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Alternative risk factors and their importance in assessment of cardiovascular risk in asymptomatic patients

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ABSTRACT

Cardiovascular diseases retain their leading position among the leading causes of death worldwide. The contribution of many factors to increasing risk of developing cardiovascular diseases was proven. The article provides an overview of current views on the role of risk factors in assessment of cardiovascular risk in asymptomatic patients. Determination of individual cardiovascular risk is not questioned. However, more information is accumulating on the need to supplement the existing cardiovascular risk assessment scales with new factors in order to more accurately predict cardiovascular risk. The value of alternative risk factors, such as psychosocial factor, level of physical activity, family history of cardiovascular diseases, coronary artery calcification, ankle-brachial index, and identification of atherosclerotic plaques during ultrasound scanning of the brachiocephalic arteries, is described. Studies that consider the impact of these risk factors on reducing discrimination against cardiovascular risk when added to the globally used risk assessment scales are presented.

Key words: cardiovascular risk, subclinical atherosclerosis, coronary artery calcification.

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Нетрадиционные факторы риска и их значение в оценке сердечно-сосудистого риска у бессимптомных пациентов

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РЕЗЮМЕ

Сердечно-сосудистые заболевания (ССЗ) сохраняют лидирующие позиции среди ведущих причин смертности во всем мире. Доказан вклад многих факторов в увеличение риска развития ССЗ. Представлен обзор современных представлений о роли факторов риска у бессимптомных пациентов в оценке сердечно-сосудистого риска. Определение индивидуального сердечно-сосудистого риска не подвергается сомнению,

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однако накапливается все больше сведений о необходимости дополнения имеющихся шкал оценки сердечно-сосудистого риска новыми факторами с целью более точного его прогнозирования. Отражены сведения о значении нетрадиционных факторов риска, таких как психосоциальный фактор, уровень физической активности, семейный анамнез развития ССЗ, коронарная кальцификация, лодыжечно-плечевой индекс, выявление атеросклеротических бляшек при ультразвуковом сканировании брахиоцефальных артерий. Приведены исследования, рассматривающие влияние этих факторов риска на улучшение дискриминации сердечно-сосудистого риска при добавлении их к используемым в мире шкалам оценки риска.

Ключевые слова: сердечно-сосудистый риск, субклинический атеросклероз, коронарная кальцификация.

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INTRODUCTION

Atherosclerosis is an inflammatory disease with damage to the arterial wall. The development of atherosclerosis is a dynamic and multifactorial process. For a long time, atherosclerosis was considered as a disease the pathogenesis of which is associated only with the deposition of lipids in the wall of the artery. The morphological substrate of the affection of the vascular wall is well understood, yet, the mechanisms that trigger this affection are still being studied. Over the past two decades, the perception of atherosclerosis has gradually changed and was supplemented with the understanding of the role of arterial wall inflammation in the disease [1]. As a result, the leading role in the pathogenesis of atherosclerosis belongs to the lipid infiltration hypothesis and the response to damage hypothesis. Complementing one other, these concepts led to the understanding that atherosclerosis is a complex inflammatory process which involves, in particular, endothelial damage, deposition of oxLDL in the intima, proliferation of smooth muscle cells, and macrophage infiltration and activation [2, 3].

Upon progression, atherosclerosis results in such socially sensitive diseases as coronary artery disease (CAD) and cerebrovascular disease (mainly ischemic stroke). CAD and stroke are the first and third leading mortality causes worldwide, respectively. These diseases account for 247.9 deaths per 100,000 people, which accounts for 84.5% of deaths from cardiovascular diseases (CVDs) and 28.2% of deaths from all causes [4]. Other, less widespread, complications of atherosclerosis include damage to the aorta and peripheral vessels. To date, CVDs maintain a leading position among the mortality causes worldwide. In the Russian Federation, according to 2016 statistics, the mortality rate from all causes amounted to 1, 284.3 per 100,000 people, of which mortality from circulatory diseases was 616.4 per 100,000 people, and the mortality rate from CAD was 328.5 per 100, 000 people [5].

The concept of cardiovascular risk factors was introduced into medical practice more than 70 years ago. Over the past few decades, there has been an increase in CVDs around the world. This epidemiological change is partially associated with changes in lifestyle and diet; however, these factors are the main modifiable causes of CVDs [2]. According to the response to damage hypothesis, there are a lot of factors causing endothelial damage, but the most common of them are smoking, dyslipidemia, hypertension, diabetes mellitus, abdominal obesity, etc. The risk of the atherosclerotic cardiovascular disease development increases with age. The assessment of individual cardiovascular risk may be relevant for patients with asymptomatic atherosclerotic vascular disease, especially for identifying high cardiovascular risk in such patients. The assessment of individual cardiovascular risk is evaluated in general clinical practice during screening of large population groups (for example, during regular health check of certain population groups).

The tool for such assessment should be simple, reliable, convenient to be used in research and specific to the country in which it was developed and used. Many algorithms have been proposed for quick and accurate calculation of individual cardiovascular risk. In the Russian Federation, along with European

countries, the SCORE scale has been used since 2003 [6, 7]. Other well-known rating scales include Framingham risk score (FRS) (USA), Reynolds (USA), Q-RISC (UK), PROCAM (Germany), ASSIGN (Sweden), CUORE (Italy), and others [6, 7].

The SCORE scale was developed based on incidence studies in 12 European countries, including the Russian Federation. More than 200,000 patients were involved. There are 2 versions for the SCORE scale for countries with high (including the Russian Federation) and low risk. The following risk factors were included: gender, age, smoking, systolic blood pressure, and total cholesterol. The 10-year risk of developing the first fatal, associated with atherosclerosis, event – stroke, myocardial infarction, aortic aneurysm – was assessed with its help. Allowing to assess the development of lethal events in the future, this rating scale did not allow to evaluate the risk of developing non-fatal diseases associated with atherosclerosis. However, such possibility exists. To evaluate a combined risk (fatal and non-fatal), it is necessary to multiply the risk values of a particular male patient by 3 and female – by 4 [6, 7].

The findings on the association of cardiovascular diseases with various risk factors, such as arterial hypertension and hypercholesterolemia, were first obtained in the Framingham Heart Study [6, 7]. The Framingham scale was developed on its basis. This scale takes into account such risk factors as age, gender, blood pressure, smoking, the use of antihypertensive drugs, total cholesterol, and high-density lipoprotein cholesterol. This rating scale predicts the occurrence of events related to coronary artery disease in asymptomatic patients over 10 years, the endpoint being CAD (angina pectoris, myocardial infarction, sudden death).

Identification of high individual cardiovascular risk results in the need for correcting modifiable risk factors. However, this fact is important not only for high-risk patients, but also for people at low and medium risk. In 1985, D. Rose formulated the prevention paradox: more low-risk individuals may have more cases of disease than a small number of high-risk patients [7, 8]. In other words, patients at high risk have the maximum individual benefit from taking measures to control risk factors.

The individual benefit of conducting risk correction measures is not so significant among low-risk individuals, but they will bring great benefits to society on the whole due to a large number of low-risk groups. Based on the Rose paradox, the identification of cardiovascular diseases at the asymptomatic stage in patients of any risk can have a great economic importance.

With regard to the advantages of using the rating scales described above, more and more information is accumulating about their defects and limitations. Therefore, search for other risk factors is underway. The addition of new risk factors to the scales will contribute to more accurate determination of cardiovascular risk in the population groups.

Despite the fact that arterial hypertension is an independent disease, it belongs to one of the main, well-studied risk factors for CVD. In the recommendations of the European Society of Cardiology / European Society for Arterial Hypertension on Treatment of Arterial Hypertension in 2018, the influence of arterial hypertension on target organ damage was considered especially significant; it leads to an increase in cardiovascular risk, even if the damage is asymptomatic [9]. Also, in 2018, new factors which increase the risk of cardiovascular complications were identified, such as hyperuricemia, resting heart rate, diabetes mellitus, a family history of early onset hypertension, early menopause, sedentary lifestyle, and psychosocial and socio-economic factors. These factors are recommended to be considered when stratifying risk in patients with arterial hypertension [9].

Cardiovascular risk factors requiring further study include the psychosocial factor (anxiety, depression), assessment of the level of physical activity, the presence of CVD in the family history (in women – under 65 years old, in men – under 55 years old), ankle-brachial index (ABI), detection of atherosclerotic plaques during ultrasound examination of the carotid arteries, and determination of the coronary artery calcium (CAC) [6].

THE EFFECT OF STRESS ON THE DEVELOPMENT OF CORONARY EVENTS

In 2017, a group of European scientists evaluated the relationship of stress in the workplace with the following development of coronary events (the first non-fatal or fatal myocardial infarction) [10]. The study is based on the fact that stress occurs as a result of the impact of work, which is characterized by high psychological stress. A model was chosen to assess the imbalance between hard work and remuneration. Based on this theory, stress is created by a repeated unsatisfactory relationship between hard work, for example the pace of work, work load, time spent at work, and received remuneration. In addition to sala-

ry, remuneration includes non-financial aspects such as respect, recognition, career prospects, and employment opportunities. Using data from questionnaires, the imbalance between hard work and remuneration was assessed. The cohort included 90, 164 people (men and women) without CAD at the time the study began. During an average follow-up of 9.8 years, 1, 078 coronary events were recorded. As a result, it was found that in individuals with an imbalance between hard work and remuneration, the risk of CAD increased by 1.16 times (relative risk (RR) was 1.16; 95% CI 1.01 – 1.34). The relationship between unfavorable psychosocial work environment and CAD was also demonstrated.

THE EFFECT OF SUBCLINICAL CAROTID ARTERY ATHEROSCLEROSIS ON CARDIOVASCULAR RISK

The importance of detecting atherosclerotic plaques in the carotid arteries as predictors of the development of cardiovascular diseases was studied by J.F. Polak et al. in 2013 [11]. The change in the predictive value of the Framingham scale was assessed with the addition to the existing criteria of atherosclerotic plaques revealed during ultrasound scanning of the carotid arteries. The cohort study consisted of 6, 562 individuals (mean age was 61.1 years; 52.6% of patients were women). In 41.9% (n = 2, 748) of individuals included in the study, plaques narrowing the lumen by less than 25% were detected; in 13.2% (n = 863) of patients, plaques narrowing the lumen by 25% or more were revealed. CVD developed in 7.9% of the examined (n = 515). The detection of any atherosclerotic plaques was reliably associated with the incidence of CVD, with the strongest association being observed for plaques that narrowed the lumen by 25% or more (RR 1.65; 95% CI 1.34 – 2.03). Therefore, the addition of atherosclerotic plaques of the carotid arteries to traditional risk factors more accurately predicts the possibility of CVD development and improves the prognosis of cardiovascular risk.

The value of coronary artery calcification

Some researchers believe that the detection of coronary artery calcification is actually pathognomonic of atherosclerosis of the coronary arteries [3]. At the same time, calcium phosphate in hydroxyapatite form accumulates in the intima affected by atherosclerosis. The calcification of the atherosclerotic plaque begins in the lipid nucleus of the atheroma and occurs as an active process resembling bone formation, controlled by complex enzymatic and cellular pathways. The underlying mechanisms are not completely understood, but apoptosis of smooth muscle cells, apparently, is an important stage in this process, which then serves as a focus of calcification. Based on histomorphometric studies, approximately 20% of atherosclerotic plaques of the coronary vessels are calcified and these macrocalcifications can be identified using non-contrast computed tomography [2, 3].

In 2008, Detrano et al. for the first time reported about the relationship between the level of CAC and following coronary events (myocardial infarction or death from coronary artery disease). Based on the results of their work, researchers concluded that adding CAC to standard risk factors improves the prognosis of following coronary events [12].

ASSOCIATIONS OF CAC WITH NEW MARKERS OF ATHEROSCLEROSIS

In the study by J.A. Delaney et al. the relationship between the level of physical activity, CAC and ABI was assessed [13]. The study included individuals with an ABI from 0.90 to 1.40 (n = 5, 656), 53% of them were women with an average age of 61 years and an average body mass index of 28 kg/m^2. At the beginning of the study, approximately 33% of individuals had dyslipidemia, 11% had diabetes, and 42% had arterial hypertension, but they did not have clinically severe coronary artery disease. Slightly more than 62% of patients reported that they were engaged in intense physical activity, and 35% – in moderate physical activity. It was found that more intense exercise reduced the risk of peripheral arterial atherosclerosis (RR 0.85; 95% CI 0.74 – 0.98), and a significant relationship was identified between the intensity of physical activity and the detection rate of coronary artery calcification (RR 0.97; 95% CI 0.94 – 1.00). In general, a reliable relationship between the intensity of physical activity and an increase in CAC was not detected, however, sedentary lifestyle was largely associated with an increase in CAC (Δ log (Agatston score +25) = 0.027; 95% CI 0.002 – 0.052). Therefore, sedentary lifestyle was associated with the progression of damage to peripheral and coronary arteries. This study showed a significant role of moderate and intense physical exertion in preventing the progression of atherosclerosis of peripheral arteries. With regard to coronary artery calcification, a similar fact was not detected, however, it was determined that any physical activity reduces its progression, and sedentary lifestyle increases it. As a result, any type of activity is better than sedentary lifestyle.

FAMILY HISTORY OF CARDIOVASCULAR DISEASE AND PROGRESSION OF CORONARY ARTERY CALCIFICATION

It has now been established that a zero CAC score is associated with a very low 10-year risk of cardiac events, but this risk is not equal to zero. In the 2014 study, an assessment of the family history of coronary artery disease was performed [14]. The purpose of this study was to evaluate the role of family history in the development of CVD in people with zero CAC. Higher incidence of subclinical atherosclerosis in individuals with a family history of CAD, as opposed to individuals without it, was established. The work included 3, 185 individuals with basic assessment of CAC = 0 (average age 58 years, 37% of men). The average risk score according to the Framingham scale was 6.1% for individuals with a family history of CAD and 6.2% for people without it ($p = 0.84$). On average, over 10 years, 101 (3.2%) individuals had CVD, and 56 (1.8%) had episodes of CAD. In analyzing age and gender, a family history of CAD was associated with an increase in CVD cases by approximately 1.73 times (RR 1.73; 95% CI 1.17 – 2.56) and with CAD (RR 1.72; 95% CI 1.01 – 2.91). The researchers concluded that asymptomatic individuals with zero CAC and a positive family history of CAD were at increased risk of cardiovascular and CAD events in comparison with those who did not have a family history of CAD, although absolute incidence rates remained low.

A similar study was conducted a year earlier [15]. It was demonstrated that a family history of early CAD was usually associated with the progression of coronary artery calcification among asymptomatic individuals. Of the total cohort, 47% were men. Overall, 52% ($n = 2, 633$) of individuals had a positive family history of CAD; 20% ($n = 1, 002$) of people had a family history of early CAD, of which 456 reported a similar history only with their parents, 471 – only with brothers and sisters, and 75 – with parents, brothers, and sisters. The average risk score according to the Framingham scale was 7.5% ($n = 2, 466$) for individuals without a family history of CAD, 8.2% ($n = 1, 631$) for people with a family history of late-onset CAD, and 7% ($n = 1, 002$) for people with a family history of early CAD. In the main group, 2, 645 people (52%) did not have coronary artery calcification at the beginning of the study. Among them, in 527 (20%) patients, CAC became higher than zero during the following examination. A significant increase in CAC was observed in patients with a family history of early CAD (7.24 per 100 person–years) compared with patients without a family history of CAD (5.87 per 100 person–years) or with a late-onset CAD in the family history (6.56 per 100 person–years) ($p < 0.05$). In individuals with a family history of early CAD, the increase in CAC was 16.7 units higher than in individuals without it ($p < 0.001$). This was more than twice as much as in the group of individuals with a family history of late CAD (8.17 units). The obtained results confirm the opinion that a family history is an important component of cardiovascular risk and suggest that accelerated coronary artery calcification in subclinical atherosclerosis may contribute to increased risk of the disease.

THE EFFECT OF NEW CARDIOVASCULAR RISK FACTORS ON RISK DISCRIMINATION ACCORDING TO THE FRAMINGHAM SCALE

In 2016, J. Yeboah et al. published the results of the study that examined the addition of new cardiovascular risk factors to traditional ones [16]. The role of factors, such as coronary artery calcification, level of C-reactive protein, ABI, and the presence of CAD in the family history, and their significance in stratification of cardiovascular risk were assessed. It should be noted that these factors were not evaluated in aggregate, but separately. The endpoints were myocardial infarction, death from CAD, or stroke. The analysis included 5, 185 individuals; the average age was 61 years; 53.1% were women. The average follow-up period was 10 year; during this time, 320 (6.2%) cases of cardiovascular diseases were registered, of which 139 (43.4%) were cases of myocardial infarction, 132 (41.3%) – strokes, and 49 (15.3%) – death from coronary artery disease. In terms of predicting the development of CAD, CAC was the only marker that significantly improved risk discrimination according to the Framingham scale (Net Reclassification Index (NRI) 0.178; 95% CI 0.080–0.256). The addition of ABI to the Framingham model improved stratification of patients less significantly (NRI 0.013; 95% CI 0.034–0.051). A total of 194 (3.7%) cases of CAD occurred. Therefore, among the four risk markers included in the analysis, CAC showed the greatest improvement in the discrimination of risk of CAD and reclassification of patients with intermediate risk according to the Framingham scale. In addition, the authors pointed out that CAC, compared with 3 other non-traditional risk markers, is more suitable not only for improving the prognosis of the risk for CAD, but may be useful for people who have not made a decision on treat-

ment based on the risk determined by the Framingham scale. Therefore, further research is needed to improve the discrimination provided by these additional risk markers in subgroups of asymptomatic individuals (primary prophylaxis), especially those who are not recommended for statin therapy.

CONCLUSION

Despite the fact that the concept of cardiovascular risk factors was introduced into clinical practice more than seventy years ago, it is still relevant today. Most significant factors of cardiovascular risk are modifiable and have enormous prognostic value. Many studies have been conducted to determine the effectiveness of existing scales for assessing cardiovascular risk. However, despite their effectiveness, they require additions and refinements. Analyzing the results of the above mentioned studies, we can definitely say that today the problem of a correct assessment of cardiovascular risk remains relevant for all groups of patients at any cardiovascular risk. An increase in cardiovascular risk in asymptomatic patients is often associated with the psychosocial factor or detection of atherosclerotic plaques during an ultrasound examination of the brachiocephalic arteries. The role of CAC has yet to be studied; however, the studies presented in this review article established mutual potentiation of risk factors, such as a family history of coronary artery disease, sedentary lifestyle, and assessment of ABI and CAC. The study of new cardiovascular risk factors in asymptomatic population shows its discriminatory and prognostic value, but requires following detailed study to develop the most convenient, accurate and effective rating scales applicable to any category of patients, including asymptomatic ones. The development of these risk scales, according to the Rose paradox, will be of great economic and social importance.

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