DOI: 10.17816/KMJ2021-510

The role of systemic inflammation in heart failure

E.V. Khazova*, O.V. Bulashova

Kazan State Medical University, Kazan, Russia

Abstract

The discussion continues about the role of systemic inflammation in the pathogenesis of cardiovascular diseases of ischemic etiology. This article reviews the information on the role of C-reactive protein in patients with atherosclerosis and heart failure in risk stratification for adverse cardiovascular events, including assessment of factors affecting the basal level of highly sensitive C-reactive protein. Research data (MRFIT, MONICA) have demonstrated a relationship between an increased level of C-reactive protein and the development of coronary heart disease. An increase in the serum level of highly sensitive C-reactive protein is observed in arterial hypertension, dyslipidemia, type 2 diabetes mellitus and insulin resistance, which indicates the involvement of systemic inflammation in these disorders. Currently, the assessment of highly sensitive C-reactive protein is used to determine the risk of developing myocardial infarction and stroke. It has been proven that heart failure patients have a high level of highly sensitive C-reactive protein compared with patients without heart failure. The level of C-reactive protein is referred to as modifiable risk factors for cardiovascular diseases of ischemic origin, since lifestyle changes or taking drugs such as statins, non-steroidal anti-inflammatory drugs, glucocorticoids, etc. reduce the level of highly sensitive C-reactive protein. In patients with heart failure with different left ventricular ejection fraction values, it was found that the regression of the inflammatory response is accompanied by an improvement in prognosis, which confirms the hypothesis of inflammation as a response to stress, which has negative consequences for the cardiovascular system.

Keywords: C-reactive protein, heart failure, systemic inflammation.

For citation: Khazova E.V., Bulashova O.V. The role of systemic inflammation in heart failure. *Kazan Medical Journal.* 2021; 102 (4): 510–517. DOI: 10.17816/KMJ2021-510.

Currently, in addition to the hemodynamic and neurohumoral concepts underlying the development of chronic heart failure (CHF), the importance of cytokine activation and immune inflammation is being widely discussed [1, 2]. This is especially true for CHF caused by ischemic heart disease due to atherosclerosis. The relationship between inflammation and atherosclerosis has been a topic of scientific discussion for over 170 years. In 1988, Munro et al. highlighted the first sources from 1825, showing the connection between inflammation and atherosclerosis [3]. In 1976, Rose and Harker substantiated the influence of metabolic, chemical, and infectious factors on the development of atherosclerosis [4].

Modern research is increasingly revealing the coexistence of humoral and cellular reactions that form the stages of inflammation; however, it is still unclear if the factors initiate the process of inflammation. In terms of functional reactions, the commonality of atherosclerosis and inflammation can be traced in the fact that both conditions involve connective tissue cells, endothelial and smooth muscle cells, fibroblasts, macrophages, monocytes, neutrophils, and platelets.

In atherosclerosis and inflammation, monocytes and neutrophils are fixed on the surface of the endothelium and activate integrin proteins, resulting in active tissue infiltration and activation of protein and lipid peroxidation [5]. In both these conditions, the death of functional phagocytes as a result of necrosis promotes the activation of interleukins, which results in the synthesis and blood secretion of acute phase proteins, including C-reactive protein (CRP) [6]. Both pathological processes are characterized by a long course with alternating periods of exacerbations and remission.

The body's immune system reacts not only to the aggression of an infectious disease but also to any stressful effect, which includes ischemia and hemodynamic overload, that is, factors that contribute to the onset and progression of heart failure [7]. The involvement of markers of systemic inflammation in the pathogenesis of CHF as well as their sig-

For correspondence: hazova_elena@mail.ru Received 26.04.2021; accepted 15.06.2021.

nificance for stratification of cardiovascular event risk continue to be studied. Patients with CHF of any etiology have an increased concentration of blood proinflammatory cytokines, which have several negative effects. The above changes made it possible to formulate the immunoinflammatory concept of the pathogenesis of heart failure [8].

Systemic inflammation can occur in patients with heart failure due to tissue hypoperfusion and neurohormonal activation [9–11]. In the early stages, in patients with heart failure with short-term overproduction of proinflammatory cytokines, a positive effect occurs owing to increased expression of heat shock proteins, as well as improved regional blood flow in the myocardium and increased resistance to arrhythmias of ischemic etiology [12]. The prolonged overproduction of proinflammatory cytokines exhibits its negative effect on the body, including disruption of endothelium-dependent dilatation of arterioles, activation of myocardial hypertrophy formation and damage to cardiomyocyte membranes, increased apoptosis, accumulation of extracellular collagen matrix of the myocardium with the subsequent development of myocardial remodeling, lung remodeling, and cachexia [12, 13].

The immunoinflammatory theory of the pathogenesis of heart failure with preserved ejection fraction (EF) explains the decrease in the functional capabilities of patients due to dysregulation of the tone of peripheral arterioles. This contributes to decreased strength and endurance of skeletal muscles and, consequently, to decreased exercise tolerance. An increase in the level of inflammatory markers in patients with preserved systolic function occurs as a result of both nonspecific activation of immunocompetent cells and formation of cytokines in the myocardium. The synthesis of myocardial cytokines is in direct proportion to the diastolic dysfunction of the myocardium [14, 15].

CRP, an acute phase protein synthesized mainly in the liver in response to the release of proinflammatory cytokines (interleukin-6, to a lesser extent interleukin-1 and tumor necrosis factor α), is mainly produced by macrophages and adipocytes [16]. In 1930, CRP in the presence of Ca^{2+} was found to bind the pneumococcal polysaccharide circulating in the blood of patients with acute inflammatory diseases [17]. This discovery initiated research into the role of CRP in cardiovascular disease. In addition, CRP binds to low-density lipoproteins and is present in atherosclerotic plaques [18]. A feature of CRP, like other acute phase proteins of inflammation, is the high correlation of its blood concentration with disease severity.

As a result of the Multiple Risk Factor Intervention Trial (MRFIT) study, data have been obtained for the first time indicating the importance of determining CRP for predicting outcomes in patients with atherosclerosis. Accordingly, the risk of myocardial infarction and death from coronary heart disease increased three-fold in patients with elevated CRP levels [19]. In the large MONICA study, the incidence of coronary heart disease after 8 years of follow-up in patients with elevated CRP levels was twice higher than in patients with normal levels [20].

Since the range of CRP levels determined in clinical trials for vascular risk was predominantly below the threshold determined by standard CRP analysis (5–10 mg/L), a more accurate method for determining the level of highly sensitive CRP (hsCRP) was developed [21–24].

The data obtained helped create an algorithm for assessing the clinical risk (Reynolds risk) for women and men [25, 26]. In addition to the traditional risk factors, information on the level of hsCRP and data on hereditary history (myocardial infarction before 60 years) are included.

The basal hsCRP level is influenced by many factors, including age, sex, alcohol and smoking, body weight and dietary habits, and comorbidities [27, 28]. Higher hsCRP levels are found in elderly patients, which is associated with a higher incidence of cardiovascular events in this cohort. The hsCRP level increases with increasing age, reaching its highest value by the age of 55.4 ± 3.2 years, after which it stabilizes. Correlation analysis revealed a close, direct relationship between age and baseline hsCRP levels [29].

Increases in serum hsCRP level occur in disorders such as hypertension, dyslipidemia, type 2 diabetes mellitus, and insulin resistance, suggesting the involvement of systemic inflammation in these disorders. CRP levels are inversely correlated with a number of potentially protective risk factors for coronary heart disease, such as physical activity, high-density lipoprotein cholesterol, apolipoprotein A1, and consumption of fruits and vegetables [18]. The Firefighters and Their Endothelium (FATE) study included men (n = 1154) without a history of cardiovascular disease. Elevated CRP levels correlated with older age, increased systolic and diastolic blood pressure, cholesterol, triglyceride levels, and body mass index [30].

Currently, to identify patients at high risk of cardiovascular events, it is recommended to determine hsCRP (detection limit: 0.02 mg/dL) [31]. According to hsCRP level, the risk of developing cardiovascular complications (myocardial infarction and stroke) is determined: the risk is low, average, and high at an hsCRP level of <1, 1–3, and >3 mg/L, respectively. If the hsCRP level exceeds

10 mg/L, it is advisable to repeat the measurement, as well as to examine the patient to detect infectious and inflammatory diseases [32]. Moderately elevated concentrations of CRP, a classic acute phase protein, are associated with long-term risk of coronary heart disease in the general population. In contrast, the main acute phase response of CRP after myocardial infarction is associated with death and cardiac complications.

According to Ridker, to be more informative, the risk of cardiovascular diseases should be assessed using hsCRP in conjunction with the determination of low-density lipoprotein level and the atherogenic index [33]. The links between increased CRP and plaque inflammation, increased thrombosis, decreased nitric oxide synthesis, expression of adhesion molecules, altered complement functions, and inhibition of physiological fibrinolysis have been extensively studied [34].

In vitro studies have shown that CRP binds with low- and very low-density lipoproteins and thus activates the complement system. Macrophages stimulate tissue growth factor and hence coagulation. In addition, CRP stimulates the expression of adhesion molecules, intercellular adhesion molecules 1, vascular cell adhesion molecules 1, and E-selectin and increases infiltration by monocytes and lymphocytes [35]. Presumably, hsCRP activates inflammation of atheromatous plaques or leads to bleeding from them or their rupture [36].

The TACTICS-TIMI study included 18 cohorts of 1635 patients with ST-segment elevation acute coronary syndrome after adjusting known clinical predictors. This study indicated the predictive value of increased CRP and natriuretic peptide levels in combination with troponin I in achieving the combined endpoint (death, myocardial infarction, and CHF). In addition, the combination of these biomarkers had an additional prognostic value: in patients with one, two, and three elevated biomarkers, the risk of death, myocardial infarction, or the development of CHF increased 2.1 times, 3.1 times, and 3.7 times, respectively [37].

Signs of chronic systemic inflammation, determined by elevated serum CRP levels, have been observed in patients with heart failure [38, 39]. In these patients, regardless of CHF etiology, a higher level of hsCRP is determined relative to patients without heart failure. The concentration of hsCRP was comparable in patients with CHF of ischemic and non-ischemic etiologies [40]. Comparison of laboratory parameters of patients with CHF with reduced EF showed that patients of the III-IV functional class (according to the classification of the New York Heart Association) had higher hsCRP values than those of the I-II functional class (15.5 [0.89–82] and 2.6 [0.33–25] mg/L, respectively) [41].

The relationship between CRP levels and left ventricular (LV) myocardial function was studied in a crossover study of 98 patients directed to cardiac catheterization. CRP level increased to a greater extent in patients with diabetes mellitus and heart failure. Elevated CRP levels were associated with increased plasma levels of natriuretic peptide, decreased LVEF, and increased LV end-diastolic pressure. After multivariate adjustment, LV end-diastolic pressure and CRP were independently related [42].

Andryukhin (2010) noted increased CRP level in 70% of patients with CHF and preserved LVEF, including 33% patients with high cardiac risk (in terms of CRP). The body mass index was higher at high risk than at low and medium risk. A correlation was found between body mass index and CRP concentration in patients with CHF with preserved LVEF. An increase in CRP in CHF was accompanied by a decrease in exercise tolerance, as determined by the 6-min walk test [43].

Tromp (2017) et al. showed that patients with CHF and preserved LVEF had a higher hsCRP level than those with decreased LVEF. When adjusted for clinical parameters (e.g., age, sex, estimated glomerular filtration rate, systolic blood pressure, previous myocardial infarction, diabetes mellitus, atrial fibrillation, and anemia), a higher hsCRP level was associated with preserved LVEF [44].

Sánchez-Lázaro et al. examined 546 patients with heart failure and reduced LV systolic function (LVEF < 45%) in the outpatient register. Overall, 69% of patients with CHF and LVEF of <45% had an increased CRP level, including 37% patients with high cardiovascular risk [45].

The prognostic value of increased CRP level has been demonstrated in an increased number of hospitalizations among patients with CHF. Patients who were hospitalized more than twice had higher hsCRP levels than those with fewer hospitalizations. There was a significant correlation between the number of hospitalizations of patients with CHF and the hsCPB level. Multiple regression analysis showed that hsCPP, NT-pro-natriuretic peptide, and hemoglobin levels were the independent predictors of readmission [41].

An increase in serum hsCRP is recognized as an independent predictor of prognosis in patients with CHF. In a study by Yin, patient outcomes were analyzed considering hsCRP level and LVEF. Patients with hsCRP >2.97 mg/L were associated with poorer outcomes than patients with hsCRP <2.97 mg/L. Poor prognosis in patients with hsCRP <2.97 mg/L and LVEF <35% was not rela-

ted to poor clinical outcome. Patients with hsCRP >2.97 mg/L and LVEF <35% were statistically significantly more likely to have a poorer prognosis than patients with hsCRP >2.97 mg/L and LVEF >35%. Multivariate analysis showed that LVEF and serum hsCRP levels were independent markers of outcomes in patients with CHF. hsCRP level is minimally correlated with LVEF [40].

Four prospective cohorts (Framingham Heart Study, Cardiovascular Health Study, Prevention of Renal and Vascular End-stage Disease, and Multi-Ethnic Study of Atherosclerosis) were analyzed to search for associations of heart failure markers by including 22,756 patients aged 60 years, with a median follow-up of 12 years. Heart failure with preserved LVEF was detected in 633 participants and with reduced LVEF in 841 patients. In models adjusted for clinical risk factors, hsCRP level was more closely associated with the development of CHF with decreased LVEF compared with the development of CHF with preserved LVEF [46].

Further studies on CRP have shown that lifestyle changes or taking certain medications can alter hsCRP levels [27]. For example, statins, fibrates, nonsteroidal anti-inflammatory drugs, glucocorticoids, and even some antidepressants reduce hsCRP levels. Prescribing carvedilol to patients with decreased LVEF who had not previously received β-blockers for 12 months led to a reduction in the number of inflammatory biomarkers [47]. Joynt (2004) analyzed 96 outpatients with heart failure and showed that β-blockers reduced blood CRP level by 37.5% [48].

The CARE study found that the clinical benefit of statins in terms of reducing cardiac events was higher among patients with elevated CRP levels. In addition, statin therapy independently reduced the concentration of CRP and, to a large extent, low-density lipoproteins [49, 50]. All statins have been shown to be effective for reducing CRP and low-density lipoprotein levels, but rosuvastatin was found to be more effective [51–55].

Patients with regression of the inflammatory response have a better prognosis. This supports the hypothesis that inflammation, like neurohormonal activation, is an attempt in response to stress to restore homeostasis, but prolonged and unbalanced activation will ultimately have deleterious effects on the cardiovascular system. Lourenço et al. (2019) observed 439 patients, of which 69.2% had heart failure with reduced LVEF (mean CRP = 12.4 mg/L). During the observation period, 247 (56.3%) patients died: 73 (54.1%) with preserved LVEF and 174 (57.2%) with reduced LVEF. The authors showed that patients with decreased hsCRP of at least 40% had a 3-year mortality rate of 0.71. Assessment of the prognosis by LVEF value was reproduced in patients with preserved LVEF and did not show statistically differences in patients with reduced LVEF. After adjusting for clinical covariates (e.g., age, sex, estimated glomerular filtration rate, systolic blood pressure, previous myocardial infarction, diabetes mellitus, atrial fibrillation, and anemia), higher hsCRP levels remained associated with preserved LVEF [56, 57].

Thus, the proinflammatory state contributes to the development and progression of heart failure not only by impairing myocardial function but also by affecting other organs and tissues, thereby adding cachexia and anemia to other aspects of CHF [58]. Patients with CHF have elevated CRP levels, and cardiac decompensation tends to further increase this level. An increase in hsCRP level in patients with CHF is associated with an increase in cardiovascular risk. Knowledge of this contributes to the optimization of therapeutic approaches to reduce it [59].

Author contribution. E.V.Kh. — collection and analysis of literature data and writing the article, O.V.B. — analysis of literature data and editing of the article.
Funding. The study had no external funding.
Conflict of interest. The authors declare no conflict of interest.

REFERENCES

1. Vasuk U.A., Dudarenko O.P., Uschuk E.N., Schkolnik E.L., Serova M.K. “Cytokine” model of pathogenesis of chronic heart failure and the opportunities of new therapeutic strategy in decompensated patients. *Rational pharmacotherapy in cardiology.* 2006; 2 (4): 63–70. (In Russ.) DOI: 10.20996/1819-6446-2006-2-4-63-70.

2. Simbirtsev A.S. Cytokines in the pathogenesis of infectious and non-infectious diseases in humans. *Medical academic journal.* 2013; (3): 18–41. (In Russ.) DOI: 10.17816/MAJ13318-41.

3. Munro J.M., Cotran R.S. The pathogenesis of atherosclerosis: Atherogenesis and inflammation. *Lab. Invest.* 1988; 58: 249–261. PMID: 3279259.

4. Beloborodova N.V., Galina D.Kh., Buslenko N.S. Current knowledge about the role of infection in genesis of atherosclerosis. *Terapevticheskiy arkhiv.* 2006; (10): 85–89. (In Russ.)

5. Titov V.N. Commonality of atherosclerosis and inflammation: specificity of atherosclerosis as an inflammatory process. *Rossiyskiy kardiologicheskiy zhurnal.* 2000; 5 (5): 48–56. (In Russ.)

6. Moskalev A.V., Sboychakov V.B., Tsygan V.N., Apchel A.V. Chemokines’ role in immunopathogenesis of atherosclerosis. *Bull. Russian Military Med. Acad.* 2018; 20 (1): 195–202. DOI: 10.17816/brmma12310.

7. Becker A.E., de Boer O.J., van Der Wal A.C. The role of inflammation and infection in coronary artery disease. *Annu Rev. Med.* 2001; 52: 289–297. DOI: 10.1146/annurev.med.52.1.289.

8. Sukmanova I.A., Yakhontov D.A., Pospelova T.I., Kuzinskaya O.S., Kosoukhov A.P. Clinical picture, mor-

phofunctional parameters and endothelial function in patients with systolic CHF of different age groups. *Tsitokiny i vospaleniye*. 2010; (9): 30–34. (In Russ.)]

9. Van Linthout S., Tschöpe C. Inflammation — cause or consequence of heart failure or both? *Curr. Heart Fail. Rep*. 2017; 14: 251–265. DOI: 10.1007/s11897-017-0337-9.

10. Buckley L.F., Abbate A. Interleukin-1 blockade in cardiovascular diseases: a clinical update. *Eur. Heart J.* 2018; 39: 2063–2069. DOI: 10.1093/eurheartj/ehy128.

11. Buckley L.F., Abbate A. Interleukin-1 blockade in cardiovascular diseases: from bench to bedside. *BioDrugs.* 2018; 32: 111–118. DOI: 10.1007/s40259-018-0274-5.

12. Conraads V.M., Bosmans J.M., Vrints C.J. Chronic heart failure: an example of a systemic chronic inflammatory disease resulting in cachexia. *Int. J. Cardiol*. 2002; 85 (1): 33–49. DOI: 10.1016/s0167-5273(02)00232-2.

13. Francis G.S. Pathophysiology of chronic heart failure. *Am. J. Med.* 2001; 110 (7A): 37S–46S. DOI: 10.1016/s0002-9343(98)00385-4.

14. Vanderheyden M., Kersschot E., Paulus W.J. Proinflammatory cytokines and endothelium-dependent vasodilation in the forearm. Serial assessment in patients with congestive heart failure. *Eur. Heart J.* 1998; 19 (5): 747–752. DOI: 10.1053/euhj.1997.0828.

15. Kapadia S.R., Oral H., Lee J., Nakano M., Taffet G.E., Mann D.L. Hemodynamic regulation of tumor necrosis factor-alpha gene and protein expression in adult feline myocardium. *Circ. Res.* 1997; 81 (2): 187–195. DOI: 10.1161/01.res.81.2.187.

16. Ridker P.M. C-Reactive protein: Eighty eighty years from discovery to emergence as a major risk marker for cardiovascular disease. *Clin. Chem*. 2009; 55: 209–215. DOI: 10.1373/clinchem.2008.119214.

17. Paleev F.N., Abudeeva I.S., Moskalets O.V., Minchenko B.I., Belokopytova I.S. Nonspecific markers of inflammation in prognostication of the course of ischemic heart disease. *Kardiologiya*. 2009; (9): 59–65. (In Russ.)

18. Casas J.P., Shah T., Hingorani A.D., Danesh J., Pepys M.B. C-reactive protein and coronary heart disease: A critical review. *J. Intern. Med.* 2008; 264 (4): 295–314. DOI: 10.1111/j.1365-2796.2008.02015.

19. Kuller L.H., Tracy R.P., Shaten J., Meilahn E.N. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. *Am J. Epidemiol.* 1996; 144 (6): 537–547. DOI: 10.1093/oxfordjournals.aje.a008963.

20. Koenig W., Sund M., Fröhlich M., Fischer H.G., Löwel H., Döring A., Hutchinson W.L., Pepys M.B. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation*. 1999; 99 (2): 237–242. DOI: 10.1161/01.cir.99.2.237.

21. Ledue T.B., Rifai N. Preanalytic and analytic sources of variations in C-reactive protein measurement: implications for cardiovascular disease risk assessment. *Clin. Chem.* 2003; 49: 1258–1271. DOI: 10.1373/49.8.1258.

22. Roberts W.L., Moulton L., Law T.C., Farrow G., Cooper-Anderson M., Savory J., Rifai N. Evaluation of nine automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. Part 2. *Clin. Chem*. 2001; 47: 418–425. DOI: 10.1093/clinchem/47.3.418.

23. Ledue T.B., Rifai N. High sensitivity immunoassays for C-reactive protein: promises and pitfalls. *Clin. Chem. Lab. Med.* 2001; 39: 1171–1176. DOI: 10.1515/CCLM.2001.185.

24. Ockene I.S., Matthews C.E., Rifai N., Ridker P.M., Reed G., Stanek E. Variability and classification accuracy of serial high-sensitivity C-reactive protein measurements in healthy adults. *Clin. Chem.* 2001; 47: 444–450. DOI: 10.1093/clinchem/47.3.444.

25. Ridker P.M., Buring J.E., Rifai N., Cook N.R. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA.* 2007; 297: 611–619. DOI: 10.1001/jama.297.6.611.

26. Ridker P.M., Paynter N.P., Rifai N., Gaziano J.M., Cook N.R. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for Men. *Circulation*. 2008; 118: 2243–2251. DOI: 10.1161/CIRCULATIONAHA.108.814251.

27. Adukauskienė D., Čiginskienė A., Adukauskaitė A., Pentiokinienė D., Šlapikas R., Čeponienė I. Clinical relevance of high sensitivity C-reactive protein in cardiology. *Medicina (Kaunas).* 2016; 52 (1): 1–10. DOI: 10.1016/j.medici.2015.12.001.

28. Salazar J., Martínez M.S., Chávez-Castillo M., Núñez V., Añez R., Torres Y., Toledo A., Chacín M., Silva C., Pacheco E., Rojas J., Bermúdez V. C-reactive protein: An in-depth look into structure, function, and regulation. *Int. Sch. Res. Notices*. 2014; 2014: 653045. DOI: 10.1155/2014/653045.

29. Blinova T.V., Rakhmanov R.S., Strakhova L.A., Kolesov S.A. To the issue of predictive significance of C-reactive protein. *Medical almanac.* 2016; (2): 39–43. (In Russ.)

30. Verma S., Wang C.H., Lonn E., Charbonneau F., Buithieu J., Title L.M., Fung M., Edworthy S., Robertson A.C., Anderson T.J.; FATE Investigators. Cross-sectional evaluation of brachial artery flow-mediated vasodilation and C-reactive protein in healthy individuals. *Eur. Heart J.* 2004; 25 (19): 1754–1760. DOI: 10.1016/j.ehj.2004.06.039.

31. Tanveer S., Banu S., Jabir N.R., Khan M.S., Ashraf G.M., Manjunath N.C, Tabrez S. Clinical and angiographic correlation of high-sensitivity C-reactive protein with acute *ST* elevation myocardial infarction. *Exp. Ther. Med*. 2016; 12 (6): 4089–4098. DOI: 10.3892/etm.2016.3882.

32. Fomin V.V., Kozlovskaya L.V. C-reactive protein and its importance in cardiological practice. *Zhurn. dokaz. med. dlya praktikuyushchikh vrachey.* 2003; 5: 70–75. (In Russ.)

33. Ridker P.M. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation.* 2001; 103 (13): 1813–1818. DOI: 10.1161/01.cir.103.13.1813.

34. Schiele F., Meneveau N., Seronde M.F., Chopard R., Descotes-Genon V., Dutheil J., Bassand J.P.; Reseau de Cardiologie de Franche Comte. C-reactive protein improves risk prediction in patients with acute coronary syndromes. *Eur. Heart J.* 2010; 31 (3): 290–297. DOI: 10.1093/eurheartj/ehp273.

35. Fichtlscherer S., Rosenberger G., Walter D.H., Breuer S., Dimmeler S., Zeiher A.M. Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. *Circulation.* 2000; 102: 1000–1006. DOI: 10.1161/01.cir.102.9.1000.

36. Kazemi-Saleh D., Koosha P., Sadeghi M., Sarrafzadegan N., Karbasi-Afshar R., Boshtam M., Oveis-Gharan S. Predictive role of adiponectin and high-sensitivity C-reactive protein for prediction of cardiovascular event in an Iranian cohort study: The Isfahan Cohort Study. *ARYA Atheroscler.* 2016; 12 (3): 132–137. PMID: 27752270.

37. Sabatine M.S., Morrow D.A., de Lemos J.A., Gibson C.M., Murphy S.A., Rifai N., McCabe C., Antman E.M., Cannon C.P., Braunwald E. Multimarker approach to risk stratification in non-*ST* elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. *Circulation*. 2002; 105 (15): 1760–1763. DOI: 10.1161/01.cir.0000015464.18023.0a.

38. Van Tassell B.W., Abouzaki N.A., Oddi Erdle C., Carbone S., Trankle C.R., Melchior R.D., Turlington J.S., Thurber C.J., Christopher S., Dixon D.L., Fronk D.T., Thomas C.S., Rose S.W., Buckley L.F., Dinarello C.A., Biondi-Zoccai G., Abbate A. Interleukin-1 blockade in acute decompensated heart failure: A randomized, double-blinded, placebo-controlled pilot study. *J. Cardiovasc. Pharmacol*. 2016; 67 (6): 544–551. DOI: 10.1097/FJC.0000000000000378.

39. Yndestad A., Damås J.K., Oie E., Ueland T., Gullestad L., Aukrust P. Systemic inflammation in heart failure — the whys and wherefores. *Heart Fail. Rev.* 2006; 11: 83–92. DOI: 10.1007/s10741-006-9196-2.

40. Yin W.H., Chen J.W., Jen H.L., Chiang M.C., Huang W.P., Feng A.N., Young M.S., Lin S.J. Independent prognostic value of elevated high-sensitivity C-reactive protein in chronic heart failure. *Am. Heart J.* 2004; 147 (5): 931–938. DOI: 10.1016/j.ahj.2003.11.021.

41. Örsçelik Ö., Özkan B., Arslan A., Şahin E.E., Sakarya O., Sürmeli O.A., Balcı Fidancı Ş., Çelik A., Çimen B.Y., Özcan İ.T. Relationship between intrarenal renin-angiotensin activity and re-hospitalization in patients with heart failure with reduced ejection fraction. *Anatol. J. Cardiol.* 2018; 19 (3): 205–212. DOI: 10.14744/AnatolJCardiol.2018.68726.

42. Shah S.J., Marcus G.M., Gerber I.L., McKeown B.H., Vessey J.C., Jordan M.V., Huddleston M., Foster E., Chatterjee K., Michaels A.D. High-sensitivity C-reactive protein and parameters of left ventricular dysfunction. *J. Card. Fail*. 2006; 12 (1): 61–65. DOI: 10.1016/j.cardfail.2005.08.003.

43. Andryukhin A.N., Frolova E.V. Systemic inflammation in heart failure with preserved systolic function. *Ural Medical Journal*. 2010; (7): 27–33. (In Russ.)

44. Tromp J., Khan M.A., Klip I.T., Meyer S., de Boer R.A., Jaarsma T., Hillege H., van Veldhuisen D.J., van der Meer P., Voors A.A. Biomarker profiles in heart failure patients with preserved and reduced ejection fraction. *J. Am. Heart Assoc*. 2017; 6 (4): e003989. DOI: 10.1161/JAHA.116.003989.

45. Sánchez-Lázaro I.J., Almenar L., Reganon E., Vila V., Martínez-Dolz L., Martínez-Sales V., Moro J., Agüero J., Ortiz-Martínez V., Salvador A. Inflammatory markers in stable heart failure and their relationship with functional class. *Int. J. Cardiol*. 2008; 129 (3): 388–393. DOI: 10.1016/j.ijcard.2007.07.138.

46. De Boer R.A., Nayor M., de Filippi C.R., Enserro D., Bhambhani V., Kizer J.R., Blaha M.J., Brouwers F.P., Cushman M., Lima J.A.C., Bahrami H., van der Harst P., Wang T.J., Gansevoort R.T., Fox C.S., Gaggin H.K., Kop W.J., Liu K., Vasan R.S., Psaty B.M., Lee D.S., Hillege H.L., Bartz T.M., Benjamin E.J., Chan C., Allison M., Gardin J.M., Januzzi J.L.Jr., Shah S.J., Levy D., Herrington D.M., Larson M.G., van Gilst W.H., Gottdiener J.S., Bertoni A.G., Ho J.E. Association of cardiovascular biomarkers with incident heart failure with preserved and reduced ejection fraction. *JAMA Cardiol*. 2018; 3 (3): 215–224. DOI: 10.1001/jamacardio.2017.4987.

47. Nessler J., Nessler B., Golebiowska-Wiatrak R., Palka I., Gackowski A., Kitlinski M., Melander O., Fedorowski A. Serum biomarkers and clinical outcomes in heart failure patients treated de novo with carvedilol. *Cardiol. J.* 2013; 20 (2): 144–151. DOI: 10.5603/CJ.2013.0027.

48. Joynt K.E., Gattis W.A., Hasselblad V., Fuzaylov S.Y., Serebruany V.L., Gurbel P.A., Gaulden L.H., Felker G.M., Whellan D.J., O'Connor C.M. Effect of angiotensin-converting enzyme inhibitors, beta blockers, statins, and aspirin on C-reactive protein levels in outpatients with heart failure. *Am. J. Cardiol*. 2004; 93 (6): 783–785. DOI: 10.1016/j.amjcard.2003.12.010.

49. Ridker P.M., Rifai N., Pfeffer M.A., Sacks F.M., Moye L.A., Goldman S., Flaker G.C., Braunwald E. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation.* 1998; 98 (9): 839–844. DOI: 10.1161/01.cir.98.9.839.

50. Ridker P.M., Rifai N., Pfeffer M.A., Sacks F., Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. *Circulation.* 1999; 100 (3): 230–235. DOI: 10.1161/01.cir.100.3.230.

51. Ridker P.M., Rifai N., Lowenthal S.P. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. *Circulation.* 2001; 103 (9): 1191–1193. DOI: 10.1161/01.cir.103.9.1191.

52. Albert M.A., Danielson E., Rifai N., Ridker P.M.; PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA.* 2001; 286 (1): 64–70. DOI: 10.1001/jama.286.1.64.

53. Jialal I., Stein D., Balis D., Grundy S.M., Adams-Huet B., Devaraj S. Effect of hydroxymethyl glutaryl coenzyme a reductase inhibitor therapy on high sensitive C-reactive protein levels. *Circulation.* 2001; 103 (15): 1933–1935. DOI: 10.1161/01.cir.103.15.1933.

54. Balk E.M., Lau J., Goudas L.C., Jordan H.S., Kupelnick B., Kim L.U., Karas R.H. Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review. *Ann. Intern. Med.* 2003; 139 (8): 670–682. DOI: 10.7326/0003-4819-139-8-200310210-00011.

55. Plenge J.K., Hernandez T.L., Weil K.M., Poirier P., Grunwald G.K., Marcovina S.M., Eckel R.H. Simvastatin lowers C-reactive protein within 14 days: an effect independent of low-density lipoprotein cholesterol reduction. *Circulation.* 2002; 106 (12): 1447–1452. DOI: 10.1161/01.cir.0000029743.68247.31.

56. Lourenço P., Pereira J., Ribeiro A., Ferreira-Coimbra J., Barroso I., Guimarães J.T., Leite-Moreira A., Bettencourt P. C-reactive protein decrease associates with mortality reduction only in heart failure with preserved ejection fraction. *J. Cardiovasc. Med. (Hagerstown*). 2019; 20 (1): 23–29. DOI: 10.2459/JCM.0000000000000726.

57. Hedayat M., Mahmoudi M.J., Rose N.R., Rezaei N. Proinflammatory cytokines in heart failure: double-edged swords. *Heart Fail. Rev*. 2010; 15 (6): 543–62. DOI: 10.1007/s10741-010-9168-4.

58. Yndestad A., Damås J.K., Oie E., Ueland T., Gullestad L., Aukrust P. Systemic inflammation in heart failure — the whys and wherefores. *Heart Fail. Rev.* 2006; 11 (1): 83–92. DOI: 10.1007/s10741-006-9196-2.

59. Prasad K. C-reactive protein (CRP)-lowering agents. *Cardiovasc. Drug Rev*. 2006; 24 (1): 33–50. DOI: 10.1111/j.1527-3466.2006.00033.x.