Indian J Med Res 159, May 2024, pp 511-518
DOI: 10.25259/ijmr_652_22

Quick Response Code:

Diagnostic utility of sortilin & other biomarkers in the diagnosis of carotid & coronary atherosclerosis in individuals with arterial hypertension

Yulia Vukolova[1], Irina Gubareva[1], Giuseppe Galati[1,2] & Olga Germanova[1]

[1]Chair of Internal Medicine, International Centre for Education and Research in Cardiovascular Pathology and Cardiovisualization, Samara State Medical University, Samara, Russian Federation, Russia & [2]Heart Failure Unit and Division of Cardiology, Cardiothoracic and Vascular Department, San Raffaele Hospital and Scientific Institute, Milan, Italy

Received March 14, 2022

***Background & objectives*: Cardiovascular diseases (CVDs) are a leading cause of mortality worldwide. The aim of this investigation was to study the role of biological markers in predicting the risk of carotid and coronary artery atherosclerosis.**

***Methods*: A total of 161 males in the age group of 30-65 yr were included in this study. All participants underwent biochemical analyses [cholesterol, low density lipoprotein cholesterol (LDL-C), triglycerides, glucose, (interleukin) IL-8, IL-10, (proprotein convertase inhibitors subtilisin/kexin type 9) PCSK9, sortilin, creatinine]; ECG; echocardiography; coronary angiography; ultrasound doppler of brachiocephalic arteries. Based on PCSK9 levels, participants were divided into four groups: group 1, n=41 individuals with PCSK9 level of 100-250 ng/ml; group 2, n=37 individuals with PCSK9 level of 251-400 ng/ml; group 3, n=51 individuals with PCSK9 level of 401–600 ng/ml and group 4, n=32 individuals with PCSK9 level of 601-900 ng/ml.**

***Results*: Sortilin level was the highest in group 2. Group 3 individuals had the highest level of IL-8. Correlation analysis of the entire data set revealed the relationship of relative left ventricular thickness index with age, cardiovascular risk, body mass index, intima-media thickness and left ventricular mass index; sortilin had a negative relationship of weak strength with age and smoking, a direct relationship between the risk of cardiovascular complications and with IL-10.**

***Interpretation & conclusions*: Sortilin is the innovative marker of CVDs. In the present investigation, we demonstrated the clear increase in the inflammatory markers (IL-8) in individuals with subclinical atherosclerosis. This fact can be explained by the oxygen stress activation. In individuals with coronary artery stenosis (50% and more), the increase in IL-10 levels demonstrates, to our opinion, the activation of antioxidant protection activation.**

Key words Arterial hypertension - atherosclerosis - cardiovascular risk - PCSK9 - sortilin

As per the World Health Organization (WHO), seven out of the 10 leading causes of death in the world are due to non-communicable diseases[1]. During 2000-2021, four nosologies were in the list of main causes

of mortality including cardiovascular diseases (CVDs), cancer, diabetes mellitus and chronic respiratory diseases[2]. As many years before, CVDs still have the leading position in this context[3].CVDs have multiple risk factors (RFs), which have a negative influence on each other[3-5]. One of the most important modifiable RF for CVDs is arterial hypertension (AH), along with others, such as smoking, obesity and hypercholesterolemia. In numerous investigations, it was estimated that AH is one of the most unfavourable RF[4]. The basis of the CVDs pathogenesis is an atherosclerotic process – a violation of lipid metabolism. The new approach is aimed at maximising CVR reduction by lowering low density lipoprotein-cholesterol (LDL-C) with proprotein convertase inhibitors subtilisin/kexin type 9 (PCSK9). The regulatory effect of PCSK9 on lipid metabolism was first discovered in 2003[6]. The role of PCSK9 was demonstrated in the atherosclerotic process[7]. Together with PCSK9, sortilin (a protein regulating intracellular transport through their Vps10p domain) also passes through the Golgi apparatus[8]. In healthy people, the level of circulating PCSK9 directly correlates with the level of sortilin in plasma[9,10]. Also, the correlation between sortilin level in serum and AH was revealed[11].

Atherogenesis involves the immune system cells, biologically active substances, with a damaging effect on the vascular wall and implementing inflammatory reactions – oxidative stress and phagocytosis with the production of cytokines such as interleukins (IL) 6, 8, 10 and others. Particular attention is paid to the innate and adaptive immune response, which is an attribute of all stages of atherosclerosis development, from initiation to the forming of unstable atherosclerotic plaque[12,13].

The present investigation was aimed at studying the role of biological markers in predicting the risk of carotid and coronary artery atherosclerosis.

Material & Methods

The study was carried out by the Department of Cardiology, Russian Railway Medicine, Samara State Medical University from September 2020 – September 2021.

Inclusion and exclusion criteria: The inclusion criteria for the study were as follows: male gender, age 30-65 yr, AH 1-2 grade who provided signed agreement of participation in the study. The exclusion criteria were as follows: patients under 30 and over 65 yr, secondary AH, myocardial infarction or stroke less than six months before the investigation, chronic heart failure NYHA II and more, type 1 diabetes mellitus, toxic diffuse goitre, familial hypercholesterolemia, chronic abdominal ischemia, chronic inflammatory diseases of any localisation, chronic hepatitis, liver cirrhosis and refusal to participate in the study.

A total of 161 males aged 30-65 yr were included in the study. All participants were men because all of them were railway workers – train drivers and assistant drivers. All participants underwent blood biochemical analysis with the determination of total cholesterol, LDL-C, triglycerides, glucose (CLIMA MC-15, IFA-BEST, Russia), interleukin (IL)-8, IL-10, PCSK9 (Quantikine ELISA, USA), sortilin (Aviscera Bioscience, Inc. Santa Clara, CA), creatinine with the calculation of GFR according to the CKD-EPI calculator. The instrumental studies included electrocardiography (ECG) on EK1T-1/3-07 Aksion, Russia, transthoracic echocardiography (EchoCG) and ultrasound Doppler examination of brachiocephalic vessels with the determination of the thickness of the carotid intima-media complex (CIMT) on Philips EN Visor, USA. In the case of atherosclerotic plaques, the percentage in diameter using the ECST (European Carotid Surgery Trial), NASCET (North American Symptomatic Carotid Endarterectomy Trial) and St. Mary's ratio criteria. Coronary angiography (CAG) was performed on all the study participants (General Electric Innova 3100, USA).

All participants were divided into four groups in accordance to the level of PCSK9: Group 1 (n=41) – individuals with a level of PCSK9 between 100-250 ng/ml; group 2 (n=37) – PCSK9 between 251-400 ng/ml; group 3 (n=51) – PCSK9 401-600 between ng/ml and group 4 (n=32) – PCSK9 between 601-900 ng/ml. The reason for this dividing was in accordance to the distribution of individuals by quartiles in statistical analysis.

The participants across all the groups were on the standard therapy for AH correction: angiotensin-converting enzyme inhibitors (perindopril), angiotensin II receptor blockers (losartan, valsartan), β-blockers (nebivolol) and statins (simvastatin, atorvastatin).

Statistical analysis: Descriptive statistics was used to evaluate data. The continuous plots were drawn as the mean ± standard deviation (SD), as well as the median and the first and third quartiles. All variables were analysed for normal distribution by the Kolmogorov-

Table I. Clinical characteristics of study participants

Parameter	Group 1 (n=41) mean ± SD, median (Q1- Q3)	Group 2 (n=37) mean ± SD, median (Q1- Q3)	Group 3 (n=51) mean ± SD, median (Q1-Q3)	Group 4 (n=32) mean ± SD, median (Q1- Q3)	*P*
Age (yr)	47.22±12.60 50 (37-56)	48.62±9.39 50 (46- 54)	49.33±8.88 52 (45-55)	51.09±7.29 53 (47.5-56.25)	χ^2=1.408, df=3, *P*=0.704
Body mass index(kg/m^2)	26.2±3.01 26 (24-28)	28.292±3.41 29 (26-31)	27.725±4.21 28 (25-31)	27.925±4.66 27 (25-29.25)	χ^2=7.482, df=3, *P*=0.058
Left ventricular mass index, (g/m^2)	118.19±39.82 110 (90-142)	123.12±39.37 117 (100.5,-136)	134.98±38.13 136 (106-152.5)	134.48±32.03 140 (109.75- 152.5)	χ^2=9.261, df=3, *P*=0.026
Systolic blood pressure (BP), (mm Hg)	120.48±14.41 119 (110-130)	125±15.10 122.5 (114-139)	110.2±8.70 110 (105-113)	127±1.41 127 (126.5- 127.5)	χ^2=5.358, df=3, *P*=0.147
Diastolic BP, (mm Hg)	74.97±7.13 72 (65, 82)	75.97±7.66 74 (66, 82)	80.9±7.31 79 (70, 88)	83.62±7.44 81 (72, 90)	χ^2=4.312, df=3, *P*=0.218
Heart rate (HR), (beats/min)	70.02±6.74 69 (63-75)	69.02±8.32 68 (60-76)	68.72±8.84 67 (59-75)	73.03±8.73 72 (63-78)	χ^2=4.165, df=3, *P*=0.678
Cholesterol, (mmol/l)	4.96±1.01 4.8 (4.4-5.7)	4.76±1.06 4.8 (4.2-5.4)	5.17±0.97 5 (4.5-5.65)	5.22±0.86 5.15 (4.55- 5.83)	χ^2=4.219, df=3, *P*=0.239
LDL-Cholesterol, (mmol/l)	3.29±0.91 3.2 (2.7-3.8)	3.10±1.09 2.9 (2.3-3.7)	3.45±0.97 3.4 (2.7-4)	3.58±0.89 3.6 (3.050-4.2)	χ^2=4.703, df=3, *P*=0.195
Triglycerides, (mmol/l)	1.48±0.79 1.2 (0.93-1.89)	1.67±0.88 1.5 (1.17-1.88)	1.32±0.55 1.19 (0.94-1.65)	1.38±0.66 1.2 (0.99-1.76)	χ^2=3.754, df=3, *P*=0.289
Glucose, (mmol/l)	5.41±0.81 5.3 (5-5.7)	5.44±0.91 5.3 (5-5.7)	5.38±0.63 5.4 (5-5.8)	5.38±0.66 5.4 (5.075, 5.93)	χ^2=0.606, df=3, *P*=0.895
eGFR, (ml/min/1,73m^2)	95.07±15.90 99 (80-107)	93.65±15.58 98 (85-105)	92±14.62 92 (80-104.5)	92.66±15.50 93.5 (80-105)	χ^2=1.335, df=3, *P*=0.721
PCSK9, (ng/ml)	190.85±43.80 2 (160-24)	320.62±52.13 3 (280-37)	493.92±55.61 480 (460-54)	746.88±88.81 760 (660-83)	χ^2=149.233, df=3, *P*=0.000
CIMT, (mm)	1.173±0.34 1.3 (0.7-1.5)	1.308±0.31 1.5 (1.2-1.5)	1.19±0.23 1.2 (1.05-1.30)	1.15±0.21 1.15 (1-1.30)	χ^2=12.625, df=3, *P*=0.006
Left ventricle posterior wall, (mm)	9.74±3.63 10 (8-12)	10.75±2.86 11 (9-12)	11.39±2.07 12 (10-12.5)	11.94±2.08 12 (10-13)	χ^2=9.722, df=3, *P*=0.021

LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; PCSK9, proprotein convertase subtilisin/kexin type 9; CIMT, carotid intima-media complex; SD, standard deviation

Smirnov method. Normally distributed features were compared by one-way ANOVA followed by pairwise comparison with Tukey's correction and skewed variables were compared by the Kruskal-Wallis test with pairwise comparison by the Dwass-Steele-Critchlow-Fligner method.

Results

The main clinical characteristics of study groups are seen in Table I. The study groups were homogeneous in gender and comparable in age, glucose level, GFR and lipid spectrum. The smokers were within all studied groups: 51.22 per cent, 59.46 per cent, 37.25 per cent and 53.13 per cent, respectively (Fig. 1). Participants in group 3 had the lowest percentage of smokers; the highest was in group 2 (*P*=0.03).

Positive family history positive for AH was observed; in 7.3 per cent in group 1, 13 per cent in the group 2, 9.8 per cent and 15.6 per cent in groups 3 and 4, respectively (Fig. 2). There were no significant differences between the groups (*P*>0.05).

Among group 4 individuals, systolic BP, diastolic BP and HR were significantly higher in comparison with other groups (*P*<0.01). Diastolic BP in the group 4 was significantly higher in comparison with group 1 and 2. Group 3 individuals, had a diastolic

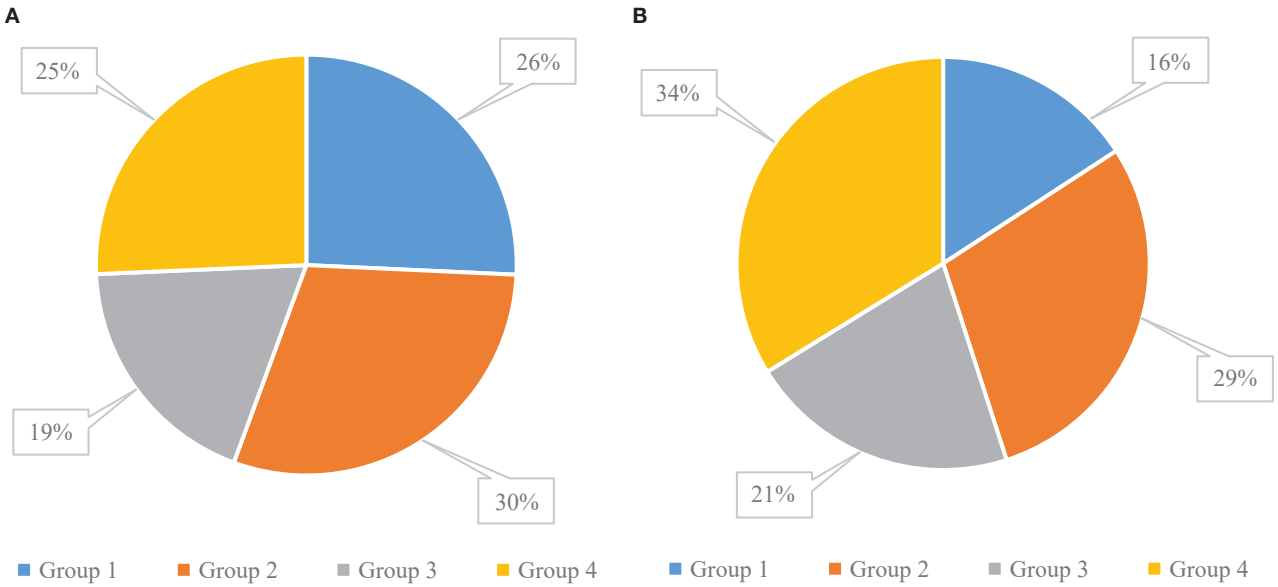

Figure 1. Pie chart showing the (**A**) smoking status (**B**) family history of arterial hypertension among the study participants.

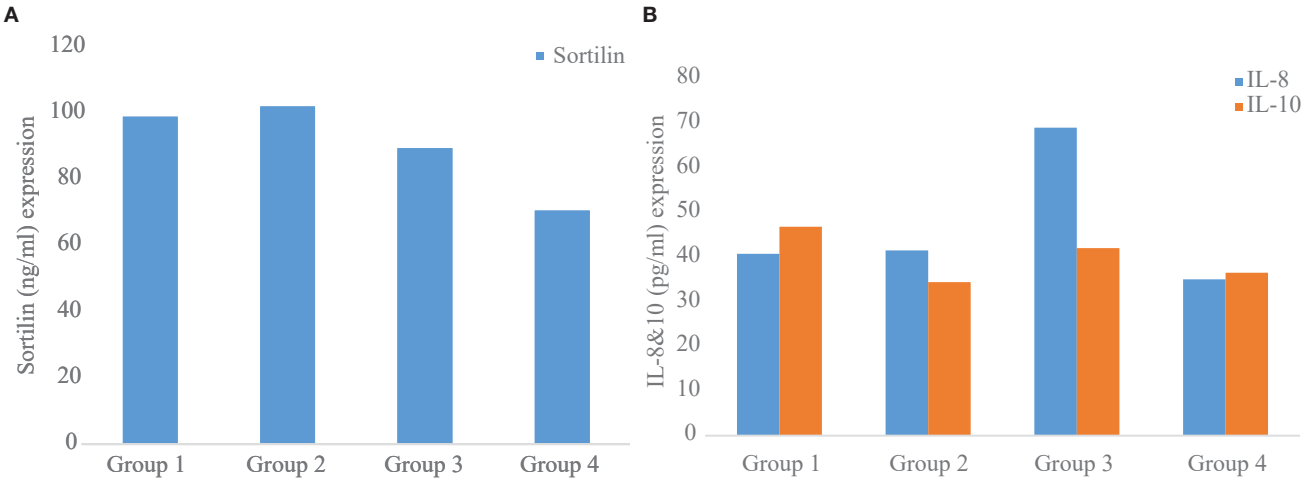

Figure 2. Expression of (**A**) sortilin and (**B**) IL-8,10 levels in group among the study participants.

BP significantly higher in comparison with group 2 ($P<0.01$). Sortilin level was the highest in group 2, however, no statistically significant differences were found. Group 3 individuals had the highest level of IL-8 in comparison with other groups ($P=0.01$).

CIMT was the highest in group 2 and was significantly higher in groups 3 and 4 ($P=0.04$ and $P=0.017$, respectively). Atherosclerotic plaques of brachiocephalic arteries were found in 70 and 80 per cent of group 1 and 2 participants, respectively, and in 90 per cent of participants in group 3 and 4. The predominance of the brachiocephalic artery stenosis of more than 50 per cent was revealed in 67.57 per cent of the participants in group 2 (Fig. 3).

The results of CAG did not demonstrate significant differences between the groups. Coronary artery stenoses were seen in 50 per cent and more in group 1 with 46.4 per cent individuals. In groups 2, 3 and 4 it was 54.05 per cent, 31.37 per cent and 43.75 per cent, respectively (Fig. 4). The highest percentage of stenosis (>50%) at 54.5 per cent was observed in group 2, while the smallest was in group 3 (31.3%). The smallest number of normal coronary arteries was seen in group 2.

Correlation analysis of the entire data set revealed the relationship of relative left ventricular thickness index with age ($r=0.43$; $P=0.005$), with CVR ($r=0.48$; $P=0.0005$), body mass index ($r=0.24$; $P=0.0024$), with

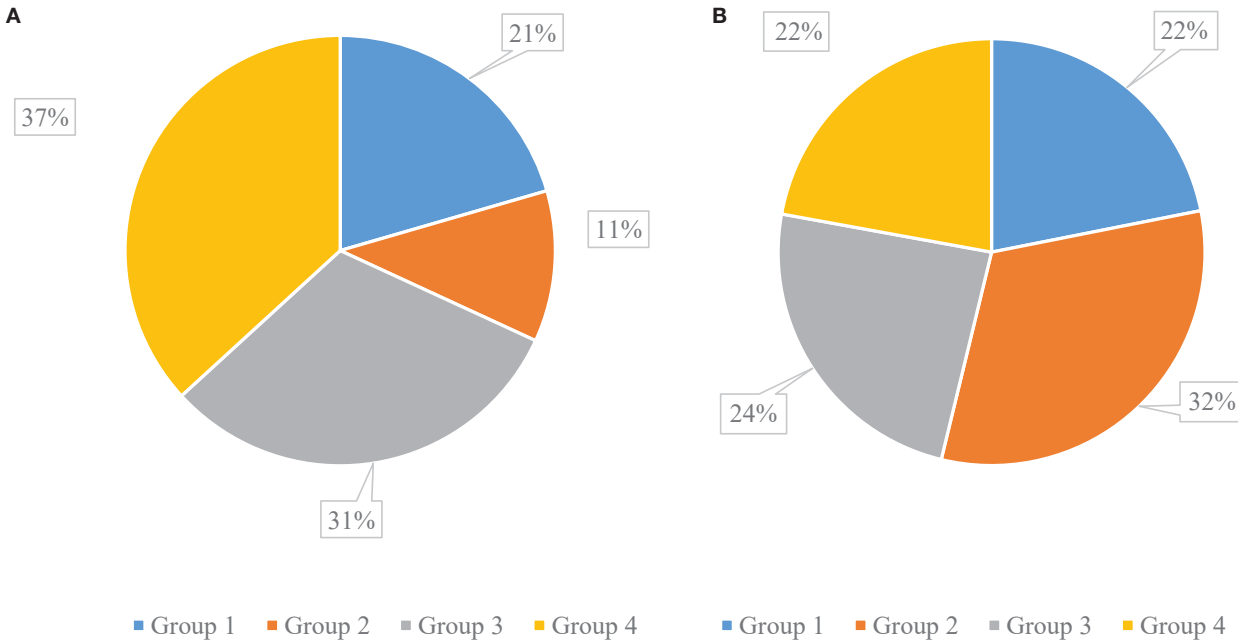

Figure 3. Atherosclerotic plaques in carotid arteries among the study participants as shown through Doppler ultrasound of brachiocephalic arteries (**A**) stenosis <50% (**B**) stenosis >50%.

the CIMT (r=0.34; P=0.0005), left ventricular mass index (r=0.70; P=0.0004), sortilin had negative relationships of weak strength with age and smoking (r=-0.22; P=0.41; r=-0.26; P=0.14, respectively). Correlation analysis within the groups demonstrated the following tendency: there was a negative relationship between sortilin level and age, a direct relationship between sortilin and the risk of cardiovascular complications (r=-0.37; p=0.24; r=0.352; P=0.24, respectively), sortilin and IL-10 (r=0.43; P=0.04) in group 1.

Intra-group analysis in group 2 revealed an inverse relationship between PCSK9 and left ventricle posterior wall (r=-0.37; P=0.22), sortilin and smoking (r=-0.5; P=0.044). The relationship between PCSK9 and glucose (r=0.30; P=0.02), sortilin with AH family history (r=0.83; P=0.09) and IL-10 (r=0.81; P=0.01), index of relative left ventricular thickness with body mass index (r=0.3; P=0.03), with CVR (r=0.57; P=0.0009), with CIMT (r=0.42; P=0.02). Intra-group analysis of group 3 revealed a strong direct relationship between sortilin and AH family history (r=0.83; P=0.03) and with IL-8 (r=0.82; P=0.01). Participants in group 4 showed an inverse relationship between PCSK9 and HR (r=-0.38; P=0.03).

Discussion

Studying of additional risk factors (RFs) of atherosclerosis is at present a promising branch of cardiological sciences because prevention, diagnostics and early treatment of this pathology is key to decrease the duration and improve the quality of life. The importance of heart arrhythmias in atherosclerosis progression has been reported previously[14,15]. Over the last few years, there have been several studies dedicated to the clarification of the role of sortilin in some pathologies particularly in AH and subclinical atherosclerosis[11,16,17,18], fibrosis[19,20], for the protection of neurons in diabetic retina[21], and as a potential biomarker and target for glioblastoma[22].

A few studies have described sortilin's immunomodulatory role in atherosclerosis; it is possible that sortilin promotes chronic inflammation and the formation of foam cells in blood vessels, causing atherosclerosis. Suggestively, this chronic inflammation can in turn reduce liver sortilin levels and disruption of the lipoprotein metabolism, further exacerbating atherosclerosis and the progression of CVDs[12,18,19]. However, given less number of studies on this literature, some controversial results require further studies and clarification.

In this study, we analysed the risk factors for the development and progression of atherosclerotic lesions of the vessels of the carotid and coronary arteries by the levels of PCSK9, sortilin and markers of inflammation. Serum PCSK9 concentration was positively associated with the sortilin levels (r=0.37, P=0.001). In the work

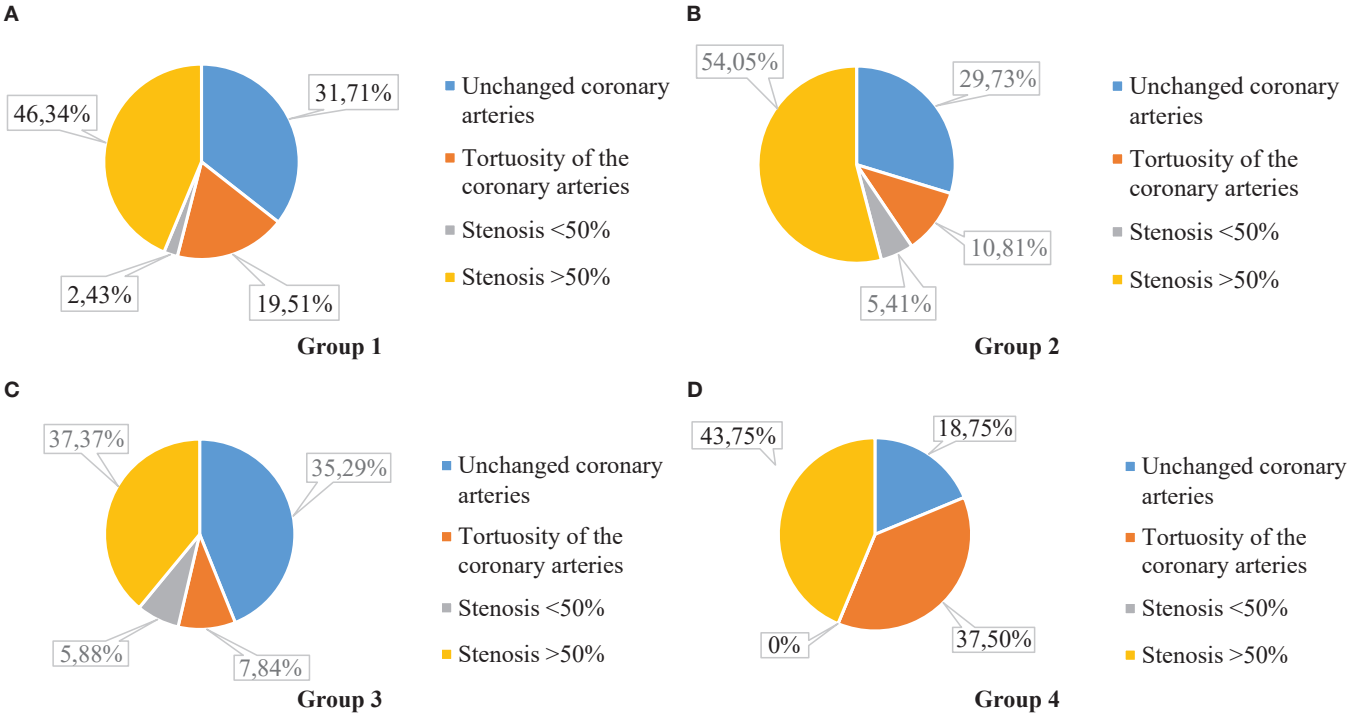

Figure 4. The coronary arteries atherosclerosis and PCSK9 level among study participants as shown through coronary angiography.

of Hu *et al*[23], in 2017 using the multiple regression analysis adjusted for age, sex, LDL-C, smoking and coronary artery disease, they found that the correlation between PCSK9 levels and serum sortilin and PCSK9 levels remained significant in all study participants (P=0.01). In this study, no relationship between sortilin and PCSK9. In the intragroup analysis, at different levels of PCSK9 was observed, but an inverse relationship between age and smoking was found. (in group 1, the minimum and in group 4, the maximum), a negative relationship between the level of sortilin with age and smoking was found, while a direct relationship between sortilin and the risk of cardiovascular complications and family history was observed. Furthermore, Ogawa *et al*[24] 2016, in their studies found that the level of sortilin was significantly higher in individuals with CVR, AH and dyslipidaemia. In contrast, Möller *et al*[25] in 2021 showed that none of the risk factors for CHD, such as gender, age and smoking, were associated with plasma sortilin levels.

Previously it has been reported, that the level of PCSK9 is higher in smokers than in non-smokers (P=0.011)[7].

In this study, it was found that the lesion of the carotid arteries with stenosis of more than 50 per cent is characteristic precisely for the group of smoking individuals. Coronary artery stenosis (50% and more) was also detected in the same group, which is confirmed by previous studies. Individuals with multiple RFs, such as AH, smoking and obesity, were identified in the two groups, which may explain the greater percentage of carotid and coronary artery lesions in the patients of this particular group.

If during an investigation of the patient we find an increased parameter of CIMT, it is recommended to evaluate the cardiovascular risk for him[26]. The Gensini scale allows us to determine the value of CIMT>1 mm as a twofold increase in the chance of moderate and severe risk of coronary artery disease[26]. At the same time, the presence of atherosclerotic lesions in the carotid arteries has a high prognostic value in cardiovascular events. The degree of echogenicity of atherosclerotic lesions in the carotid arteries is an independent predictor of the coronary artery disease severity (P<0.002)[26]. Our study demonstrated that in patients in group 2 with the maximum CIMT was revealed the largest number of cases of coronary artery disease (stenosis of more than 50%), in comparison with other groups (Figs. 4 and 5).

In atherosclerosis pathogenetic theories, the risk factors are associated with genetic predisposition, peroxide, lipid infiltration in response to endothelial damage, autoimmune, monoclonal and infectious theories[1-3]. There is no doubt in the role of the immune-inflammatory mechanism of atherosclerosis[12,13,27].

Dyslipidaemia and hyperlipidaemia, with the direct participation of LDL-C and VLDL, acquire auto-antigenic properties inducing the formation of an immune response to vascular antigens in case of arterial wall damage, which contributes to the progression of atherosclerosis[3].

The main active components of the inflammatory process are immune cells (macrophages, T- and B-cells, etc.), which are attracted to the inflammation focus by pro-inflammatory cytokines. Studies confirm the effect of sortilin on the regulation of cytokine secretion in various immune processes through IL-6, IL-8, IL-10, IL-12, IL-17, tumour necrosis factor alpha (TNF-α) and interferons I, II, III[12,13]. In experimental mice, the inactivation of sortilin induced a defect in IL-6 secretion (cytokines), at the same time reducing the inflammatory component of atherosclerosis and vascular lesions, regardless of lipid metabolism. Pro-inflammatory cytokines play the main role in plaque progression[25]. Therefore, sortilin may act as a key regulator of the inflammatory response that enhances atherogenesis.. Our data showed a high level of IL-8 in group 3, where the highest rates of left ventricle hypertrophy, left ventricle mass index and index of relative left ventricular thickness were found.

In this work, we demonstrated a clear increase in inflammatory markers (IL-8) in patients with subclinical atherosclerosis. We can explain with oxygen stress activation. In patients with coronary artery stenosis (50% and more), we revealed an increase of IL-10 that demonstrates, to our opinion, the activation of antioxidant protection. Overall, Sortilin is the innovative marker of CVR in the human population. The role of sortilin in cardiovascular pathology needs furtherinvestigation. Most of the data are contradictory, and they are not enough to make the direct conclusion of its leading role in CVR.

***Financial support & sponsorship*:** None.

***Conflicts of Interest*:** None.

***Use of artificial intelligence (AI)-assisted technology for manuscript preparation*:** The authors confirm that there was no use of AI-assisted technology for assisting in the writing of the manuscript and no images were manipulated using AI.

References

1. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, *et al*. European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J.* 2022; *43* : 716-99.
2. GBD 2021 Forecasting Collaborators. Burden of disease scenarios for 204 countries and territories, 2022-2050: a forecasting analysis for the Global Burden of Disease Study 2021. *Lancet.* 2024; *403* : 2204-56.
3. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, *et al.* 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; *41* : 111-88.
4. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, *et al.* 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens* 2023; *41* : 1874-2071
5. Germanova O, Shchukin Y, Germanov V, Galati G, Germanov A. Extrasystolic arrhythmia: is it an additional risk factor of atherosclerosis? *Minerva Cardiol Angiol* 2022; *70* : 32-9.
6. Abifadel M, Varret M, Rabes JP. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet* 2003; *34* : 154-6.
7. Vukolova Y, Gubareva I, Galati G, Germanova O. Proprotein convertase subtilisin kexin type 9 and main artery atherosclerosis in patients with arterial hypertension. *Minerva Cardiol Angiol* 2023; *71* : 129-34.
8. Venkat S, Linstedt AD. Manganese-induced trafficking and turnover of GPP130 is mediated by sortilin. *Mol Biol Cell* 2017; *28* : 2569-78.
9. Siddiq AA, Martin A. Crocetin exerts hypocholesterolemic effect by inducing LDLR and inhibiting PCSK9 and Sortilin in HepG2 cells. *Nutr Res* 2022; *98* : 41-9.
10. Hu D, Yang Y, Peng DQ. Increased sortilin and its independent effect on circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) in statin-naive patients with coronary artery disease. *Int J Cardiol* 2017; *227* : 61-5.
11. Varzideh F, Jankauskas SS, Kansakar U, Mone P, Gambardella J, Santulli G. Sortilin drives hypertension by modulating sphingolipid/ceramide homeostasis and by triggering oxidative stress. *J Clin Invest* 2022; *132* : e156624.
12. Rocha VZ, Rached FH, Miname MH. Insights into the role of inflammation in the management of atherosclerosis. *J Inflamm Res* 2023; *16* : 2223-39.
13. Liu F, Wang Y, Yu J. Role of inflammation and immune response in atherosclerosis: Mechanisms, modulations and therapeutic targets. *Hum Immunol* 2023; *84* : 439-49.
14. Germanova O, Shchukin Y, Germanov V, Galati G, Germanov A. Extrasystolic arrhythmia: is it an additional risk factor of atherosclerosis? *Minerva Cardiol Angiol* 2022; *70* : 32-9.
15. Germanova O, Galati G, Germanov A, Stefanidis A. Atrial fibrillation as a new independent risk factor for thromboembolic events: Hemodynamics and vascular consequence of long ventricular pauses. *Minerva Cardiol Angiol* 2023; *71* : 175-81.
16. Avvisato R, Jankauskas SS, Varzideh F, Kansakar U, Mone P, Santulli G. Sortilin and hypertension. *Curr Opin Nephrol Hypertens* 2023; *32* : 134-40.

17. Chu X, Liu R, Li C, Gao T, Dong Y, Jiang Y, *et al*. The association of plasma sortilin with essential hypertension and subclinical carotid atherosclerosis: A cross-sectional study. *Front Cardiovasc Med* 2022; *9* : 966890.
18. Su X, Chen L, Chen X, Dai C, Wang B. Emerging roles of sortilin in affecting the metabolism of glucose and lipid profiles. *Bosn J Basic Med Sci* 2022; *22* : 340-52.
19. Ishiyama S, Hasegawa T, Sugeno N, Kobayashi J, Yoshida S, Miki Y, *et al.* Sortilin acts as an endocytic receptor for α-synuclein fibril. *FJ* 2023; *37* : e23017.
20. Iqbal F, Schlotter F, Becker-Greene D, Lupieri A, Goettsch C, Hutcheson JD, *et al.* Sortilin enhances fibrosis and calcification in aortic valve disease by inducing interstitial cell heterogeneity. *Eur Heart J* 2023; *44* : 885-98.
21. Jakobsen TS, Østergaard JA, Kjolby M, Birch EL, Bek T, Nykjaer A, *et al.* Sortilin inhibition protects neurons from degeneration in the diabetic retina. *Invest Ophthalmol Vis Sci* 2023; *64* : 8.
22. Marsland M, Dowdell A, Faulkner S, Gedye C, Lynam J, Griffin CP, *et al.* The membrane protein sortilin is a potential biomarker and target for glioblastoma. *Cancers (Basel)* 2023; *15* : 2514.
23. Hu D, Yang Y, Peng DQ. Increased sortilin and its independent effect on circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) in statin-naive patients with coronary artery disease. *Int J Cardiol* 2017; *227* : 61-5.
24. Ogawa K, Ueno T, Iwasaki T, Kujiraoka T, Ishihara M, Kunimoto S, *et al.* Soluble sortilin is released by activated platelets and its circulating levels are associated with cardiovascular risk factors. *Atherosclerosis* 2016; *249* : 110-5.
25. Møller PL, Rohde PD, Winther S, Breining P, Nissen L, Nykjaer A, *et al.* Sortilin as a biomarker for cardiovascular disease revisited. *Front Cardiovasc Med* 2021; *8* : 652584.
26. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, *et al*. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Circulation* 2019; *140* : e596-e646.
27. Shang D, Liu H, Tu Z. Pro-inflammatory cytokines mediating senescence of vascular endothelial cells in atherosclerosis. *Fundam Clin Pharmacol* 2023; *37* : 928-36.

For correspondence: Prof Olga Germanova, International Centre for Education and Research in Cardiovascular Pathology and Cardiovisualization, Samara State Medical University, 443079, Russian Federation
e-mail: olga_germ@mail.ru