,96 (3,90-6,17)
LDL cholesterol, mmol / l, Me (Q_1-Q_3)	2,93 (1,95-3,97)
HDL cholesterol, mmol / l, Me (Q_1-Q_3)	1,22 (1,00-1,52)
Triglycerides, mmol/l, Me (Q_1-Q_3)	1,54 (1,12-2,05)
HsCRP, mg / L, Me (Q_1-Q_3)	2,16 (1,04-4,41)
Glycated hemoglobin, %, Me (Q_1-Q_3)	5,50 (4,90-6,50)
GFR, ml/min / 1,73 m^2, Me (Q_1-Q_3)	60,0 (52,0-71,0)

Note: RAAS — renin-angiotensin-aldosterone system, HsCRP — highly sensitive C-reactive protein, Q_1-Q_3 — interquartile range.

Table 2

Results of CA and lower limb arteries DUS

Indicators	Patients (n=171)
Atheroma in CA, n (%)	142 (83,0)
MaxSt CA,%, Me (Q_1-Q_3)	35,0 (25,0-45,0)
CA stenosis ⩾50%, n (%)	36 (21,0)
Atheroma in the lower limb arteries, n (%)	129 (75,4)
Lower limb artery stenosis ⩾50%, n (%)	55 (32,2)
Intact CA and lower limb arteries, n (%)	15 (8,77)
Atheroma in vascular territory, n (%)	42 (24,5)
Atheroma in two vascular territories, n (%)	114 (66,6)

Note: MaxSt — maximum stenosis, Q_1-Q_3 — interquartile range.

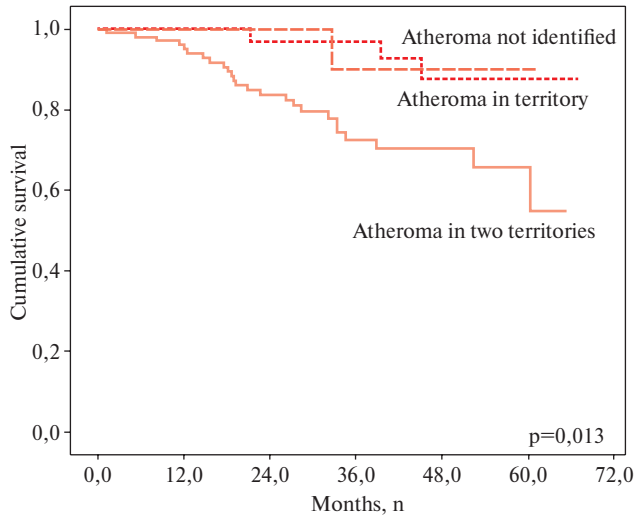

Figure 1 Results of the analysis of Kaplan-Meier curves in relation to the development of adverse cardiovascular events depending on the number of affected vascular territories.

lesions of one or more vascular regions were comparable (16,5 vs 18,3%; p=0,468).

The duration of the follow-up period was 31,1 (17,8; 47,9) months. CE events occurred in 29 (16,9%) patients: cardiovascular death was registered in 3 (1,75%) patients; nonfatal myocardial infarction — in 7 (4,09%) patients; nonfatal stroke — in 6 (3,51%) patients; coronary revascularization — in 13 (7,60%) patients. An analysis was carried out aimed at assessing the prognostic significance of various variants of peripheral arterial lesions in relation to the development of events that make up the CE. Kaplan-Meier curves showing patient survival depending on the number of affected vascular territories are shown in Figure 1.

Cumulative survival of high and very high-risk patients with atheroma in vascular territory did not statistically significantly differ from that in patients with intact peripheral arteries (p=0,977). In contrast, the event-free survival of patients with combined lesions of the carotid arteries and lower limb arteries was statistically significantly lower compared to patients with a single vascular lesion (p=0,011). According to Cox regression analysis, adjusted for sex and age, the presence of atheroma in vascular territory was not associated with an increase in the RR of the occurrence of events included in the CE (RR 0,32; 95% confidence interval (CI): 0,095-1,077; p=0,066). The combined lesion of the carotid and lower limb arteries was associated with a 3,23-fold increase in the RR for adverse cardiovascular events (95% CI: 1,06-9,87; p=0,040) adjusted for gender and age. Moreover, the statistical significance of this type of vascular lesion as a predictor of cardiovascular events persisted regardless of the presence of symptoms of peripheral arterial disease (after adjusting for a history of stroke or intermittent claudication) — RR 3,15 (95% CI: 1,02-9,74; p=0,046). However, when factors such as gender, age, smoking, obesity, diabetes, coronary artery disease, LDL cholesterol and GFR levels were added to the model, the effect of concomitant peripheral arterial disease at

the CE became statistically insignificant (RR 2,13; 95% CI: 0, 64-7,11; p=0,217).

Discussion

Discussion It is now generally accepted that patients with high and very high CVR represent an extremely heterogeneous group, significantly differing in the residual risk of cardiovascular events during therapy [14]. This requires a search for new markers and phenotypes, the use of which in clinical practice will improve the risk stratification in this category of patients [15].

The main results of the study are: 1) in patients with high and very high CVR, atherosclerosis of one basin of the peripheral arteries was not associated with an increase in the RR of adverse cardiovascular events in comparison with patients with intact peripheral arteries; 2) the presence of atheroma in two vascular territories was associated with an increase in the RR of cardiovascular events by 3.15 times, adjusted for gender, age, and the presence of symptoms of peripheral arterial lesions.

Previously, it was found that the prevalence or burden of systemic atherosclerosis is one of the main determinants of the long-term prognosis of patients [16]. Thus, it has been demonstrated that the presence of symptomatic peripheral arterial lesions is associated with an increased risk of adverse cardiovascular events in patients with myocardial infarction [17]. A study by Miao B, et al, including 1302856 patients with established atherosclerotic CVD or >3 risk factors, found a statistically significant increase in the RR of major cardiovascular events as the number of vascular lesions increased [18]. Thus, both symptomatic and asymptomatic lesions of several vascular pools are a predictor of an adverse prognosis, including in patients with high and very high CVR.

In low/moderate-risk patients, imaging of the atheroma in vascular territory in accordance with current clinical guidelines is sufficient to reclassify a patient to the high CVR group and, in most cases, initiate pharmacological correction of risk factors [5]. In our opinion, in patients with high and very high CVR, the most justified is the so-called multifocal ultrasound approach [19, 20]. In this category of patients, atheroma imaging in vascular territory (with stenosis <50%) as part of a standard ultrasound protocol does not provide additional prognostic information. Identification of MFAs and/or assessment of indicators of the burden (load) of atherosclerosis of a particular vascular territory are some of the least costly methods that make it possible to personalize the assessment of CVR [21]. In this case, the absence of symptoms of atherosclerotic lesions of the carotid arteries or lower limb arteries should not be a contraindication to screening ultrasound examination, because the very fact of the presence of atheroma has predictive value. The relatively low incidence of severe asymptomatic atherosclerotic lesions of these vascular territories, requiring prophylactic revascularization, should not be considered as a factor limiting the feasibility and effectiveness of diagnostic intervention [22].

Diabetes and smoking are classic risk factors for diseases associated with atherosclerosis, including MFA [20]. The presence of diabetes is associated with a statistically significant increase in the RR of the presence of MFA and the development of adverse cardiovascular events [23, 24]. The synergistic effects of diabetes and MFA on the development of cardiovascular catastrophes may explain the lack of statistical significance of the effect of MFA on the risk of CE when type 2 diabetes is added to the predictive model in this study. A number of authors consider the combination of diabetes and atherosclerotic lesions of several vascular territories as an independent malignant cardiovascular phenotype [25].

Conclusion

In patients with high and very high CVR, atherosclerotic lesion of the two vascular pools of the peripheral arteries was associated with an increase in the RR of adverse cardiovascular events, adjusted for gender, age, and the presence of symptoms of peripheral arterial disease. The presence of atheroma in vascular territory was not associated with an increase in the risk of events constituting CE.

Relationships and Activities: none.

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