BIOMARKERS OF ACUTE MYOCARDIAL INFARCTION: DIAGNOSTIC AND PROGNOSTIC VALUE. PART 2 (LITERATURE REVIEW)

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In the second part of the review, we continue the discussion of biomarkers that have a diagnostic and prognostic significance in acute myocardial infarction (AMI). The study of the AMI pathophysiology through the experimental and clinical research contributes to the discovery of new regulatory molecules and pathogenetic mechanisms underlying AMI. At the same time, many molecules involved in the pathogenesis of AMI can be used as effective biomarkers for the diagnosis and prediction of AMI. This article discusses in detail the diagnostic and prognostic value of inflammatory biomarkers of AMI (C-reactive protein, interleukin-6, tumor necrosis factor-alpha, myeloperoxidase, matrix metalloproteinases, soluble form of CD40 ligand, procalcitonin, placental growth factor) and a number of recently discovered new biomarkers of AMI (microribonucleic acids, galectin-3, stimulating growth factor expressed by gene 2, growth differentiation factor 15, proprotein convertase of subtilisin-kexin type 9).

Keywords: *laboratory diagnostics, acute myocardial infarction, AMI, biomarkers, C-reactive protein, interleukin-6, tumor necrosis factor-alpha, myeloperoxidase, matrix metalloproteinases, procalcitonin, microribonucleic acids, galectin-3, proprotein convertase subtilisin-Kexin type 9.*

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List of abbreviations

AHA — American Heart Association
CDC — Centers for Disease Control and Prevention
MACE — major adverse cardiovascular events
PGF — placental growth factor
PCSK9 — proprotein convertase of subtilisin-kexin type 9
TNF-α — tumor necrosis factor alpha
LDL — low density lipoprotein
MPO — myeloperoxidase
AMI — acute myocardial infarction
ACS — acute coronary syndrome
PCT — procalcitonin
CRP — C-reactive protein
CVD — cardiovascular disease

INTRODUCTION

The pathophysiological and pathomorphological mechanisms underlying acute myocardial infarction (AMI) are very diverse and include necrosis, apoptosis, inflammation, oxidative stress, neuroendocrine disorders, fibrosis, myocardial remodeling, etc. [1]. Many regulatory molecules involved in these processes are considered by researchers as promising biomarkers and targets for therapeutic action. There is a close relationship between the individual mechanisms in AMI. So, for example, the lack of oxygen and nutrient (energy) substrates due to the occlusion of the coronary vessels leads to necrosis of the cardiac muscle tissue, after which an inflammatory reaction is triggered. In the first hours after the onset of ischemia and necrosis of cardiomyocytes, neutrophils (polymorphonuclear granulocytes) are attracted to the inflammation focus, which generate a large amount of reactive oxygen species and enzymes (myeloperoxidase, proteases) that cause local damage to tissues and blood vessels, thereby aggravating the course of AMI. Subsequently, the area of damage to the heart muscle is infiltrated by macrophages, which destroy the destroyed remnants of the heart muscle tissue and activate the reparative pathways necessary for scar formation (fibrosis) [2, 3]. Given the important role of inflammation in the pathogenesis of AMI, many participants in inflammatory processes can be used as biomarkers. The diagnostic value of inflammatory biomarkers in AMI is usually low, since it has low specificity; moreover, these agents

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increase in all inflammatory processes not associated with AMI. However, the activity of the inflammatory process in AMI, determined by the level/degree of increase in the main inflammatory biomarkers (C-reactive protein, interleukin-6 and some others) in the blood serum, has a high prognostic value, often determining the further prognosis of patients [2–4].

In accordance with the previously designated classification, the main biomarkers used for laboratory diagnosis and prognosis of AMI can be conditionally subdivided into 4 groups. The diagnostic and prognostic value of the first two groups of cardiomarkers is described in the first part of the review [5].

The main inflammatory biomarkers of AMI include C-reactive protein, interleukin-6, tumor necrosis factor alpha, myeloperoxidase, matrix metalloproteinases, soluble form of CD40 ligand, procalcitonin, placental growth factor. In addition, in the process of studying the pathophysiology of AMI using experimental and clinical studies, new pathogenetic mechanisms and new regulatory compounds were discovered, in particular galectin-3, microribonucleic acids, proprotein convertase of subtilisin-kexin type 9, which can be distinguished into a separate group of AMI biomarkers [5]. These molecules may also be of interest as agents for improving laboratory diagnosis and prognosis of AMI and are currently being actively studied.

MAIN LABORATORY BIOMARKERS OF ACUTE MYOCARDIAL INFARCTION

III. Inflammatory biomarkers of AMI0

C-reactive protein, CRP

Due to the fact that inflammation plays an important role in the pathogenesis of atherothrombosis and AMI, the main participants in inflammatory processes can be considered as biomarkers and targets for therapeutic action. C-reactive protein (CRP) is a biomarker of the acute phase inflammatory response produced by hepatocytes when stimulated by inflammatory cytokines, primarily interleukin-6 (IL6). It has been shown that IL6 and CRP are associated with an increased risk of developing cardiovascular diseases (CVD) in patients with established atherosclerosis [6, 7]. Several studies have reported that elevated CRP levels are an independent predictive marker for recurrent nonfatal AMI or cardiac death. The CRP level also reflects the degree of myocardial damage in AMI [7, 8]. Researchers J. Wang et al. [9] found that the serum CRP level was increased in patients with AMI compared with control patients (20.96 ± 1.64 versus 0.00 ng/ml, p <0.001), which suggests that circulating CRP is a potential diagnostic biomarker. In addition, in patients who died from AMI, the concentration of CRP was significantly higher than in survivors (36.70 ± 10.26 versus 19.41 ± 1.43 ng/ml, p = 0.002), which indicates a high predictive value of this biomarker [9]. Nevertheless, despite a number of consistent data on an increase in CRP in AMI, an increase in this marker is observed in many inflammatory processes; therefore, it does not have sufficient specificity and sensitivity to be used as the only reliable diagnostic marker of AMI [10, 11].

It should be noted that the methods for determining CRP were improved towards increased sensitivity, which increased its clinical and diagnostic value. For comparison, traditional moderately sensitive immunoassays could detect CRP in the range from 5 to 20 mg/L, while highly sensitive detection methods detect even small levels of CRP in blood plasma (0.5–1 mg/L). The Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) recommend the use of high-sensitivity CRP as a biomarker for detecting CVD risk, including in patients with acute coronary syndrome (ACS) or stable coronary disease [12]. It is necessary to adhere to the following CRP ranges to predict the risk of CVD: <1.0 mg/L — low risk, 1.0–3.0 mg/L — medium risk,> 3.0 mg/L — high risk in the future. A number of studies have demonstrated the effectiveness of the designated ranges for assessing the risk of major adverse cardiovascular events (MACE). Thus, A. Lukin et al. [8] found that even a moderately elevated level of CRP (from 1 to 3 mg/L) in blood plasma predicts adverse cardiac events in patients with ACS during a 2-year follow-up period. A large meta-analysis also confirms that a higher CRP level (≥ 3 mg/L) is associated with an increased long-term risk of recurrent cardiovascular events or death in AMI patients [13]. The concentration of highly sensitive CRP in the blood serum is a sensitive indicator of inflammation, which is closely associated with the formation of atherosclerotic plaques and is an independent prognostic marker in patients with ACS. That is why the values of highly sensitive CRP were recommended to be used for making decisions on the choice of treatment tactics for patients — using an early invasive strategy, antithrombotic therapy [14, 15]. At the same time, several other studies have shown that an increase in CRP is not associated with the occurrence of AMI, and that only the concentration of cardiac troponins, but not CRP, is informative for identifying patients with AMI for whom an invasive strategy or antithrombotic treatment is indicated [16, 17].

Interleukin-6, IL6

IL6, one of the major pro-inflammatory markers, is involved in the activation and recruitment of inflammatory cells and stimulates the liver to produce acute phase proteins such as CRP. In addition, IL6 has a negative inotropic effect directly or indirectly through nitric oxide synthase (NOS). X. Wang et al. [18] found that IL6 has a high predictive value in patients with ACS. According to the results of the study, serum IL6 concentrations in patients with AMI (32.50 ± 9.32 pg/ml) and unstable angina pectoris (24.41 ± 8.68 pg/ml) were significantly higher than in patients with stable angina pectoris (10 , 70 ± 8.10) and in healthy patients (8.15 ± 6.39). The CRP concentration showed a trend similar to IL6 in these patient groups. IL6 levels closely correlated with CRP (r = 0.836) in ACS patients. Given the pathophysiological role of IL6 in CVD, the researchers concluded that serum IL6 levels can be used to determine the stability of atherosclerotic plaque, which is important for assessing the prognosis of patients with ACS [18, 19].

Another study examined the predictive value of inflammatory cytokines, including IL6, IL18, in serum and urine in ACS patients. It was found that the mean IL6 values in serum were significantly increased in the deceased (median 10.3 [2.3–19.4] pg/ml) compared with the surviving patients (median 1.52 [0.55–5.3] pg/ml), p = 0.007. Multivariate Cox regression analysis showed that only serum IL6 is an independent risk factor for mortality in patients with ACS (hazard ratio 61.7; 95% confidence interval, CI, 2.1–1851.0; p = 0.018) [14]. According to a prospective study, the deceased patients had a higher IL6 level (8.58 [5.13–20.95] ng/L) compared with the surviving patients (6.12 [4.16–9.14] ng/L, p = 0.043). At the same time, even in troponin-negative patients with elevated IL6 levels, a high risk of adverse events also remained. According to multivariate analysis, only elevated IL6 levels (> 12.40 ng/L) were an independent predictor of adverse outcomes (hazard ratio 3.62; 95% CI 1.69–7.75; p = 0.001) [20].

Thus, the serum IL6 concentration can be used to predict the risk of death in patients with ACS and to identify those patients who will benefit from targeted interventional or intensive therapy.

Tumor necrosis factor alpha, TNF-α

TNF-α is an important inflammatory factor with a wide range of biological effects, including participation in inflammatory reactions, myocardial repair, regulation of apoptosis of cardiac muscle cells, and other processes [21]. Experimental studies have shown that TNF-α is involved in the regulation of cardiomyocyte apoptosis, mediates ventricular remodeling, and has a significant effect on the morphofunctional features of the heart [21–23]. TNF-α is actively produced in several tissues, including endothelial cells, smooth muscle cells, and macrophages. By analogy with IL6, TNF-α has the ability to reduce cardiac contractility, either directly or by inducing NOS. Despite the insignificant diagnostic value in AMI due to low specificity, elevated TNF-α levels in patients with ACS have a high prognostic value. Thus, the study showed that when the level of TNF-α> 9 pg/ml, measured in the first 24 hours in patients with ACS, the risk of MACE significantly increases in the long term (relative risk 5.0; p = 0.02) [24]. Another study also reported that inflammatory cytokines, including TNF-α and CRP, can predict 6-month survival in ACS admitted patients [25].

Procalcitonin, PCT

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin, which is involved in calcium homeostasis. The main conditions causing an increase in serum procalcitonin are severe bacterial infections, sepsis, major surgery and burns, multiple trauma, cardiogenic shock, and cardiac surgery. N. Kafkas et al. [26] found an increase in serum PCT in all patients with AMI. The average PCT concentration in AMI patients on admission was 1.3 ng/ml (95% CI 0.89–1.80), and after 24 hours it increased to 3.57 ng/ml (95% CI 2.89–4.55). By the seventh day, the PCT values fell to the reference level (<0.5 ng/ml). Thus, the kinetics of PCT values in AMI was similar to the kinetics of the concentration of creatine phosphokinase-MB (CPK-MB) and cardiac troponin I. PCT concentrations positively correlated with the levels of IL6 (r = 0.59; p = 0.001) and CRP (r = 0.65 ; p = 0.001). Based on the results obtained, the researchers consider PCT as a sensitive indicator of myocardial damage. The mechanism of PCT increase is probably due to the development of the inflammatory process in AMI [26].

At the same time, according to other researchers, the diagnostic value of PCT in AMI is much less significant than that of CPK-MB and cardiac troponin I [27–29]. So, according to T. Buratti et al. [27], PCT concentration does not increase in serum in patients with uncomplicated AMI. Researchers M. Remskar et al. Also came to a similar conclusion. [28]. In their study, an increase in PCT was observed only in those patients with AMI who developed severe left ventricular heart failure; cardiac arrest occurred, and resuscitation was required, as well as if patients had concomitant

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bacterial infections. D. Kelly et al. [29] studied the relationship between PCT and MACE, left ventricular function and left ventricular remodeling in patients with AMI (n = 977). According to univariate and multivariate analyzes, PCT was associated with MACE, left ventricular dysfunction, and remodeling after AMI. According to another randomized controlled trial, higher PCT levels within 48 hours after hospitalization for AMI may reflect an inflammatory condition associated with increased early and six-month mortality [30].

Myeloperoxidase, MPO

Myeloperoxidase (MPO) is a heme-containing enzyme concentrated in azurophilic granules of neutrophils and lysosomes of monocytes. MPO plays a decisive role in inflammatory processes and oxidative stress at the cellular level [31]. According to clinical studies, the diagnostic value of MPO is significantly less than that of a number of other biomarkers of AMI (cardiac troponins, CPK, cardiac fatty acid binding protein, copeptin, etc.) [32–34]. However, despite the rather low diagnostic value, elevated MPO levels can independently predict the future risk of coronary heart disease and myocardial infarction in both ACS patients and healthy people [35]. Thus, according to a clinical study, in patients with coronary artery disease (IHD), confirmed by angiography, the MPO level (median 74.5 [52.5-135.3] μg/L) is significantly higher than in the control group (61, 2 [44.6–80.9] μg/L). With the progression of IHD, the concentration of MPO in patients with ACS (129.5 [72.2–216.0] μg/L) significantly exceeded that in patients with stable IHD (99.2 [62.2–154.9] μg/L). In addition, it was shown that among patients with ACS, baseline MPO level is an independent predictor of adverse cardiac events [36].

Thus, MPO has predictive value and may be of interest as a marker for assessing the severity of coronary artery disease. M. Omran et al. [37] also found that the use of baseline levels of three biomarkers in combination (MPO, CPK-MB, and cardiac troponin I) can improve the accuracy of early diagnosis of AMI.

Matrix metalloproteinases, MMPs

Matrix metalloproteinases (MMPs) are a family of zinc-containing endoproteinases whose main function is to break down components of the extracellular matrix. MMPs play an important role in the development, physiology, and pathology of the cardiovascular system. Metalloproteinases also play a key role in unfavorable remodeling of the cardiovascular system, the formation of atherosclerotic plaques and their destabilization (increasing the likelihood of rupture), migration of vascular smooth muscle cells and restenosis, which leads to coronary artery disease, myocardial infarction and progressive heart failure. In addition, MMP functions can be regulated by pharmacological agents which opens up new possibilities for the treatment of CVD. Studying the functions of MMPs using animal modeling methods helped to establish the important role of MMPs in the pathogenesis of CVD in humans. The increased content of MMP-2 (685 ± 271 ng/ml) and MMP-9 (15 ± 21 ng/ml) in peripheral blood in ACS may be a useful test to identify the vulnerability of atherosclerotic plaques. Elevated levels of MMP-9 correlated with deterioration of left ventricular function (decreased left ventricular ejection fraction) in the long term [38, 39]. It has been shown that MMPs, in particular MMP-9, play an important role in collagen breakdown and structural changes associated with ventricular remodeling after AMI, and are valuable biomarkers of inflammation [40]. In addition, it is very interesting to study the levels of MMP in the oral fluid in coronary artery disease and myocardial infarction [41, 42], which may in the future become a valuable additional non-invasive diagnostic approach for patients with CVD [43].

Soluble form of ligand CD40 (CD40 ligand, CD40L)

Binding of the soluble form of the CD40 ligand (CD40L) to the CD40 protein stimulates inflammatory processes in the atherosclerotic plaque, including the release of pro-inflammatory cytokines and the expression of adhesion molecules, causing additional leukocytes to be attracted to the inflammation site, which implies an important role for CD40L in the development and progression of atherosclerosis. Patients with hypercholesterolemia, unstable angina, or AMI have elevated serum CD40L levels (> 1.5 ng/ml). Clinical data suggest that elevated soluble CD40L levels (> 1.5 ng/ml) are not only a risk factor for CVD, but also predict future adverse events, especially in patients with ACS [44, 45]. In a study by J. Yan et al. [46] the levels of soluble ligand CD40 were determined in 128 patients with ACS and 68 patients admitted with acute chest pain. Based on the analysis results, CD40L levels were increased (> 8.0 ng/ml) in 57.8% of patients with ACS and 35% of patients with acute chest pain. The concentration of soluble CD40 ligand was not significantly correlated with the measured levels of cardiac troponin T (r = 0.21; p <0.05), and increased levels of soluble CD40L (> 8.0 ng/ml) were associated with a higher risk of AMI, sudden death and repeated AMI afterwards.

Moreover, patients with elevated serum CD40L and cardiac troponin T levels had a significant risk of serious cardiovascular events (including AMI, sudden death, and relapse of angina pectoris) in two groups within 30 days and 6 months of follow-up [46]. Other clinical studies have also shown that elevated CD40L levels have a high predictive value and allow the identification of ACS patients with an increased risk of recurrent AMI and death independently of other prognostic biomarkers, including cardiac troponins and CRP [47, 48].

Thus, in patients with unstable coronary artery disease, an increase in the level of soluble CD40L in serum indicates an independent increased risk of MACE.

Placental growth factor, PGF

PGF is a member of the family of vascular endothelial growth factors, acts through the flt-1 receptor, promotes endothelial activation and the recruitment of macrophages to the focus of atherosclerotic lesions. Experimental data indicate that PGF causes destabilization of atherosclerotic plaque and thus may be useful as a biomarker for predicting risk in patients with ACS [49]. In their clinical study, C. Heeschen et al. [49] studied the predictive value of PGF in patients with acute chest pain. In ACS patients, elevated PGF levels (> 27.0 ng/L; 40.8% of patients) indicated a markedly increased risk of events after 30 days (14.8% versus 4.9%; hazard ratio 3.34; 95% CI 1.79-6.24; p <0.001). Plasma PGF levels may be an independent biomarker of poor outcome in patients with suspected ACS [49]. In another study, M. Marković et al. [50] also found that elevated PGF levels (> 13.2 ng/L) in hospitalized patients with ACS without ST-segment elevation increased the risk of death during a 30-day follow-up period.

A. Bui et al. [51] investigated the relationship of PGF with cardiovascular outcomes in a large cohort of patients (n = 3760) with ACS. PGF was measured at admission and after 4 months. Elevated baseline PGF levels (> 14.3 ng/L) were associated with a higher incidence of adverse outcomes over the 2-year follow-up period. The risk of death or myocardial infarction was also higher in patients with elevated baseline PGF levels. Even after adjusting for baseline characteristics and risk factors, elevated baseline PGF was independently associated with a poor prognosis in patients. Increased PGF concentration in patients at 4 months (> 14.3 ng/L) after ACS was also associated with a high risk of death. In addition, a higher PGF concentration after ACS is associated with a long-term risk of recurrent cardiovascular events independent of traditional risk factors. This association is present both at the beginning and after ACS and, apparently, is stronger after 4 months [51].

IV. Other new cardiac biomarkers

MicroRNA (miRNA)

MicroRNAs are single-stranded noncoding RNAs containing from 18 to 28 nucleotides [52]. They were first discovered in Caenorhabditis elegans in 1993 [53], and are currently the most studied subgroup of noncoding RNAs. In recent years, several cardiospecific microRNAs have been identified that play an important role in the development of CVD, including AMI, atrial fibrillation, and heart failure [52–55]. MicroRNAs play an essential role in the development of myocardial infarction, regulating apoptotic, necrotic, and autophagic cell death [55]. In the myocardium and blood plasma of a person with AMI, the following miRNAs are most often determined using the polymerase chain reaction method: miRNA-1, miRNA-21, miRNA-133, miRNA-134, miRNA-181, miRNA-208 and a number of others [55–64].

O. Gidlöf et al. [56] found increased levels of miRNA-208, miRNA-499, miRNA-1 in blood serum in patients with AMI. Elevated levels of these miRNAs also correlated with left ventricular ejection fraction and were associated with an increased risk of mortality or heart failure within 30 days [56]. In another study by Y. Devaux et al. [57] showed that the concentrations of miRNA-208, miRNA-499, and miRNA-320 were significantly increased in patients with AMI, but the diagnostic value of these miRNAs was less than that of cardiac troponin by T. J. Zhu et al. [58] studied the diagnostic value of microRNA-181 in patients with AMI. The levels of miRNA-181 significantly increased in AMI and correlated positively with the concentrations of CPK-MB and cardiac troponin I. The researchers also found a positive correlation between the levels of miRNA-181 with the severity coronary artery disease, quantified by the Gensini Score (r = 0.573; p <0.05), and a negative correlation with the left ventricular ejection fraction (r = -0.489; p <0,05). The data obtained indicate the high diagnostic value of microRNA-181 as a potential biomarker of AMI.

Y. Zhang et al. [59] reported a high diagnostic value of miRNA-92 in AMI. M. Oerlemans et al. [60] noted that a combination of three microRNAs (miRNA-1, miRNA-21, and miRNA-499) has a higher diagnostic value than high-sensitivity troponin T for early diagnosis of AMI. In addition to the diagnostic value, miRNAs can be more useful for risk stratification of patients with AMI, and therefore can be used as prognostic biomarkers [61]. Plasma circulating miRNA-197 and miRNA-223

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were identified as predictors of death from CVD in a large cohort of patients with coronary artery disease (*n* = 873) [62]. Several studies have also shown that increased levels of miRNA-134, miRNA-328, miRNA-34, and miRNA-208 were associated with the development of heart failure and an increased risk of death after AMI [63, 64].

Thus, the following microRNAs may have diagnostic and prognostic value in AMI: miRNA-1, -21, -34, -92, -133, -134, -181, -197, -208, -223, -320, -328 , -499. However, it should be noted that absolute cardiospecificity has not yet been proven for any of these microRNAs.

Growth stimulation expressed gene 2, ST2

The soluble form of stimulating growth factor expressed by gene 2 (ST2) is a member of the IL1 receptor family and is considered a promising biomarker of cardiovascular and inflammatory diseases [65, 66]. Identified in 1989, ST2 was originally considered an orphan receptor (orphan receptor) until the discovery of the ligand for ST2, IL33, in 2005. Its main effects include the activation of T-helper type 2 (Th2) and the production of Th2-associated cytokines.

ST2 also plays an important role in the pathogenesis of CVD, and therefore it is considered as a biomarker of the disease. It was found that in patients with heart failure and myocardial infarction, ST2 is closely associated with both the severity of the disease and mortality. ST2 expression noticeably increases as early as 1 h after mechanical stress in an experimental in vitro study on cultured cardiac myocytes and in patients with AMI [67, 68].

ST2 is considered a biomarker of stress and myocardial fibrosis, which has been shown to be significantly elevated in AMI and acute heart failure causing myocardial overload [69]. Studies have also reported an elevated ST2 level in patients with ACS, however, due to the lack of specificity in these states, ST2 cannot be a reliable diagnostic marker.

Studies have also shown that ST2 can predict mortality and heart failure in patients with ACS, which makes ST2 a valuable prognostic biomarker for AMI [70, 71].

Growth differentiation factor-15, GDF-15

GDF-15 is a member of the transforming growth factor beta (TGF-β)/bone morphogenetic protein (BMP) superfamily. Based on the data obtained that GDF-15 inhibits TNF-α production in macrophages stimulated by lipopolysaccharides, it was also named macrophage inhibitory cytokine-1 (MIC-1) [72]. Circulating GDF-15 levels are elevated in patients admitted to hospital with ACS. Moreover, people with elevated GDF-15 levels (> 1800 ng/L) had a high risk of death within one year [73]. In accordance with data from a clinical study, it was shown that a higher level of GDF-15 is associated with a predominant calcium content in the coronary artery and mortality from CVD. People with a GDF-15 concentration ≥ 1800 ng/L had an increased risk of all-cause death and CVD compared with those with a GDF-15 concentration <1200 ng/L. Increases in GDF-15 concentration have been associated with age, diabetes, impaired renal function, and a marker of inflammation (CRP). The increase in GDF-15 was significantly correlated with dark-skinned race, smoking, and hypertension [74]. According to several clinical studies, elevated levels of circulating GDF-15 in individuals with AMI correlate with inflammatory biomarkers, suggesting a link between GDF-15 and inflammation [75–77].

An experimental study demonstrated that GDF-15 protects against fatal heart rupture in a mouse model of myocardial infarction. Local induction of GDF-15 in the affected heart reduces heart wall rupture by acting as an anti-inflammatory cytokine and suppressing the recruitment of myeloid cells to the infarction area [78]. GDF-15 also inhibits chemokine-driven activation of β2 integrin on leukocytes, which are one of the main components causing cell damage in AMI. In mice with GDF-15 deficiency and inactivation (knockout) of β2 integrin, the incidence of fatal complications (rupture of the heart walls) and mortality from AMI decreased [79].

According to clinical studies, an increased concentration of GDF-15 in patients with AMI can independently predict mortality or a combination of death and nonfatal AMI [79]. Other studies have also shown that risk stratification can be improved by detecting a combination of three biomarkers in the blood — troponin T, NT-proBNP, and GDP-15 [80].

Galectin-3

Galectin-3, a small protein (molecular weight 30 kDa) of the family of lectins that bind beta-galactosidase, has recently been considered as a valuable prognostic biomarker of heart failure, myocardial infarction, and ischemic stroke [81–87]. In an experimental study, U. Sharma et al. [81] in rats, it was shown that galectin-3 increases cardiac fibrosis. Administration of galectin-3 to experimental animals leads to progressive fibrosis and systolic dysfunction of the left ventricle, thus stimulating ventricular remodeling. Through these observations, galectin-3 has emerged as a po-

tential biomarker for heart failure that may reflect ongoing ventricular remodeling.

At the cellular level, galectin-3 is secreted by activated macrophages and causes the proliferation of cardiac fibroblasts, increased collagen production, and ultimately leads to cardiac fibrosis [81]. A clinical study has shown that galectin-3 is an independent predictor of adverse outcomes in patients with acute heart failure [82]. Several studies have reported an increase in serum levels of circulating galectin-3 in patients with AMI [83, 84]. According to Q. Kang et al. [83], the concentration of galectin-3 in the group of patients with AMI is significantly higher than in the groups of patients with unstable (p <0.05) and stable (p <0.05) angina pectoris. In addition, in patients with multivessel coronary artery disease, the level of galectin-3 was significantly higher than in patients with single coronary artery disease (p <0.05). The content of galectin-3 in patients with AMI also negatively correlated with the value of the left ventricular ejection fraction (r = -0.405; p <0.05) [83]. Thus, according to the results of the study, galectin-3 is a marker of the severity of ischemia and myocardial dysfunction.

In a study by G. Bivona et al. [84] studied the kinetics of galectin-3 concentrations in AMI patients. The measurement of the concentration of galectin-3 in patients was carried out within 1 hour from the moment of admission to the emergency department and 5 days after AMI. It was found that in the acute period of AMI, the levels of galectin-3 are significantly higher than 5 days after the development of a heart attack (18 [14.2–25] versus 16.8 [12.7–23.4], respectively; p = 0.006). Galectin-3 levels correlated with cardiac troponin concentrations and glomerular filtration rate on admission (r = 0.2; p <0.001 and r = -0.25; p <0.001, respectively). Linear regression analysis revealed an association between galectin-3 and ejection fraction (r^2 = 0.037; p = 0.005) [84].

In an experimental study on mice, G. González et al. [85] showed that galectin-3 in the postinfarction period promotes early wound healing (scarring).

A. Lisowska et al. [86] reported that in patients with IHD and AMI, the levels of galectin-3 were significantly higher than in healthy patients (median 7.9–10.7 versus 5.5 ng / ml, respectively; p = 0.0001). In patients with lesions of three or more coronary vessels, the concentration of galectin-3 was significantly higher than in those with lesions of one or two vessels (9.2 versus 7.4 ng / ml; p = 0.003). In patients who died during the 3-year follow-up period after AMI, galectin levels were higher than in survivors (20.0 versus 8.0 ng / ml; p = 0.0005). According to the results of the study, the authors concluded that galectin-3 is an independent risk factor for CHD and AMI, as well as an independent prognostic indicator of an increased risk of death in the long term in patients after AMI [86]. A similar pattern is also typical for patients with ischemic stroke [87].

Proprotein convertase of subtilisin-kexin type 9, PCSK9

PCSK9 is a serine protease whose main function is to regulate the uptake of apolipoprotein B-containing (apoB) atherogenic low-density lipoproteins (LDL) by hepatocytes. By increasing the degradation of LDL receptors, PCSK9 causes an increase in atherogenic LDL levels and increases the risk of atherosclerosis and CVD. Thanks to the discovery and study of this mechanism, new groups of lipid-lowering drugs (PCSK9 inhibitors) were developed and the possibilities of using PCSK9 as a new early biomarker of atherosclerosis and CVD appeared [88, 89]. At the same time, there is a lot of data according to which the functions of PCSK9 go far beyond the regulation of LDL metabolism, extending to the immune response, hemostasis, glucose metabolism, neuronal survival, and other processes [90]. The study of these mechanisms could subsequently expand both the diagnostic value of PCSK9 as a biomarker and the indication for the prescription of PCSK9 inhibitors.

In a study by S. Li et al. [91] assessed the relationship between serum PCSK9 levels and the severity of coronary artery disease. In patients with IHD, the concentration of PCSK9 in the blood serum was significantly higher than in the control group (228.03 ± 1.01 versus 219.28 ± 1.02 ng / ml; p = 0.019). PCSK9 levels were also associated with the severity of coronary artery disease, as measured by the Gensini scoring system. A logistic regression analysis showed that PCSK9 levels were associated with an increased risk of CHD (odds ratios of 3.296 and 5.130 for morbidity and severity, respectively) [91].

In a number of clinical studies, PCSK9 levels have been assessed in patients with AMI [92–95]. N. Almontashiri et al. [92] found that in patients with AMI, the concentration of PCSK9 is higher than in the group of patients with coronary artery disease, but without AMI, and in the group of healthy patients. According to Y. Gao et al. [93], serum PCSK9 levels during the acute phase of AMI are associated with triglyceride levels and inflammatory activity. Z. Zhang et al. [94] noted the presence of gender differences in PCSK9 concentrations in AMI. For example, female patients

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presenting with AMI have higher PCSK9 levels than men [94].

In a study by G. Miñana et al. [95] found a relationship between increased PCSK9 concentrations in AMI and lower values of left ventricular ejection fraction 6 months after the development of AMI. As for the predictive value of PCSK9 in AMI, according to the above studies, it is controversial and needs further clarification.

CONCLUSION

Thus, based on experimental and clinical studies, the concentration of inflammatory biomarkers (CRP, IL6, TNF-α, MPO, PGF, CD40L, MMPs) can be considered as effective prognostic biomarkers in patients with AMI. The diagnostic value when using inflammatory biomarkers as the only biomarkers of AMI is low, since any inflammatory process will cause their increase in blood serum. At the same time, when using inflammatory agents in combination with a group of biomarkers of ischemia and necrosis of cardiomyocytes, it is possible not only to improve the risk stratification of patients with AMI, but also to improve laboratory diagnosis of myocardial infarction.

Among the new biomarkers of AMI, microRNAs seem to be the most promising in terms of early diagnosis. As for biomarkers such as galectin-3, GDF-15, ST2, and PCSK9, they are not highly specific for early diagnosis when used as the only biomarkers and are more suitable for the role of prognostic biomarkers of AMI.

Given the high morbidity, mortality and disability of the population around the world, further study of the diagnostic and prognostic value of laboratory biomarkers of AMI is one of the most urgent research directions.

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AUTHOR CONTRIBUTIONS

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