Russian Journal of Cardiology 2021;26(9):4700
doi:10.15829/1560-4071-2021-4700
https://russjcardiol.elpub.ru

EXPERT COUNCIL OPINION
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

New opportunities for biomarkers in cardiovascular risk stratification. Resolution of Advisory board

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Early detection of people with a high-risk of developing cardiovascular diseases is a key point of the prevention strategy. The existing risk scales have a number of limitations: insufficient accuracy for an individual or the appearance of a "residual risk". Existing approaches to improving the accuracy of risk prediction include the use of biomarkers. Troponin I is promising, which has proven its prognostic value in healthy and asymptomatic individuals at the population level. For example, the BiomarCARE study with the participation of 74 thousand people from 5 countries showed an association of increased troponin I concentration and the frequency of cardiovascular events and overall mortality. Similar results were obtained in other cohorts. The simulation results indicate the potential economic feasibility of using troponin I for the purpose of risk stratification. The first pilot Russian study was conducted, which made it possible to describe the population distribution of troponin levels. It confirmed the prognostic significance of the biomarker in relation to the development of cardiovascular outcomes in men in the Russian population. Further studies on large cohorts are needed to clarify the results of the pilot project.

Keywords: cardiovascular diseases, biomarkers, troponin I, cardiovascular risk, risk stratification.

Relationships and Activities. Resolution have prepared with the support of Abbott.

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CI — confidence interval, MI — myocardial infarction, CVD — cardiovascular diseases, CVR — cardiovascular risk, RF — risk factor, ESSE-RF — Epidemiology of cardiovascular diseases and their risk factors in the regions of the Russian Federation, cTn — cardiac troponin, hs-Tn — highly sensitive troponin, Tn — troponin.

Received: 16.09.2021
Accepted: 22.09.2021

For citation: Drapkina O. M., Kontsevaya A. V. on behalf of the working group. New opportunities for biomarkers in cardiovascular risk stratification. Resolution of Advisory board. *Russian Journal of Cardiology*. 2021;26(9):4700. (In Russ.) doi:10.15829/1560-4071-2021-4700

Despite significant advances in modern medicine and increased life expectancy, cardiovascular disease (CVD) remains the leading cause of death worldwide. A large number of studies demonstrate the role of primary prevention in reducing the burden of CVDs and increasing the length of "healthy life". Primary prevention includes population-based prevention, the main task of which is to promote a healthy lifestyle at the level of the population of a country, region or municipality through a range of measures based on intersectoral interaction, and individual prevention at the health care system level. Individual prevention is based on two basic fundamental actions: accurate cardiovascular risk (CVR) stratification and optimal interventions with proven effect, which include nonmedicamental correction of risk factors (RF) and drug therapy [1, 2].

One of the main tasks of individual primary prevention is the early detection of persons with high CVR. Prediction tools are risk scales and risk stratification tables, which typically include traditional CVD RFs such as hypertension, diabetes mellitus, smoking and hypercholesterolemia, and are intended for use in conditionally healthy individuals. Examples of such scales are the Framingham Scale [3], SCORE (Systematic Coronal Risk Evaluation) [4], Q2-Risk [5], etc. In 2021, a new SCORE2 scale was published, which includes not only fatal cardiovascular events but also nonfatal complications [6]. The SCORE2 scale includes the same RFs as the basic SCORE scale, except for cholesterol: total cholesterol has been replaced by non-lipo high-density cholesterol. The SCORE2 scale is built on new data and will certainly stratify risk more accurately than the previous version, but is unlikely to solve all risk stratification problems. Risk scales predict risk for the population as a whole, but are not always accurate enough for the individual. For example, the American study showed that acute coronary syndrome developed in 74,9% of those with low CVR (<10% on the Framingham Risk Score) and in 12,7% of those with intermediate risk (10-20%) [7].

There is a concept of so-called "residual risk" due to other RFs and expressed in the development of cardiovascular events in individuals who reach the target RF parameters, such as lipids, in clinical trials [8]. The presumed mechanisms of residual risk can be inflammatory, thrombotic and metabolic [9]. For each mechanism, biomarkers such as C-reactive protein for inflammation are sought.

A number of specific cardiovascular markers, including cardiovascular troponins (Tn), are associated with the risk of cardiovascular events and may contribute to more accurate risk stratification [10, 11]. Cardiovascular Tn are structural proteins that are found mainly in myofibrils and cardiomyocytes. Three types of Tn are detected in myocardium: TnI, TnT and TnC. While the latter is also found in skeletal muscle, the first two TnI and TnT are specific for cardiomyocytes. Today, new technologies allow accurate measurement of low concentrations of circulating Tn, which can directly reflect various pathophysiological processes, including apoptosis and cardiomyocyte necrosis [12].

The use of biomarkers, such as Tn, for CVR stratification has been actively discussed recently [13]. TnI meets the basic requirements for biomarkers and is detected in the majority of asymptomatic and healthy individuals. The requirements for a biomarker applicable as a screening tool, which meets TnI, are: cardiospecificity, predictive value, change depending on CVR level, level dynamics against the background of interventions, evidence-based value, cost-effectiveness [11].

The possibility of highly sensitive methods for determining low concentrations of cardiac Tn (cTn) in the population and in asymptomatic individuals allowed to hypothesize that this biomarker can be considered as a component of CVR assessment, capable of clarifying its level and becoming an element of personalized medicine.

TnI: connection with cardiovascular outcomes

Large studies in the general population have demonstrated an association of cTnI levels with the development of adverse cardiovascular events. Thus, the largest BiomarCaRE study, which involved >74 thousand participants from 5 countries (follow-up period is 13,8 years), showed that individuals from the fifth quintile (the highest levels) of TnI compared to individuals from the first quintile, the risk of death from cardiovascular events was 160% higher, the risk of the first cardiovascular event was 92% higher, and the risk of overall mortality was 63% higher [14].

In studies (HUNT, n=9005, follow-up is 13,9 years), TnI levels were associated with the risk of fatal and nonfatal cardiovascular events [15], including cardiovascular death, myocardial infarction (MI) and hospitalization for heart failure.

The Scottish WOSCOP study with 3 thousand participants and the use of statins (pravastatin) showed that baseline Tn levels were an independent predictor of MI development or death from cardiovascular causes. Treatment of patients with elevated levels of low-density lipoproteins with pravastatin was accompanied by a 13% decrease in the level of highly sensitive TnI (hs-TnI) during the year [16].

In the PEGASUS-TIMI study, TnI levels were used to reclassify risk and determine treatment tactics in very high-risk patients [17]. Among the 8635

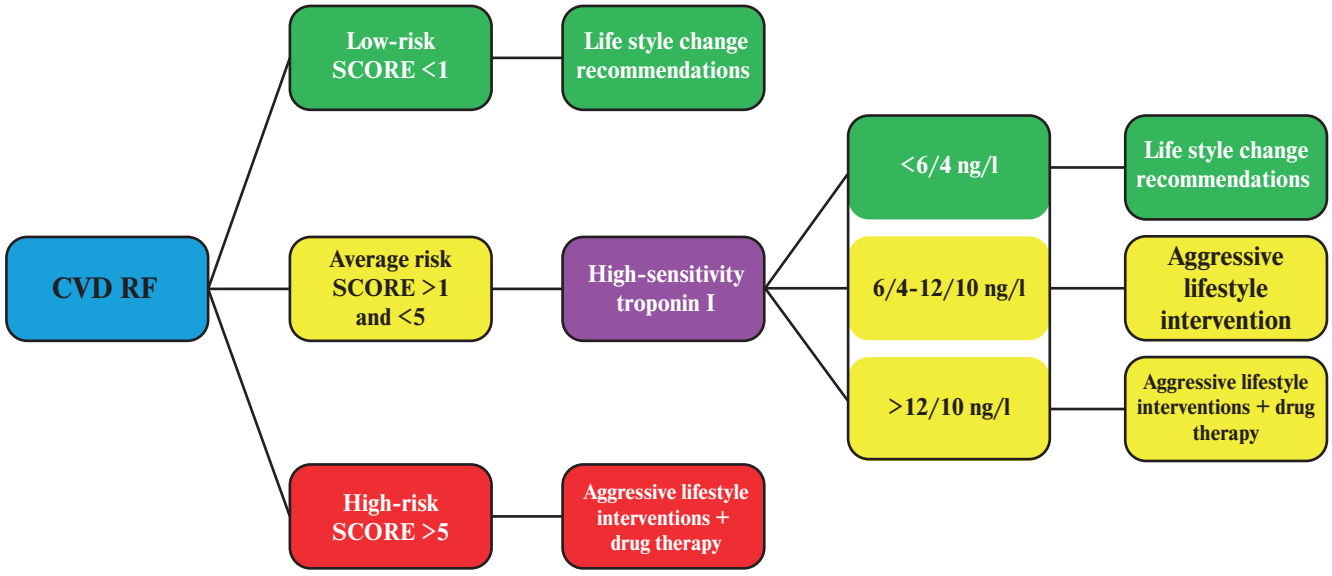

Figure 1. The proposed strategy of CVR stratification for the population as a whole, based on the established RF and tools with the addition of hs-TnI (adapted from [11]).
Abbreviations: CVD — cardiovascular diseases, RF — risk factor.

patients in this cohort study, patients with low-risk atherosclerotic coronary artery lesions and hs-TnI levels greater than 6 ng/l had the same incidence of cardiovascular events as patients classified as very high-risk patients with atherosclerotic coronary artery lesions. Similarly, in patients with very high-risk atherosclerotic lesions and undetectable hs-TnI levels, the event rate was comparable to that in patients classified as lower-risk coronary atherosclerotic patients. Tn allowed 11,9% of patients to be reclassified into a more appropriate risk group (1 of 11 patients at very high risk and 1 of 4 at low risk).

A meta-analysis of 28 cohort studies confirmed the association between hs-TnI and risk of cardiovascular complications. Those with the highest tercile of TnI levels had a risk of CVD 1,43 (95% confidence interval (CI) 1,31-1,56), CVD death 1,67 (95% CI 1,50-1,86), coronary heart disease 1,59 (95% CI 1,38-1,83), and stroke 1,35 (95% CI 1,23-1,48) compared with the lowest [18].

TnI. Economic arguments for risk stratification

In terms of health economics, a secondary analysis of BiomarCaRE [19] among 47796 people over 10 years showed that adding hs-TnI to ESC-SCORE would result in a 48 percent relative reduction in CVD, as measured by the prevention of 17 cardiovascular events (MI/stroke), 6 fatal cases and 107 saved years per 1000 people surveyed.

Cost-effectiveness modeling of TnI was performed to estimate CVR in the general population in countries with low CVR (Germany) and high CVR (Kazakhstan) [20]. Screening and effective prevention would reduce cardiovascular events by 5,1 and 5,0 per 1 thousand people over 10 years in Kazakhstan and Germany. In Kazakhstan, this strategy resulted in cost savings because the incremental cost of conducting a risk assessment using TnI was lower than the cost savings to the health care system and the economic effect through averted deaths. In Germany, this strategy turned out to be economically reasonable, as the cost per year of preserved quality of life was $6755, well below the "willingness-to-pay" threshold for that country ($27 thousand).

Pilot Russian study of the predictive role of TnI

In the Russian Federation, together with Abbott Diagnostics, a study was conducted to assess the significance of a number of biomarkers in predicting the risk of cardiovascular outcomes in men and women of productive age. The study included two stages:

— assessment of TnI level in population sample of one of the regions of the Russian Federation, formed and examined as part of the ESSE-RF study (Epidemiology of cardiovascular diseases and their risk factors in the regions of the Russian Federation), and analysis of association of Tn levels with the probability of adverse cardiovascular events during 6 years of prospective follow-up in this region;

— case-control study with cardiovascular endpoints based on data from the prospective part of the ESSE-RF study.

The first stage results of the study have been partially published [21]. The asymmetric distribution of cTnl in a sample of the Vologda region population is shown. The median cTnl level in the sample was 1,5 pg/ml (95% CI 0,80-2,50), a high Tn level was detected in men aged 45-54 years. Young men have higher Tn levels than women of the same age group. However, women's cTnl grows faster with age, at 5,9% per year, while men's cTnl grows only 2,6%. The difference in the cTnl level in men and women is leveled by the age of 72. According to the multivariate model, age, obesity, arterial hypertension, elevated levels of low-density lipoprotein cholesterol and brain natriuretic peptide were significantly associated with Tn levels. A comparison of the Tnl levels recommended for risk stratification with the SCORE risk levels revealed the following. In 25% of men and 37% of women with elevated cTnl levels, the SCORE risk was low to moderate, suggesting that the SCORE scale is not accurate enough for this population and that risk could be reclassified based on Tn levels.

Part of the results of the first stage will be published in a paper that is currently in print [22]. Men showed a tendency to reclassify intermediate risk when the number of hard cardiovascular endpoints (death from CVD and nonfatal MI) was higher in individuals with elevated Tnl levels. In assessing risk reclassification using the Cox model with $NRI_{survival}$ for survival analysis, the cTnl in the model is shown to significantly improve the risk classification of hard endpoints in men. When comparing the probability of combined endpoint (death from CVD, MI, acute cerebrovascular accident, coronary revascularization), a significant difference between three quintiles with low values and two quintiles with high levels of Tnl was obtained.

Thus, the results of the first pilot study indicate that the accuracy of SCORE risk determination in the Russian population was insufficient, and part of the sample should be reclassified. This refers to men who showed a significant increase in the likelihood of developing both severe and combined endpoints in the moderate, high, and very high-risk SCORE groups as cTnl levels increased. In addition, the probability of developing a cardiovascular event occurred at lower Tn levels compared with cutoff points of European studies. For our population, the upper quartile corresponds to the cTnl level 3,5/2,1 pg/ml, in which a connection with cardiovascular endpoints was revealed. No such association was detected in women, which may be due to the relatively short follow-up period and, consequently, the low frequency of endpoint development in women of working age. The study limitations (short follow-up period and small number of endpoints among those of working age) still allowed to obtain reliable results about the association of Tn level with the probability of cardiovascular complications, which, however, are preliminary and require refinement on a larger volume of participants in population-based studies.

The second stage of the case-control study includes an assessment of predictive significance of hs-Tnl levels in individuals with cardiovascular outcomes compared with a comparable control group, including comparison with other cardiovascular biomarkers. The resultant article has been submitted to an international journal and is in the peer-review stage. The study included 111 cases (48 cardiovascular deaths and 63 MIs, which were recorded during 6,5 years of follow-up in 8 regions of the ESSE-RF1 study) and 111 controls (individuals of comparable sex, age, region of residence, and a number of FRs who had no cardiovascular event). Tnl, cortisol, lipoprotein a, adiponectin, leptin, endo-1, interleukin-6, galectin, PCSK9, Ang ptl3 and total nitric oxide (NOx) metabolites were included in the analysis.

Elevated levels of Tnl, C-reactive protein, and nitric oxide metabolites were significantly ($P<0,001$) and independently associated with a high risk of death from cardiovascular causes.

Prospects for risk stratification

Based on the largest BiomarCaRE study, a risk stratification strategy using TnI was developed (Figure 1). TnI is important for reclassification of the average risk level according to the SCORE scale (1-4%). In determining Tn levels, there are 3 categories with gender-specific features: Tn levels <6 (in men) and 4 (in women) ng/l are reclassified as low risk and lifestyle changes are recommended for these individuals; average troponin levels of 6/4-12/10 ng/l require aggressive lifestyle changes; high levels (>12/10 ng/l) allow reclassification as high risk and are grounds for prescription of drug therapy.

The results of the first domestic TnI pilot study at the population level suggest that the risk thresholds for Tn in the Russian population may be lower than in the European population. In addition, significant associations were obtained for men, whereas no association was demonstrated for women due to the small number of cardiovascular outcomes.

The Republic of Kazakhstan plans to create a cardiovascular registry with a 10-year follow-up of middle-aged people without previously known cardiovascular disease. The main objectives of this registry are: assessment of the hs-TnI risk stratification model and implementation of hs-TnI in all health checks (screening) in the country. The register plans to use the following hs-TnI risk stratification model:

Low risk — women <4 pg/ml, men <6 pg/ml;
Average risk — women 4-10 pg/ml, men 6-12 pg/ml;
High risk — women >10 pg/ml, men >12 pg/ml.

Conclusion

One of the foundations of primary prevention of CVDs is accurate risk stratification. Risk scales are constantly being improved, but nevertheless all existing scales have limited ability to accurately stratify risk at the individual level. One way to improve the accuracy of risk stratification is to supplement the scales with biomarkers that have the ability to predict CVRs. One of these biomarkers is TnI. A significant body of data has accumulated that this biomarker is associated with the risk of cardiovascular events and meets other requirements for predictive biomarkers. The first pilot Russian study was conducted to describe the population distribution of Tn levels and to confirm the predictive significance of this biomarker with regard to the development of cardiovascular outcomes in men. Further studies on large cohorts are needed to refine the pilot project results.

Relationships and Activities. Resolution have prepared with the support of Abbott.

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