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REVIEW

Prediction of cardiovascular events: extension of indications for the use of a highly sensitive troponin I test. A review

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Abstract

Data from clinical and population studies demonstrating the value of a highly sensitive troponin I test in predicting cardiovascular disease in the general population and patients without signs of acute coronary syndrome/acute myocardial infarction are presented. New indications for using a highly sensitive troponin I test are discussed.

Keywords: cardiovascular risk, prognosis, general population, troponin I

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ОБЗОР

Прогнозирование сердечно-сосудистых событий: расширение показаний к применению высокочувствительного теста на тропонин I

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Аннотация

Представлены данные клинических и популяционных исследований, демонстрирующих значение высокочувствительного теста на тропонин I в прогнозировании сердечно-сосудистых заболеваний в общей популяции и у пациентов, не имеющих признаков острого коронарного синдрома/острого инфаркта миокарда. Обсуждаются новые показания к применению высокочувствительного теста на тропонин I.

Ключевые слова: сердечно-сосудистый риск, прогноз, общая популяция, тропонин I

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Over the past few years, the diagnostic value of troponins, proteins with the greatest specificity for car-diomyocyte damage, has undergone significant rethinking. Previously, a highly sensitive troponin I test (hsTnI) was considered only as a marker of acute coronary syndrome, with its trends used to assess the risk of an adverse outcome. Currently, this test is a valuable indicator of cardiovascular risk (CVR) in the general population [1].

Troponin I (TnI) is a member of the troponin family of proteins considered to be relatively cardiospe-cific, having the ability to inhibit calcium-stimulated magnesium-adenosine triphosphatase of actimyo-sin in the cardiomyocyte [2]. The NH2 site of TnI directly interacts with the surface of the N-domain of TnI C, forming one of the main sites that binds the calcium ion, thus modulating the cardiomyocyte contraction [3]. That is why the release of TnI is one of the reliable signs of myocardial damage, even minimal [4, 5]. Large multicenter studies [6] clearly showed that even a single value of hsTnI reliably characterizes the prognosis of patients with acute myocardial infarction (AMI): the level <5 ng/mL is recorded in more than 1/2 of patients who do not show signs of AMI and do not die from coronary events over the next 30 days. Therefore, hsTnI is a reliable marker of the AMI risk in patients with sus-pected acute coronary syndrome [7]. It was also found that an increase in the TnI level was associated with an increase in the incidence of adverse outcomes during hospital stay and mortality from any cause in normotensive patients with pulmonary embolism [8].

Since the second half of the 2010s, a sufficient body of evidence has been accumulated, primarily the results of population studies, indicating that the measurement of TnI using a highly sensitive method can successfully predict cardiovascular events both in stable patients with high CVR (atherothrombosis, diabetes mellitus [DM], etc.) and in the general population. Therefore, the indications for this diagnostic test can be significantly extended. In addition, in the general population, hsTnI can be used to more clearly stratify the risk of cardiovascular complications and describe its change over time since it re-sponds to lifestyle changes and the use of drugs that affect the relevant risk factors [9].

Thus, in one of the analyses of the population of the widely known HOPE study [10], which estab-lished many components of the modern preventive strategy in cardiology, TnI was measured using a highly sensitive method in 2572 patients with high CVR. It was found that those with a TnI level >6 ng/L were 38% more likely to reach the primary endpoint (myocardial infarction [MI], cerebral stroke, or cardiovascular death). Moreover, at a level of TnI>10 ng/L, the risk of cardiovascular death increased by 2.15 times and the risk of MI by 1.49 times. In the HIMS study [11], which included 1151 males aged 70

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to 89 years, residents of Western Australia who did not have documented cardio-vascular diseases at the baseline, at a 10-year follow-up, 252 (22%) had cardiovascular complications. Compared with using the Framingham risk scale alone, the additional measurement of TnI using a highly sensitive method led to a decrease of subjects classified as high-risk in the group without cardio-vascular complications by 7%. In contrast, the proportion of these subjects in the group with cardiovas-cular complications increased. These data indicate that hsTnI is an effective and reliable risk marker in population groups with the most unfavorable prognosis. The results of the HIMS study are all the more interesting in this regard, as they demonstrate the predictive value of hsTnI in a population of elderly males with the highest risk of cardiovascular complications, with all else being equal.

Another example demonstrating the prognostic value of hsTnI is the population of individuals with type 2 DM. K. Yiu et al. (2014) showed that in more than 99% of patients with type 2 DM, the TnI lev-el can be measured using a highly sensitive method. In 21% of patients, its level was increased to >8.5 ng/L in males and >7.6 ng/L in females (Abbott, Architect) [12]. During at least 4 years of follow-up, it was found that an increase in the TnI level measured using a highly sensitive method was associ-ated with a significant increase in the frequency of major cardiovascular complications (heart failure, MI, and cardiovascular death).

The hsTnI value as a marker of a high risk of cardiovascular complications was, to some extent, sup-ported by the established correlations between this indicator and the prevalence of coronary artery ath-erosclerosis. A. Tahhan et al. (2018) examined 3,087 patients (aged 49 to 75 years; 64% males) who had no evidence of AMI on coronary angiography [13]. The severity of coronary artery atherosclerosis was assessed using the Gensini score and the number of large coronary arteries with stenosis of ≥50%. An increased level of TnI, measured using a highly sensitive method, was associated with greater sever-ity of atherosclerotic lesions of the coronary arteries according to the Gensini score and its progression. In addition, TnI levels appeared to be an independent predictor of death, including cardiovascular death, MI, revascularization, and hospitalizations due to cardiovascular diseases. The predictive role of TnI was independent of race, sex, age, smoking, body mass index, kidney function, and whether the pa-tient had hypertension or diabetes. According to the analysis of the PEACE study population [14], which included more than 3,500 patients with stable angina pectoris (98.5% of them showed an in-creased level of TnI), the TnI levels in the upper quartile were associated with an increase in cases of heart failure and cardiovascular death by 1.88 times compared with the other three quartiles.

In the TRA 2oP TIMI study, in more than 15,800 patients with stable atherosclerosis (previous MI, cerebral stroke, or the presence of proven atherosclerotic lesions of the arteries of the lower extremi-ties), the TnI level was measured using a highly sensitive method [15]. An increased TnI was associated with an older age, a greater severity of atherosclerosis, and the male sex. The TnI level increase was associated with an increase in the risk of cardiovascular death, MI, and cerebral stroke over 3 years by 5.0-18.6%; this association remained significant regardless of the levels of C-reactive protein, B-type natriuretic peptide, as well as clinical indicators characterizing the CVR. The SCOT-Heart Trial [16], in which the extent of coronary atherosclerosis was determined using computed tomography (CT) in patients with suspected stable angina, showed that increasing TnI levels across quintiles were associat-ed with a 5-fold increase in the probability of having obstructive coronary artery disease. Similar data confirming the relationship between the TnI levels and the severity of coronary calcification, assessed by CT, were also obtained in the PROMISE study [17]. The relationship between the TnI levels meas-ured using a highly sensitive method and the severity of atherosclerosis of the coronary arteries has also been confirmed in more specific populations, for example, in female patients with rheumatoid arthri-tis [18].

Pharmacoeconomic rationale for the introduction of hsTnI screening into real-world practice

HsTnI screening can be considered an indicator of the effectiveness of pharmacological strategies for reducing CVR. Thus, the WOSCOPS study [19] showed that the upper quartile of TnI levels compared to the lower quartile was associated with an increase in the frequency of MI and death from coronary heart disease by 2.3 times. The use of statins led to a significant decrease in the level of TnI by 13% and increased twice the number of males with TnI decreased by more than 1/4. Thus, drugs with proven ability to reduce CVR affect the TnI levels measured using a highly sensitive method, which further confirms their positive effect on the long-term prognosis.

In a large JUPITER study [20], which evaluated the use of statins for the primary prevention of cardi-ovascular complications, almost 13,000 participants had their TnI levels measured before randomiza-tion. It exceeded reference values in 2.9% of males and 4.1% of females (99% gender-specific percen-tile). The TnI level in the upper tertile was associated with an increase in the probability of a major cardiovascular complication by 2.19 times and death from any cause by 2.61 times. These data can be considered a rationale for using hsTnI to assess CVR in the general population.

The data from the JUPITER study became the first stage in forming an evidence base for the role of TnI as a general population predictive marker, meeting the volume requirements of big data medicine. A large BiomarCaRe project [21], which combined data from 10 large studies (almost 75,000 patients, including patients from the JUPITER study), showed that an increase in the level of TnI as measured by a highly sensitive method is associated with a 1.37-fold increase in the risk of cardiovascular death, 1.23-fold for cardiovascular diseases, and 1.24-fold for death from any cause. These data have become the basis for considering TnI as an independent risk marker in the general population.

According to the results of a large Nord-Trondelag Health (HUNT) Study [22], in 9005 participants with TnI level measured for an average of 13.9 years, it was shown that an increase >12 ng/L in males and >10 ng/L in females was associated with an increase in the frequency of hospitalizations due to MI, heart failure, and cardiovascular death (primary endpoint) by 3.61 times. Depending on the TnI levels, the researchers proposed the following classification of CVR (Table 1).

Later in this study [23], it was found that both absolute and relative increments of TnI can be a relia-ble risk marker.

In the general population (not only in patients with stable angina pectoris), CT screening demonstrat-ed an association between TnI level and coronary artery calcification [24]. The reliability of TnI as a risk marker for cardiovascular complications has been confirmed in the population of patients with type 2 DM [25]. It should be emphasized once again that the level of TnI responds to pharmacological strategies that reduce the risk of cardiovascular complications, such as antihypertensive therapy [26].

P. Jülicher et al. (2022) investigated the cost-effectiveness of using hsTnI to assess the risk of cardio-vascular diseases (CVD) in the general population for primary prevention [27]. The analysis was con-ducted in countries with low CVD risk (Germany) and high CVD risk (Kazakhstan). They compared the screening (use of hsTnI) and prevention strategy among the working-age population with the observa-tion strategy. Prophylactic treatment based on elevated hsTnI values resulted in a 9% reduction in CVD risk, an 8.8% (Germany) or 9.8% (Kazakhstan) reduction in CVD mortality, and an increase in the pe-riod of healthy life (without CVD) before retirement age by 27 years (Germany) and 28 years (Kazakh-stan) per 1,000 people. In both countries, <200 people would need to be screened to prevent one event of CVD.

Later, P. Jülicher et al. (2024) conducted a comparison analysis of the Systematic COronary Risk Evaluation (SCORE) and hsTnI screening in combination with SCORE (S-SCORE) [28]. Only 9.4% of subjects received prophylactic treatment in the SCORE group versus 14.5% in the S-SCORE group. Also, 7.5% of subjects who did not receive treatment in SCORE were assigned to a higher risk group and received prophylactic treatment in S-SCORE; in 2.5% of subjects who received treatment in SCORE, the risk category was lowered in S-SCORE. The rate of cardiovascular events in the SCORE group was 5.38% compared to 4.85% in S-SCORE (p<0.001). A statistically significant decrease was observed for all clinical endpoints. The S-SCORE strategy resulted in a 9.9% relative risk reduction for CVD events (95% confidence interval 7.3–13.5%).

Opportunities to extend the scope of hsTnI use

The indications for using hsTnI will expand in the coming years, including for the so-called non-coronary myocardial lesions, such as thyrotoxic cardiomyopathy [29]. This test has certain prospects in diagnosing heart damage associated with the new coronavirus infection (COVID-19) [30], which often has an unfavorable prognosis and, as it is already known, is not always detected promptly. In addition, TnI can be considered a potential marker for assessing CVR in COVID-19 survivors. Recent studies showed the degree of involvement of the heart in the recovery phase after COVID-19, active myocardi-al inflammation, and scar formation. TnI may be key in identifying patients at high risk of myocardial damage during recovery [31].

In 2022, the European Society of Cardiology published guidelines for the management of cancer pa-tients [32], which recommended the assessment of the level of cTnI or natriuretic peptides (B-type or N-terminal propeptide) to stratify the risk of CVD in patients receiving chemotherapy. This screening will identify patients needing cardioprotective therapy and reduce cardiotoxicity during cancer therapy.

The guidelines for the management of patients undergoing non-cardiac surgery [33] also recommend assessing the level of hsTnI T/I in patients with known CVDs, CVD risk factors (including age ≥65 years) or symptoms indicative of CVD at 24 and 48 hours after mid- and high-risk surgery. An in-crease of hs-cTn above the upper limit of the reference range at day 1 or 2 postoperatively compared to the preoperative level is defined as a perioperative MI. Without data on the hs-cTn T/I level before sur-gery, its high concentration on day 1 after surgery (e.g., more than 5-fold increase) or increase for 2 days also reliably indicates a perioperative MI.

Prospects for hsTnI

Due to its high reliability, the most definite prospect of the hsTnI application is identifying individu-als with high CVR in the general population. Based on the analysis of the available data on hsTnI, D. Farmakis et al. concluded that the addition of hsTnI level measurement to the standard SCORE risk stratification would allow paying special attention to patients of the medium risk category (SCORE≥1% and <5%) [9]. This approach can facilitate therapy modification and prevent patients from moving into the high-risk group.

These findings formed the basis for the study to determine the prognostic significance of hsTnI in as-sessing CVR in the Russian population [34]. The results of the Russian observational multicenter stud-ies ЭССЕ-РФ1 and ЭССЕ-РФ2 were used as the data for the analysis to assess the prevalence of the main behavioral and biological risk factors in the Russian population. Analysis of data from 13,976 males and females aged 25–64 showed that an increased hsTnI level was statistically significantly associated with a higher incidence of any cardiovascular events in people aged 35–64 without a history of MI and cerebrovascular accident. The risk reclassification index for the hard clinical end-point was found to be higher in males than in females. Adding a hs-cTnI level to the SCORE risk model significantly improves the accuracy of the CVR estimation. Thus, after adding the hs-cTnI level to the risk model, 201 (7%) subjects were reassigned to a high-risk group.

Table 1. CVR classification

CVR	HsTnI level (Abbott), ng/L	
	males	females
Low	<6	<4
Moderate	6–12	4–10
High	>12	>10

The diagnostic value of hsTnI needs further testing in various categories of representatives of the Russian general population, including patients with diabetes, the elderly, those with chronic kidney dis-ease, as well as COVID-19 survivors. However, the results of such studies can support the expansion of indications for hsTnI use, primarily in outpatient settings, during follow-up medical examinations, screening, and periodic medical check-ups in specific population categories.

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References/Литература

1. Passimo C, Almo A, Masotti S, et al. Cardiac troponins as biomarkers for cardiac disease. *Biomark Med.* 2019;13(5):325-30.
2. Perry SV. Troponin I: inhibitor or facilitator. *Moll Cell Biochem.* 1999;190(1-2):9-32.
3. Kachooei E, Cordina NM, Potluri PR, et al. Prosphorylation of troponin I finely controls the positioning of troponin for the optimal regulation of cardiac muscle contraction. *J Moll Cell Cardiol.* 2021;150:44-53.
4. Ni CY. Cardiac troponin I: a biomarker for detection and risk stratification of minor myocardial damage. *Clin Lab.* 2001;47(9-10):483-92.
5. Katrukha IA, Katrukha AG. Myocardial injury and the release of troponin I and in blood of patients. *Clin Chem.* 2021;67(1):124-30.
6. Sandoval Y, Nowak R, deFilippi CR, et al. Myocardial infarction risk stratification with a single management of high-sensitivity troponin I. *J Am Coll Cardiol.* 2019;74(3):271-82.
7. Chapman AR, Lee KK, McAllister DA, et al. Association of high-sensitivity cardiac troponin I concentration with cardiac outcomes in patients with suspected acute coronary syndrome. *JAMA.* 2017;318(19):1913-24.
8. Ebner M, Guddat N, Keller K, et al. High-sensitivity troponin I in risk stratification in normotensive pulmonary embolism. *ERJ Open Res.* 2020;6(4):00625-2020.
9. Farmakis D, Mueller C, Apple FS. High sensitivity cardiac troponin I assays for cardiovascular risk stratification in the general population. *Eur Heart J.* 2020;40(41):4050-6.
10. Kavsak PA, Xu L, Yusuf S, McQueen MJ. High-sensitivity cardiac troponin I management for risk stratification in stable high-risk population. *Clin Chem.* 2011;57(8):1146-53.
11. Ran NSR, Bell DA, McCaul KA, et al. High sensitivity cardiac troponin I improves cardiovascular risk prediction in older men: HIMS (The Health In Men Study). *J Am Heart Assoc.* 2019;8(5):e011818.
12. Yiu KH, Lau KK, Zhao CT, et al. Predictive value of high-sensitivity troponin-I for future adverse events cardiovascular outcomes in stable patients with type 2 diabetes mellitus. *Cardiovasular Dabetol.* 2014;13:63.
13. Tahhan AS, Sandesara P, Hayek SS, et al. High-sensitivity troponin I levels and coronary arteries disease severity, progression, and long-term outcomes. *J Am Heart Assoc.* 2018;7(5):e007914.
14. Omland T, Pfeffer MA, Solomon SD, for PEACE Investigators. Prognostic value of cardiac troponin I measured with a highly sensitive assay in patients with stable coronary artery disease. *J Am Coll Cardiol.* 2013;61:1240-9.
15. Eisen A, Bonaca MP, Jarolim P, et al. High-sensitivity troponin I in stable patients with atherosclerotic disease in TRA 2oP TIMI trial. *Clin Chem.* 2017;63(1):307-15.

16. Adamson PD, Hunter A, Madsen DM, et al. High sensitivity cardiac troponin I and the diagnosis of coronary artery disease in patients with suspected angina pectoris. *Circ Cardiovasc Qual Outcomes.* 2018;11:e004227.
17. Januzzi JL, Suchindran S, Coles A, et al. on behalf on PROMISE Investigators. High sensitivity troponin I and coronary computed tomography in symptomatic patients with suspected CAD. Insights from the PROMISE Trial. *JACC Cardiovasc Imag.* 2019;12(6):1047-55.
18. Hromadka M, Seidlerova J, Baxa J, et al. Relationship between hsTnI and coronary stenosis in asymptomatic women with rheumatoid arthritis. *BMC Cardiovasc Disord.* 2016;16(1):184.
19. Ford I, Shah ASV, Zhang R, et al. High sensitivity cardiac troponin, statin therapy and risk of coronary heart disease. *J Am Coll Cardiol.* 2016;68(25):2719-28.
20. Everett BM, Zeller T, Glynn RJ, et al. High sensitivity cardiac troponin I and B-type natriuretic peptide as predictors of vascular events in primary prevention. Impact of statin therapy. *Circulation.* 2015;131:1851-60.
21. Blankenberg S, Salomaa V, Makarova N, et al. for BiomarCaRe Investigators. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRe consortium. *Eur Heart J.* 2016;37(30):2428-37.
22. Sigurdardottir FD, Lyngbakken MN, Holmen OL, et al. Reactive prognostic value of cardiac troponin I and C-reactive protein in the general population (from the Nord-Trondelag Health (HUNT) Study). *Am J Cardiol.* 2018;121:949-51.
23. Lyngbakken ML, Rosjo H, Holmen OL, et al. Events in the general population: Nord-Trondelag Health Study. *Clin Chem.* 2019;65(7):871-81.
24. Olson F, Engborg J, Gronhoj MH, et al. Association between high-sensitive troponin I and coronary artery calcification in Danish general population. *Atherosclerosis.* 2016;245:88-93.
25. Tang O, Matsushita K, Coresh J, et al. High-sensitivity cardiac troponin I and T for cardiovascular risk stratification in adults with diabetes. *Daibetes Care.* 2020;43:e144-6.
26. Jagodzinski A, Neumann JT, Ojeda F, et al. Cardiovascular biomarkers in hypertensive patients with medical treatment – results from the randomized TEAMSTA Protect I Trial. *Clin Chem.* 2017;63(12):1877-85.
27. Jülicher P, Varounis C. Estimating the cost-effectiveness of screening a general population for cardiovascular risk with high-sensitivity troponin-I. *Eur Heart J.* 2022;8(3):342-51. DOI:10.1093/ehjqcco/qcab005
28. Jülicher P, Makarova N, Ojeda F, et al. Costeffectiveness of applying high-sensitivity troponin I to a score for cardiovascular risk prediction in asymptomatic population. *PLoS ONE.* 2024;19(7):e0307468. DOI:10.1371/journal
29. Watanabe N, Noh JY, Hattori N, et al. Cardiac troponin is elevated in patients with thyrotoxicosis and decreases as thyroid function improves and brain natriuretic peptide levels decrease. *Eur Thyroid J.* 2020;10(6):468-75.
30. Wu X, Deng KQ, Li C, et al. Cardiac involvement in recovered patients form COVID-19: a preliminary 6-month follow-up study. *Front Cardiovasc Med.* 2021;13(8):654405.
31. Maino A, Di Stasio E, Grimaldi MC, et al. Prevalence and characteristics of myocardial injury during COVID-19 pandemic: A new role for high-sensitive troponin. *Int J Cardiol.* 2021;338(4):278-85. DOI:10.1016/j.ijcard.2021.06.028
32. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS) Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). *Eur Heart J Cardiovasc Imag.* 2022;10:e333-465.
33. Halvorsen S, Mehilli J, Cassese S, et al. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery: Developed by the task force for cardiovascular assessment and management of patients undergoing non-cardiac surgery of the European Society of Cardiology (ESC) Endorsed by the European Society of Anaesthesiology and Intensive Care (ESAIC). *Eur Heart J.* 2022;43(39):3826-924.
34. Драпкина О.М., Шальнова С.А., Концевая А.В., и др. Прогностическая значимость тропонина I в оценке сердечно-сосудистого риска в российской популяции. По результатам многоцентровых исследований ЭССЕ-РФ1 и ЭССЕ-РФ2. *Кардиоваскулярная терапия и профилактика.* 2023;22(5):3548 [Drapkina OM, Shalnova SA, Kontsevaya AV, et al. Prognostic significance of troponin I in assessing cardiovascular risk in the Russian population. Data from ESSE-RF1 and ESSE-RF2 multicenter studies. *Cardiovascular Therapy and Prevention.* 2023;22(5):3548 (in Russian)]. DOI:10.15829/1728-8800-2023-3548

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