

MODERN APPROACHES TO THE ASSESSMENT OF SUBCLINICAL ATHEROSCLEROSIS AND MULTI-BIOMARKER RISK PREDICTION: PROSPECTS FOR PERSONALIZED PREVENTION OF CARDIOVASCULAR DISEASES

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ABSTRACT

The article discusses modern approaches to the assessment of subclinical atherosclerosis and multi-biomarker risk prediction in conditions of continuing high mortality from diseases of the circulatory system and limited accuracy of traditional stratification scales. It was shown that the use of averaged prognostic models did not fully reflect the individual characteristics of atherogenesis, which justified the need to identify subclinical atherosclerosis as an early and clinically significant stage of the cardiovascular continuum, as well as the integration of instrumental imaging methods and laboratory panels into personalized prevention algorithms focused on preventing events at the preclinical stage. The information base of the study was made up of Russian and foreign clinical recommendations and data from population and clinical trials in 2021-2025 on subclinical atherosclerosis, methods of its instrumental diagnosis and multi-biomarker risk assessment models. The methodological basis was an analytical and comparative review of publications with an assessment of the prognostic significance of imaging and laboratory markers, their impact on risk reclassification and the possibility of inclusion in personalized prevention strategies. The study systematized modern approaches to the diagnosis of subclinical atherosclerosis, assessment of its prognostic role, and the inclusion of imaging data and multi-biomarker panels in models of personalized prevention of cardiovascular diseases. It was found that methodological limitations remained due to the heterogeneity of diagnostic criteria, the variability of imaging protocols and laboratory techniques, as well as insufficient external validation of integral models and the uncertainty of their impact on clinical decisions in Russian populations. The necessity of developing unified risk stratification algorithms providing for the standardized inclusion of instrumental and biochemical markers followed by a clinical and economic assessment of their effectiveness in practical healthcare is substantiated. The results obtained confirmed the feasibility of integrating signs of subclinical atherosclerosis and multi-biomarker models into clinical risk assessment algorithms, which was of practical importance for earlier detection of latently high cardiovascular risk and the justification of personalized preventive interventions in real clinical practice.

KEYWORDS: subclinical atherosclerosis, multi-biomarker prognosis, risk stratification, personalized prevention, coronary calcium index, cardiovascular diseases.

INTRODUCTION

The increase in life expectancy and the transformation of behavioral factors have shifted healthcare priorities towards the prevention of chronic diseases, where the prevention of complications is crucial. In the structure of non-communicable pathology, cardiovascular diseases occupy leading positions: according to WHO, about 74% of all deaths in the world are associated with non-communicable causes, and a significant part of them are due to cardiovascular pathology. At the same time, the key problem is that clinical events often occur in patients without pronounced symptoms who already have subclinical atherosclerotic vascular damage that develops long before the manifestation of a heart attack or stroke, which actualizes modern approaches to its early assessment and multi-biomarker risk prediction [1-3].

In the Russian Federation, the scale of the problem is confirmed by official statistics: according to the USISZ for 12 months of 2024, the total mortality rate from circulatory system diseases and neoplasms was 60.6%, and in some regions, the mortality rate from CVD reached 453.8 per 100 thousand population [4]. Even with historically low mortality rates in 2024-2025, diseases of the circulatory system remain the leading cause of death [5]. In these

conditions, subclinical atherosclerosis is reasonably considered as an early stage of the cardiovascular continuum, and its detection using instrumental methods and biomarkers is of fundamental importance for personalized prevention and reduction of the number of complications in the future [6, 7].

Current Russian approaches to the prevention of cardiovascular diseases are based on consistent risk stratification with its subsequent refinement through an instrumental assessment of subclinical atherosclerosis, including the calculation of SCORE2 and the use of imaging methods to determine the volume and intensity of preventive interventions [8]. The detection of atherosclerotic plaques and signs of vascular remodeling is considered as the basis for a review of management tactics, especially in patients with an intermediate risk category. The lack of sensitivity of traditional scales to inflammatory, metabolic, and neurohumoral mechanisms of atherogenesis leads to the development of integrative models combining carotid artery ultrasound and coronary calcium assessment data with multi-biomarker profiles, which, within the framework of modern approaches to assessing subclinical atherosclerosis, makes it possible to more reasonably reclassify risk and personalize prevention, subject to their standardization and clinical applicability.

Despite the active development of imaging methods and laboratory technologies, modern approaches to assessing subclinical atherosclerosis and multi-biomarker risk prediction remain unresolved issues of standardizing diagnostic criteria, selecting optimal biomarker panels and confirming their additional predictive value in Russian populations, as well as integrating heterogeneous data into clinical algorithms. In domestic practice, the integrated integration of instrumental and laboratory parameters into a single forecast model has not yet been sufficiently considered, which increases the importance of systematic analysis and emphasizes the relevance of research on modern strategies for early risk stratification and personalized prevention of cardiovascular diseases at the preclinical stage.

The purpose of this review is to summarize current Russian and foreign data and analyze the role of subclinical atherosclerosis, instrumental methods for its detection and biomarker models in clarifying cardiovascular risk, as well as to assess their capabilities and limitations in the formation of personalized prevention of cardiovascular diseases.

METHODOLOGICAL APPROACHES

The work is based on current Russian and foreign clinical recommendations, as well as data from population and clinical studies in 2021-2025 on preclinical forms of atherosclerotic lesions, instrumental verification (ultrasound assessment of the carotid arteries, measurement of the intima-media complex, coronary calcium index) and the construction of multi-biomarker models of cardiovascular risk stratification. Methodologically, the study was carried out in the format of an analytical and comparative review of publications with an assessment of the prognostic significance of imaging and laboratory markers, their role in risk reclassification and the potential for integration into personalized prevention algorithms for cardiovascular diseases. Additionally, a critical analysis of data on the implementation of machine learning algorithms and digital risk stratification models in Russian clinical practice was carried out, taking into account their limitations and validation requirements.

RESULTS

In the context of modern approaches to the assessment of subclinical atherosclerosis, it is defined as an independent stage of the cardiovascular continuum, in which structural and functional changes in the vascular wall are already present, but the clinical manifestation of coronary heart disease or cerebrovascular pathology has not yet occurred. ESC European Recommendations (Visseren et al., 2021; SCORE2 Working Group, 2021) [8, 9] emphasize that the detection of subclinical vascular lesions is important for risk reclassification in patients with an intermediate probability of events, including the use of coronary calcium index and imaging of atherosclerotic plaques [10-14], which enhances the possibilities of personalized prevention.

In Russian practice, instrumental verification of subclinical atherosclerosis is considered as a way to clarify individual risk beyond traditional scales and as an element of a multi-parametric assessment. Researchers Safaryan A. S. and Vygodin V. A. (2023) [15] have shown that comparing SCORE and the Agatston index often leads to different stratification, and the presence of coronary calcification reveals a higher risk than the clinical model suggests [16-18], which confirms the need to integrate visualization data into prediction algorithms.

The systemic nature of subclinical vascular damage was demonstrated in the work of Skripnikova I. A., Kolchina M. A. (2023) [19], where the relationship between indicators of subclinical atherosclerosis and signs of osteoporosis and their prognostic significance in prospective follow-up was established. These results indicate a connection between vascular remodeling and general tissue processes and confirm that subclinical atherosclerosis can be considered as a marker of an unfavorable prognosis outside the exclusively cardiological population [20-23].

The prevalence of subclinical coronary calcification in individual clinical cohorts was demonstrated by Yusupova A.V. (2023) [24], who, when analyzing standard CT scans of the chest organs in cancer patients, revealed a significant proportion of asymptomatic coronary calcification. These data confirm that within the framework of modern approaches to the assessment of subclinical atherosclerosis, coronary calcium is often detected by incident, but it has independent prognostic value and should be taken into account in models of personalized prevention of cardiovascular diseases.

The results of foreign studies strengthen the argument in favor of an instrumental assessment of the "atherosclerotic burden." The work of Emily S. La (2022) [25] showed that the inclusion of the coronary calcium index improves risk stratification compared to traditional scales, whereas Petra Mamic (2023) [26] demonstrated the association of high CAC with an increased likelihood of cardiovascular events and, conversely, low short-term risk at zero, which emphasizes its importance for clarifying an individual forecast.

The transition to multi-biomarker and algorithmic risk assessment models is reflected in the works of Bakulin G. G., Serezhina E. K. and Obrezan A. G. (2025) [27], which compares the contribution of traditional scales and machine learning methods and substantiates the need to integrate clinical, instrumental and laboratory parameters into a single predictive model. A similar position is held by Gusev A.V., Kuznetsova T. Y. and Boytsov S. A. (2021) [28], who showed that machine learning algorithms can improve prediction accuracy compared to the isolated use of clinical scales, but their use requires standardization and external validation to implement personalized prevention in practice.

Modern foreign data show that when using modern approaches to assessing subclinical atherosclerosis and multi-biomarker risk prediction, the inflammatory component remains a significant predictor of cardiovascular events even when target lipid levels are reached. In a multicenter study by Paul M. Ridker et al. (2024), which included 13,970 patients with statin intolerance, the baseline level of hs-CRP was significantly associated with the risk of myocardial infarction, stroke, revascularization, cardiovascular and total mortality, while the association of LDL-C with these outcomes was less pronounced and statistically neutral for total mortality. Increased values of hs-CRP when included in the study were associated with an increase in the frequency of events even with controlled LDL-C, which confirms the independent prognostic role of the inflammatory link of atherogenesis and justifies its inclusion in personalized prevention models [29].

Taken together, Russian and foreign studies confirm that subclinical atherosclerosis and related biomarker profiles have independent prognostic significance and should be considered as elements of integrative risk stratification models. At the same time, unresolved issues remain regarding the unification of diagnostic criteria, standardization of multi-biomarker panels and assessment of their real impact on clinical decisions, which determines further research directions in the framework of personalized prevention of cardiovascular diseases.

Instrumental methods for detecting subclinical atherosclerosis and their prognostic value

Within the framework of modern approaches to the assessment of subclinical atherosclerosis as the basis of a multi-biomarker risk prognosis, imaging and functional diagnostic methods are gaining priority, allowing to identify preclinical changes in the vascular wall and refine the individual cardiovascular prognosis before the development of events. In Russian guidelines for the prevention of CVD, instrumentally confirmed signs of subclinical damage — atherosclerotic plaques, increased vascular stiffness, and other markers of remodeling — are considered as an argument for risk reclassification, especially in patients with SCORE/SCORE2 borderline values. In clinical practice, ultrasound examination of the carotid arteries remains the basic method with an assessment of the intima-media complex and the identification of plaques, which directly affects the choice of target lipid levels and the volume of preventive interventions [30-35]. The addition of morphological assessment with indicators of arterial stiffness and "vascular age" expands the possibilities of integrative risk stratification, however, differences in measurement protocols and thresholds limit the comparability of the results and emphasize the need for their standardization in building valid models of personalized prevention [36-42].

CT determination of coronary calcium (CAC, Agatston index) plays an important role in the system of modern approaches to the assessment of subclinical atherosclerosis as a quantitative indicator of the total atherosclerotic burden. In a population-based study of coronary calcification among Moscow residents, Yu. A. Vasiliev and I. V. Goncharova (2023) [43] showed that automated analysis of previously performed CT scans of the chest organs makes it possible to detect a high prevalence of subclinical coronary calcification, including in people without diagnosed coronary artery disease, which expands the possibilities of secondary risk stratification in real practice. Complementing these data, E. V. Grakova et al. (2025) [44] demonstrated the association of the presence of coronary calcium with changes in instrumental and humoral markers of sympathetic activity, which indicates the association of structural calcification with systemic neurohumoral risk mechanisms.

Thus, the inclusion of CAC indicators and other markers of subclinical atherosclerosis in multifactorial assessment algorithms makes it possible to identify latently high risk before clinical manifestation and justify earlier preventive interventions, however, their widespread use requires the unification of techniques, standardization of thresholds and prospective validation in different populations.

A multi-biomarker approach to predicting cardiovascular risk

In the context of modern approaches to the assessment of subclinical atherosclerosis, lipoprotein(a) is considered as an independent, genetically determined cardiovascular risk factor capable of influencing the formation of coronary heart disease, peripheral atherosclerosis, stroke, and calcifying aortic stenosis, regardless of traditional factors, including LDL levels. In a review by Kamstrup P.R. et al. (2024) emphasized that elevated Lp(a) concentrations are detected in a significant proportion of the population and are associated with an increase in the absolute risk of atherosclerotic events, and its inclusion in stratification algorithms leads to a marked reclassification of risk, which enhances the importance of this marker in the framework of personalized CVD prevention [45].

At the same time, the authors note that the definition of Lp(a) is still limited in routine practice, despite the recommendations of international societies (EAS, ESC, AHA/ACC), which is associated with the need to unify measurement methods, standardize thresholds, and improve data comparability. Additionally, it is emphasized that ongoing clinical studies of targeted therapy aimed at reducing Lp(a) expand its importance not only as a predictive tool in biomarker models, but also as a potential therapeutic target in a personalized prevention system [46-51].

In domestic publications on the problem of modern approaches to the assessment of subclinical atherosclerosis, Polyakova E. A., Khalimov Yu.Sh., Bazhenova E. A., Bacher T. M. (2024) consider lipoprotein(a) as an independent, genetically determined atherosclerotic risk factor, which is not reflected in traditional stratification scales. The authors emphasize the expediency of including Lp(a) in personalized risk assessment algorithms, especially in patients with signs of subclinical vascular damage and a discrepancy between the standard lipid profile and the actual atherosclerotic burden [52]. A structured representation of the key groups of biomarkers that form the basis of a multi-biomarker model for predicting cardiovascular risk is shown in the table (Table 1).

Table 1: Main biomarker groups in a multi-biomarker model of cardiovascular risk

A group of biomarkers	Specific indicators	The reflected pathogenetic mechanism	Clinical significance	Limitations
Lipids	LDL, non-HDL, ApoV, Lp(a)	Atherogenic load, the number of atherogenic particles	Basic risk stratification, definition of lipid-lowering therapy goals	Underestimation of the residual inflammatory risk; variability of Lp(a)
Inflammatory	hs-CRP	Systemic inflammation, residual risk	Identification of the inflammatory component of atherogenesis in normal LDL	Non-specificity, influence of concomitant diseases
Metabolic	Glucose, HbA1c, insulin resistance	Metabolic dysfunction	Assessment of diabetic and metabolic risk	Addiction to lifestyle and therapy
Neurohumoral	NT-proBNP, BNP	Myocardial stress	Prognosis of adverse outcomes, latent myocardial dysfunction	Age dependence, the impact of CHF
Cardiospecific	Highly sensitive troponins	Subclinical myocardial injury	Prognosis of events even without a coronary heart disease clinic	Requires standardization of thresholds
Markers of remodeling	Galectin-3, GDF-15, sST2	Fibrosis, remodeling	Fine risk stratification in chronic conditions	Insufficient validation in population studies

Thus, within the framework of modern approaches to the assessment of subclinical atherosclerosis, a multi-biomarker model allows taking into account the main links of atherogenesis — lipid disorders, inflammatory activity, metabolic shifts and neurohumoral dysfunction, which increases the accuracy of personalized stratification of cardiovascular risk. At the same time, its practical implementation requires the unification of analytical techniques, the harmonization of thresholds, and the confirmation of the clinical effectiveness of integrated panels in prospective studies focused on real outcomes [53-59].

Integration of subclinical atherosclerosis data and biomarkers into personalized prevention models

Modern concepts of personalized prevention of cardiovascular diseases in the framework of subclinical atherosclerosis assessment and multi-biomarker risk prediction are based on step-by-step stratification, in which the SCORE/SCORE2 calculation is supplemented by imaging results and laboratory markers in patients with uncertain or intermediate risk. The ESC recommendations emphasize that the detection of subclinical atherosclerotic lesions — coronary calcium or carotid plaques — can change the risk category and influence the decision to initiate or enhance lipid-lowering therapy.

Domestic studies confirm the importance of including instrumental markers in personalized prevention algorithms. The work of Kaveshnikov V. S., Trubacheva I. A., Shalnova S. A. (2025) showed that the presence of carotid atherosclerosis in people aged 40-64 years is accompanied by a higher predicted risk compared with the SCORE scale alone, which justifies risk reclassification based on subclinical vascular damage and earlier intervention in asymptomatic patients [60].

The development of integrative models in Russian practice is associated with the use of machine learning algorithms for predicting subclinical carotid atherosclerosis. Gavrillov D. V., Kuznetsova T. Yu., Druzhilov M. A., Korsakov I. N., Gusev A.V. (2022) showed the possibility of predicting carotid lesions in overweight patients using algorithmic models, which makes it possible to form targeted routes for instrumental examination [61]. Subsequently, Druzhilov M. A. et al. (2022) demonstrated that verification of subclinical atherosclerosis within

the framework of risk stratification in obesity using such models increases the accuracy of diagnosis, but requires standardization and external validation on independent samples [62-66].

The integrative use of subclinical atherosclerosis imaging data and laboratory markers forms the basis of modern approaches to personalized prevention of cardiovascular diseases. The inclusion of multi-biomarker parameters — lipid fractions, Lp(a), hs-CRP, highly sensitive troponins, NT-proBNP — allows us to identify the leading pathogenetic risk mechanism and thus more reasonably choose both drug and non-drug interventions. The ACC/AHA international guidelines emphasize the role of so-called "risk-enhancing factors", including Lp(a) and inflammatory markers, in making therapeutic decisions [67]. In this regard, the modern prevention strategy is focused on the transition from isolated consideration of risk factors to complex models combining clinical, instrumental and biochemical parameters, subject to their standardization and confirmed clinical validity.

Clinical prospects and limitations of the introduction of personalized approaches in the prevention of cardiovascular diseases

Within the framework of modern approaches to assessing subclinical atherosclerosis and multi-biomarker risk prediction, personalized CVD prevention is based on combining traditional risk factors with vascular lesion imaging data and laboratory markers to more accurately determine the risk category and select the scope of interventions. The main clinical effect of the multimodal models is manifested in the reclassification: the identification of carotid plaques, high coronary calcium, or an unfavorable biomarker profile makes it possible to recognize a latently high risk in asymptomatic patients and justify earlier and intensive prevention. However, the importance of such approaches is determined not only by their predictive ability, but also by their proven influence on clinical decisions and outcomes in real practice [68-70].

At the same time, the introduction of integrative models into the Russian healthcare system is accompanied by a number of limitations. The variability of subclinical atherosclerosis criteria and reclassification thresholds, differences in laboratory platforms and reference values, as well as limited availability of CT diagnostics and resource constraints of primary care are noted. Additional difficulties are associated with the use of machine learning algorithms, which require standardized data sets, external validation and transparency of models, without which their widespread use in clinical practice remains difficult.

Further improvement of modern approaches to the assessment of subclinical atherosclerosis and multi-biomarker risk prediction involves the unification of diagnostic criteria, the development and external verification of integrated models in Russian prospective cohorts, as well as mandatory assessment of their clinical and economic feasibility. Only with a proven impact on clinical decisions ("decision impact") and the inclusion of such algorithms in the dispensary monitoring system can we expect a real reduction in cardiovascular events, rather than a formal complication of risk stratification procedures.

CONCLUSION

The results of the review conducted within the framework of modern approaches to the assessment of subclinical atherosclerosis and multi-biomarker risk prediction show that subclinical vascular lesion has independent prognostic value and is reasonably considered as a key stage of the cardiovascular continuum. The combination of instrumental imaging and multi-biomarker panels expands the possibilities of risk reclassification and makes personalized prevention more reasonable in asymptomatic patients. At the same time, the practical implementation of such models requires the unification of criteria for subclinical atherosclerosis, standardization of biomarker indicators, external validation of algorithms and assessment of their clinical and economic effectiveness in Russian populations.

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