Review paper

Circulating biomarkers as predictors of left ventricular remodeling after myocardial infarction

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Abstract

Introduction: The main impact of myocardial infarction is shifting from acute mortality to adverse remodeling and chronic left ventricle dysfunction. Several circulating biomarkers are explored for better risk stratification of these patients. Biomarker testing is a very attractive idea, since it is non-invasive, not operator-dependent and widely available.

Aim: In the present paper we analyze data from the years 2005–2020 about circulating biomarkers of remodeling after myocardial infarction.

Material and methods: We assessed 53 articles, which examined 160 relations between biomarkers and remodeling. We analyze inclusion criteria for individual studies, time points of serum collection and remodeling assessment as well as imaging methods.

Results: The main groups of assessed biomarkers included B-type natriuretic peptides, markers of cardiomyocyte injury and necrosis, markers of inflammatory response, markers of extracellular matrix turnover, microRNAs and hormones. The most common method of remodeling assessment was echocardiography and the most frequent time point for remodeling evaluation was 6 months.

Conclusions: The present analysis shows that although a relatively large number biomarkers were tested, selecting one ideal marker is still a challenge. A combination of biomarkers from different groups might be appropriate for predicting remodeling. Data presented in this analysis might be helpful for designing future studies, evaluating clinical use of an individual biomarker or a combination of different biomarkers.

Key words: myocardial infarction, remodeling, biomarkers, narrative review, combined biomarker testing.

Introduction

Mortality during the acute phase of myocardial infarction (MI) has steadily decreased over the past 3 decades [1, 2]. The main impact of MI is shifting from acute mortality to adverse remodeling, chronic left ventricle (LV) dysfunction and eventually clinically apparent heart failure [1, 3]. Occurrence of adverse remodeling increases long-term mortality after MI [4]. Several biomarkers are screened in order to identify patients who are at risk of LV remodeling development. Biomarker testing is a very attractive idea, since it is non-invasive, not operator-dependent and widely available. However, because of the complex pathophysiology of remodeling, selecting one ideal marker is challenging.

The aim of this narrative review was to assess and discuss data about circulating biomarkers of remodeling in patients after MI.

Data assessment

We performed a Medline search of articles published in the years 2005–2020 using the keywords: "myocardial infarction AND ventricular remodeling AND biomarkers". We examined original studies of patients, admitted with acute MI, reporting measurement of ≥ 1 circulating biomarker. Articles with a follow-up of LV imaging and presenting LV volumes as an indicator of remodeling were analyzed. Studies with sample size of less than 30 patients and with follow-up of < 1 month were excluded. Finally, we selected and assessed 53 studies, which examined 160 relations between biomarkers and remodeling. In Table I we present details about examined publications. Main groups of assessed biomarkers included: B-type natriuretic peptides (BNPs); markers of cardiomyocyte injury and necrosis (troponin, creatinine kinase); markers of inflammatory response including C-reactive

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Table I. Studies of circulating biomarkers associated with left ventricle adverse remodeling after myocardial infarction in chronological order of publication date

Article details	Biomarkers	Patient no. main incl. criteria	LVAR assessment method	LVAR definition	Time of serum collection	LVAR evaluation time	Correlation with LVAR
Jirmar *et al.* Int Heart J 2005 [22]	PIIINP PICP	35 STEMI PCI	Echocardiography	LVEDV	Admission, day 2, 4, 7, 1 month	Day 1, 4, 1, 6 months	Positive Positive
Matsunaga *et al.* Int J Cardiol 2005 [23]	MMP-2 + MMP-9	52 STEMI PCI	Echocardiography	LVEDVI LVESVI	Week 2	Admission, week 2, 6 months	Positive
Wagner *et al.* J Card Fail 2006 [24]	MMP-9	109 STEMI PCI	Echocardiography Ventriculography	LVEDV LVESV	Admission	Admission, 6 months	Positive
Hirayama *et al.* Am J Cardiol 2006 [25]	BNP	106 First anterior MI PCI	Ventriculography	LVEDV	1, 6 months	1, 6 months	Positive
Webb *et al.* Circulation 2006 [26]	MMP-9 Other biomarkers: MMP-2 MMP-7 MMP-8 TIMP-1 TIMP-2	32 STEMI NSTEMI	Echocardiography	LVEDV	Day 1, 2–5, 1, 3, 6 months	Day 1, 5, 1, 3, 6 months	Positive Not associated Not associated Not associated Not associated Not associated
Orn *et al.* J Card Fail 2007 [27]	MMP-2 MMP-9 NT-proBNP	52 STEMI NSTEMI PCI Fibrinolysis	CMR	LVEDVI	Admission, 1 month, 1, 4 years	4 years	Not associated Positive Positive
Kelly *et al.* Eur Heart J 2008 [28]	TIMP-1 MMP-9 NT-proBNP	404 STEMI NSTEMI Fibrinolysis Conservative	Echocardiography	LVEDV LVESV	Day 1, discharge	Discharge, 6 months	Positive Positive Positive
Kelly *et al.* J Card Fail 2008 [29]	Copeptin	274 STEMI NSTEMI PCI Fibrinolysis	Echocardiography	LVEDV LVESV	Discharge	Discharge, mean of 155 days	Positive
Kuribara *et al.* J Cardiol 2009 [30]	DNaseI	45 STEMI NSTEMI PCI	Echocardiography	LVEDV LVESV	Admission, day 2, 3, 7, 14, 6 months	Admission, 6 months	Positive
Garcia-Alvarez *et al.* Am J Cardiol 2009 [31]	BNP	82 STEMI PCI Fibrinolysis	Echocardiography CMR	> 20% increase in LVEDV	Day 4, 1, 6 months	6 months	Positive
Weir *et al.* Eur J Heart Fail 2009 [32]	Apelin Other biomarkers: NT-proBNP Norepinephrine	100 LVEF < 40% STEMI NSTEMI PCI Fibrinolysis	CMR	LVEDVI LVESVI	Day 2, 6 months	Discharge, 6 months	Not associated Positive Positive
Fertin *et al.* Am J Cardiol 2010 [33]	BNP TnI CRP	246 First anterior Q-wave MI PCI Fibrinolysis	Echocardiography	> 20% increase in LVEDV	Discharge, 1, 3, 12 months	Discharge, 3, 12 months	Positive Positive Not associated

Table I. Cont.

Article details	Biomarkers	Patient no. main incl. criteria	LVAR assessment method	LVAR definition	Time of serum collection	LVAR evaluation time	Correlation with LVAR
Weir *et al.* Cytokine 2010 [34]	MCP-1	100 LVEF < 40% STEMI NSTEMI PCI Fibrinolysis	CMR	LVESVI	Day 2, 3, 6 months	Day 2, 3, 6 months	Negative
Weir *et al.* J Am Coll Cardiol 2010 [35]	ST2 protein Other biomarkers: NT-proBNP Aldosterone Norepinephrine	100 LVEF < 40% STEMI NSTEMI PCI Fibrinolysis	CMR	LVEDVI LVESVI	Admission, 3, 6 months	Admission, 3, 6 months	Positive Positive Positive Positive
Weir *et al.* J Thromb Thrombolysis 2010 [36]	t-PA vWF MMP-2 MMP-3 MMP-9 BNP	100 LVEF < 40% STEMI NSTEMI PCI Fibrinolysis	CMR	LVESVI	Day 2, 3, 6 months	Day 2, 3, 6 months	Positive Positive Not associated Positive Not associated Positive
Kelly *et al.* Biomarkers 2010 [37]	Procalcitonin	273 STEMI NSTEMI Fibrinolysis Conservative	Echocardiography	LVEDV LVESV	Discharge	Discharge, 4 months	Positive
Hallén *et al.* Heart 2010 [38]	TnI	132 STEMI PCI	CMR	LVEDVI LVESVI	Day 1, 2	Day 5, 4 months	Positive
Lamblin *et al.* Eur J Heart Fail 2011 [39]	Hepatocyte growth factor	246 First anterior Q-wave MI PCI Fibrinolysis	Echocardiography	LVEDV LVESV	Discharge, 1, 3, 12 months	Discharge, 3, 12 months	Positive
Weir *et al.* Eur J Heart Fail 2011 [40]	Aldosterone Cortisol metabolites	50 LVEF < 40% STEMI NSTEMI PCI Fibrinolysis	CMR	LVESVI	Admission	Admission, 6 months	Positive Positive
Dominguez-Rodriguez *et al.* Am J Cardiol 2011 [41]	GDF15 Other biomarkers: TnI BNP	97 STEMI PCI	Echocardiography	> 20% increase in LVEDV	Day 1	First 4 days, 12 months	Positive Not associated Not associated
Aoki *et al.* J Cardiol 2011 [42]	Peak PBMC FPG Peak WBC Peak monocyte	131 STEMI PCI	Ventriculography	> 10% increase in LVEDVI	Day 1–5	Admission, 6 months	Positive Positive Positive Positive
Erkol *et al.* Atherosclerosis 2012 [43]	Osteoprotegerin Other biomarkers: Peak TnI	92 STEMI PCI	Echocardiography	> 20% increase in LVEDV	Admission	Day 1, 6 months	Positive Positive
Wyderka *et al.* Mediators Inflamm 2012 [44]	CD34+/CXCR4+	50 STEMI PCI	Echocardiography	LVEF	Admission, 12 months	Admission, 12 months	Negative
Devaux *et al.* J Card Fail 2012 [45]	VEGFB	290 STEMI PCI	Echocardiography	LVEDV	Day 4	Discharge, 6 months	Negative

Table I. Cont.

Article details	Biomarkers	Patient no. main incl. criteria	LVAR assessment method	LVAR definition	Time of serum collection	LVAR evaluation time	Correlation with LVAR
Fertin *et al.* J Cardiol 2012 [46]	sFas ligand Other biomarkers: BNP	246 First anterior Q-wave MI PCI Fibrinolysis	Echocardiography	LVEDV LVESV	1 month	Discharge, 3, 12 months	Not associated Positive
Urbano-Moral *et al.* Heart 2012 [47]	NT-proBNP TnT hsCRP MMP-9 PINP	112 STEMI PCI	Echocardiography	> 20% increase in LVEDV	Discharge	Discharge, 6 months	Positive Positive Positive Positive Not associated
Weir *et al.* Cytokine 2012 [48]	IL-21 Other biomarkers: MMP-2 MMP-3 MMP-9 TIMP-1 TIMP-2 TIMP-4 MCP-1 BNP	100 LVEF < 40% STEMI NSTEMI PCI Fibrinolysis	CMR	LVESVI LVEDVI	Admission, 6 months	Admission, 6 months	Positive Not associated Positive Negative Negative Positive Positive Positive Positive
Devaux *et al.* Cir Cardiovasc Genet 2013 [49]	miR-150	90 First STEMI Fibrinolysis Conservative	Echocardiography	LVEDV	Day 3–4	Discharge, 6 months	Negative
Bauters *et al.* Int J Cardiol 2013 [50]	miR-133a miR-423-5p	246 Anterior Q-wave MI PCI Fibrinolysis	Echocardiography	LVEDV	Admission, 1, 3, 12 months	Discharge, 3, 12 months	Not associated Not associated
Mather *et al.* Int J Cardiol 2013 [51]	hsCRP TnI NT-proBNP H-FABP	48 First STEMI PCI	CMR	LVEDVI LVESVI	Day 2, 1 week, 1, 3 months	Day 2, 1 week, 1, 3 months	Positive Positive Positive Not associated
Meng *et al.* Postgrad Med J 2013 [52]	Catestatin Other biomarkers: BNP	31 STEMI PCI	Echocardiography	> 20% increase in LVEDV	Admission, day 3, 7, 3 months	Week 1, 3 months	Positive Positive
Weir *et al.* Circ Heart Fail 2013 [53]	Galectin 3	100 LVEF < 40% STEMI NSTEMI PCI Fibrinolysis	CMR	LVESVI	Admission, 6 months	Admission, 6 months	Not associated
Eschalier *et al.* Circ Heart Fail 2013 [54]	PINP PIIINP PICP Other biomarkers: BNP TnI CRP	246 First anterior Q-wave MI PCI Fibrinolysis	Echocardiography	> 20% increase in LVEDV	1 month	Discharge, 12 months	Not associated Not associated Positive Positive Positive Not associated
Reinstadler *et al.* Heart 2013 [55]	Copeptin	54 STEMI PCI	CMR	LVEDV LVESV	Day 2	Admission, 4 months	Positive
Kleczynski *et al.* Dis Markers 2013 [56]	NT-proBNP	45 STEMI PCI	CMR	LVEDV LVESV	Admission, 6 months	6 months	Positive

Table I. Cont.

Article details	Biomarkers	Patient no. main incl. criteria	LVAR assessment method	LVAR definition	Time of serum collection	LVAR evaluation time	Correlation with LVAR
Fertin *et al.* PLoS One 2013 [57]	MMP-1 MMP-2 MMP-3 MMP-8 MMP-9 MMP-13 TIMP-1 TIMP-2 TIMP-3 TIMP-4	246 First anterior MI PCI Fibrinolysis	Echocardiography	> 20% increase in LVEDV	Admission, 3 months, 1 year	Discharge, 1, 3, months, 1 year	Not associated Not associated Not associated Not associated Positive Positive Not associated Not associated Not associated Not associated
Lv *et al.* Int J Mol Sci 2014 [58]	miR-208b miR-34a Other biomarkers: TnT Peak CK BNP	359 PCI Fibrinolysis	Echocardiography	> 10% increase in LVEDV	Admission	Baseline, 6 months	Positive Positive Positive Not associated Positive
Kumarswamy *et al.* Circ Res 2014 [59]	Mitochondrial long noncoding RNA uc022bqs.1	246 First anterior Q-wave MI PCI Fibrinolysis	Echocardiography	> 20% increase in LVEDV	Day 3–7, 1, 3, 12 months	Day 3–7, 3, 12 months	Positive
Manhenke *et al.* Eur Heart J 2014 [60]	PINP MMP-2 MMP-3 Other biomarkers: TnT hsCRP NT-proBNP	42 First STEMI PCI	CMR	LVEDVI LVSVI	Admission, day 2, 7, 2, 12 months	Day 2, 7, 2, 12 months	Negative Negative Positive Positive Positive Positive
Liu *et al.* Cardiology 2015 [61]	miR-146a miR-21 Other biomarkers: NT-proBNP CRP TnI CK-MB	198 STEMI PCI	Echocardiography	> 20% increase in LVEDV	Admission	Day 5, 1 year	Positive Positive Positive Positive Not associated Positive
Abdel Hamid *et al.* J Interv Cardiol 2016 [62]	Circulating endothelial cells	78 PCI Fibrinolysis	Echocardiography	> 20% increase in LVEDV	Day 1	Day 2, 1 month	Positive
Türkoğlu *et al.* Coron Artery Dis 2016 [63]	M30 antigen M60 antigen Other biomarkers: BNP	255 STEMI PCI	Echocardiography	> 20% increase in LVEDV	Day 1	Day 1, 6 months	Positive Positive Positive
Reindl *et al.* Heart 2017 [64]	FGF 23 Other biomarkers: cTnT hsCRP NTproBNP	88 STEMI PCI	CMR	> 20% increase in LVEDV	Day 2	Day 2, 4 months	Positive Positive Positive Positive
Grabmaier *et al.* Int J Cardiol 2017 [65]	miR-1 miR-29b miR-21	44 STEMI PCI	CMR	LVEDV	Day 4, 9, 6 months	Day 4, 6 months	Not associated Negative Not associated
Hendriks *et al.* Int J Cardiovasc Imaging 2017 [66]	Peak CK Peak CK-MB Peak TnT NT-proBNp	271 First STEMI PCI	CMR	LVEDVI LVESVI	Admission, week 2, 6	4 months	Positive Positive Positive Positive

Table I. Cont.

Article details	Biomarkers	Patient no. main incl. criteria	LVAR assessment method	LVAR definition	Time of serum collection	LVAR evaluation time	Correlation with LVAR
Hsu *et al.* Int J Med Sci 2017 [67]	BNP decrease ratio Peak CK-MB Peak TnI CRP	97 STEMI NSTEMI PCI	Echocardiography	> 20% increase in LVEDV	Day 2, 7, 3 months	Day 2, 7, 3 months	Negative Positive Not associated Not associated
Di Tano *et al.* Heart 2017 [68]	Galectin 3 Other biomarkers: NT-proBNP	103 First STEMI LAD culprit PCI	Echocardiography	> 15% increase in LVESV	Day 2, 1, 6 months	Day 2, 1, 6 months	Positive Not associated
Miñana *et al.* Int J Cardiol 2018 [69]	ST2 protein Other biomarkers: TnT NT-proBNP	109 First STEMI PCI	CMR	LVEDVI LVESVI	Day 1	1 week, 6 months	Positive Not associated Not associated
de Gonzalo-Calvo *et al.* Sci Rep 2018 [70]	miR-1254	70 First STEMI PCI	CMR	LVESVI	Admission	Week 1, 6 months	Negative
Orrem *et al.* Int J Cardiol 2018 [71]	IL-1Ra sIL-1RAcP sIL-1R2 sIL1-R1 Other biomarkers: Peak TnT Peak CRP NTproBNP	320 STEMI PCI	CMR	LVEDVI LVESVI	Admission, day 1, 4, 12 months	Day 2, 4 months	Not associated Not associated Positive Not associated Positive Positive Not associated
Padoan *et al.* Int J Cardiol 2019 [72]	Vitamin D Other biomarkers: CRP Peak TnI	253 STEMI NSTEMI PCI CABG	Echocardiography	> 15% increase in LVESV	During hospitalization	During hospitalization, 4 months	Negative Positive Positive
Garcia *et al.* Int J Mol Sci 2019 [73]	Peak CK TnI NT-proBNP CRP WBC Neutrophil count Creatinine	64 STEMI PCI Fibrinolysis	CMR	> 10% increase in LVESV	Day 2	Admission, 3, 12 months	Positive Not associated Not associated Positive Positive Positive Not associated
Reindl *et al.* Eur Heart J Acute Cardiovasc Care 2019 [74]	TSH Other biomarkers: Peak TnT Peak CRP	102 STEMI PCI	CMR	> 20% increase in LVEDV	Day 1, 4 months	Week 1, 4 months	Negative Positive Positive

PIIINP – type III procollagen propeptide, PICP – carboxy terminal propeptide of type I collagen, MMP – matrix metalloproteinases, BNP – B-type natriuretic peptide, TIMP – tissue inhibitor of MMP, Tn – troponin, CRP – C reactive protein, MCP – monocyte chemoattractant protein, tPA – tissue plasminogen activator, vWF – von Willebrand Factor, GDF – growth differentiating factor, PBMC – peripheral blood mononuclear count, FPG – fasting plasma glucose, WBC – white blood count, VEGFB – vascular endothelial growth factor B, PINP – procollagen type I amino terminal propeptide, Il – interleukin, miR – micro RNA, HFABP – heart type fatty acid binding protein, CK – creatinine kinase, FGF – fibroblast growth factor, TSH – thyroid stimulating hormone, Incl – inclusion, MI – myocardial infarction, STEMI – ST elevation MI, NSTEMI – non-ST elevation MI, PCI – percutaneous coronary intervention, LAD – left anterior descending, LVEF – left ventricle ejection fraction, LVAR – left ventricular adverse remodeling, CMR – cardiac magnetic resonance, LVEDV(i) – left ventricle end diastolic volume (index), LVESV(i) – left ventricle end systolic volume (index).

protein (CRP), white blood count (WBC), soluble ST2 and galetctin-3; markers of extracellular matrix turnover including matrix metalloproteinases (MMPs), tissue inhibitors of matrix metalloproteinases (TIMPs) and collagen propeptides; microRNAs and hormones (aldosterone, cortisol, norepinephrine, copeptin) (Figure 1).

A positive correlation between examined biomarkers and remodeling was found in 101 (63%), a negative correlation was found in 13 (8%) and no significant association was found in 46 (29%) cases. Figure 2 presents the relationships between the most common individual biomarkers and remodeling. BNPs, troponin, CRP and creatinine kinase were the most frequent biomarkers and they were positively correlated with remodeling. MMP-9 was the most commonly analyzed member of metalloproteinases. It occurred in 9 studies and in 7 a positive

correlation with remodeling was reported. MMP-2 was assessed in 7 studies, but in 5 reports no significant association with remodeling was found. MMP-3 was analyzed in 4 studies and in 3 it was positively correlated with remodeling. Less frequent biomarkers included soluble ST2, TIMPs and procollagen type I amino terminal propeptide (PINP).

The majority of presented studies (68%) included ST-elevation MI (STEMI) patients exclusively. In most studies (57%) patients were treated with primary percutaneous coronary intervention (PCI). In 38% of studies patients underwent PCI and fibrinolysis and in 5% of studies patients underwent fibrinolysis or conservative treatment only. In Figure 3 we show the most commonly assessed biomarkers in patients treated exclusively with primary PCI. We observed that TIMPs were less frequently and microRNA-21 was relatively more frequently assessed in studies which included patients treated exclusively with primary PCI.

In the presented articles remodeling was defined as an increase in LV end diastolic volume (LVEDV) or less often LV end systolic volume (LVESV) during follow-up. Twenty (38%) studies utilized specific cut-off values for LV volume increase. Most commonly it was a 20% increase in LVEDV. Echocardiography and cardiac magnetic resonance (CMR) were the most common methods of remodeling assessment. Echocardiography was used in 57% and CMR was used in 41% of studies. In more recent studies, from the years 2015–2019, CMR was used in 57% of cases and echocardiography in 43%. Time points of LVAR assessment differed vastly among analyzed papers. The shortest period of LVAR evaluation after MI was 1 month (1 study), the longest was 4 years (also in 1 study). The most frequent time point for LVAR assessment was 6 months (73% of studies).

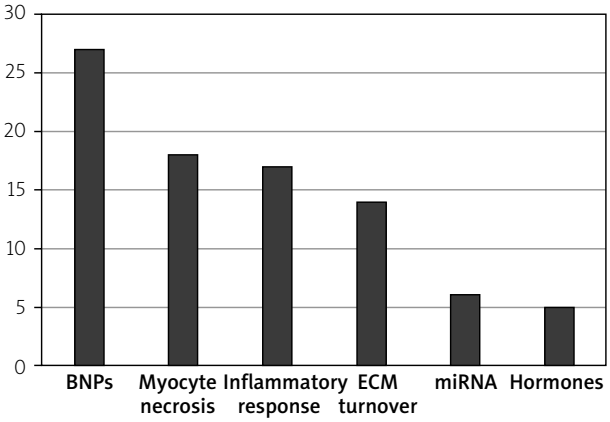

Figure 1. Groups of most commonly assessed biomarkers. Data are shown as number of studies evaluating groups of biomarkers

BNP – B type natriuretic peptide, ECM – extracellular matrix.

Description of biomarkers

The present analysis shows that a relatively large number of circulating biomarkers were tested, which reflects the complex pathophysiology of remodeling. Main groups of assessed biomarkers included BNPs, markers of cardiomyocyte injury and necrosis, markers of inflammatory response, markers of extracellular matrix turnover and microRNAs.

B-type natriuretic peptides

BNP is secreted predominantly from heart ventricles. It is a marker of volume overload and high filling pressure. In response to myocardial wall stretch, pre-proBNP is synthesized and processed to proBNP, which is further processed to the biologically inactive N-terminal prohor-

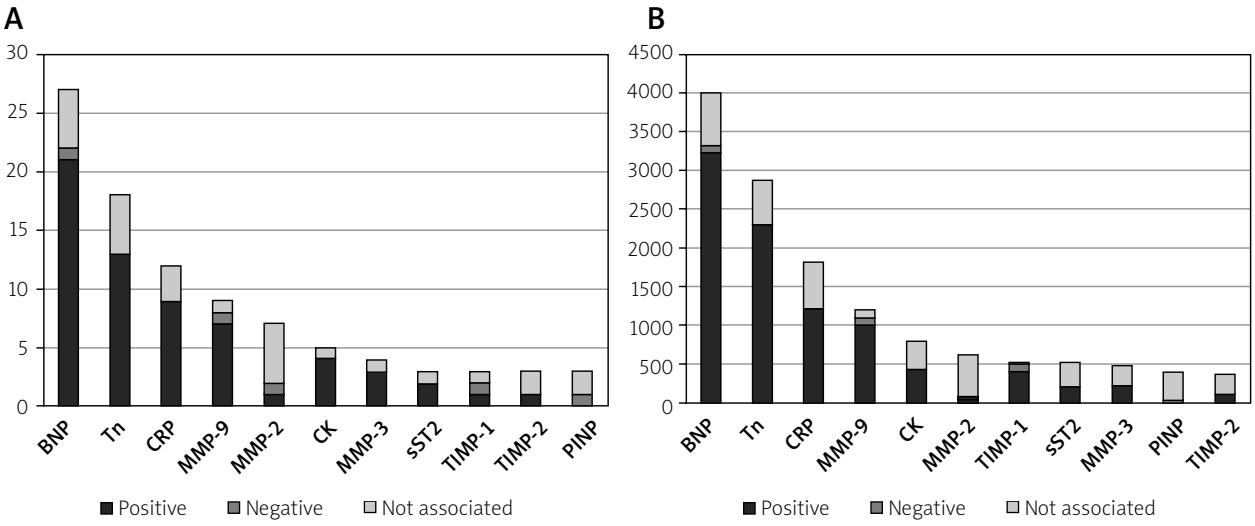

Figure 2. Relationships between individual biomarkers and remodeling. **A** – Data are shown as number of studies evaluating specific biomarkers. **B** – Data are shown as number of patients enrolled in studies evaluating biomarkers

BNP – B type natriuretic peptide, Tn – troponin, CRP – C reactive protein, MMP – matrix metalloproteinase, CK – creatinine kinase, TIMP – tissue inhibitor of MMP, PINP – procollagen type I amino terminal propeptide.

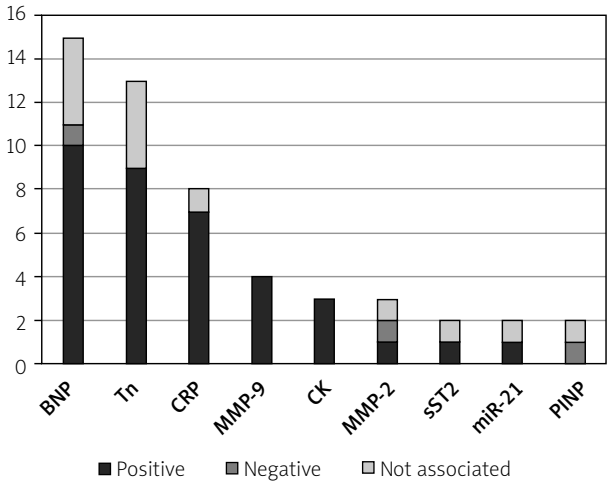

Figure 3. Relationships between individual biomarkers and remodeling in patients treated exclusively with primary percutaneous coronary intervention. Data are shown as number of studies evaluating specific biomarkers

BNP – B type natriuretic peptide, Tn – troponin, CRP – C reactive protein, MMP – matrix metalloproteinase, CK – creatinine kinase, miR – microRNA, PINP – procollagen type I amino terminal propeptide.

mone fragment (NT-proBNP) and biologically active BNP [5]. Biological effects of BNP include diuresis, natriuresis, vasodilatation and inhibition of the renin-angiotensin system. BNP is an established biomarker of LV systolic dysfunction and heart failure progression [6]. Higher BNP concentrations in patients after MI were reported to predict long-term mortality [6]. According to ESC guidelines BNP and NT-proBNP provide prognostic information regarding the risk of death and acute heart failure in MI patients [7]. Although the cut-off values are different for BNP and NT-proBNP, the guidelines give no indication which marker presents better accuracy for heart failure [7]. In the present analysis NT-proBNP was analyzed in 13 studies and BNP was assessed in 14 reports. Both markers were positively correlated with remodeling.

Cardiac troponins

The cardiac troponin complex consists of 3 subunits: troponin C, troponin T and troponin I. Troponin I and T form an actin-myosin complex and are released into peripheral blood after myocyte injury. Elevated concentration of troponin I and T is a diagnostic marker of acute coronary syndromes. Peak levels of both troponin I and T are predictive for mortality, recurrent MI and newly developed post-MI heart failure. Early troponin measurement provides an estimate of infarct size [5]. Although both troponins present comparable diagnostic accuracy for MI, troponin T provides greater prognostic value [7]. Currently, high sensitivity (hs) troponin assays are recommended for diagnosis and prognosis of MI instead of conventional assays. In the present analysis troponin I was examined in 10 studies and troponin T was assessed in 8 studies. Both troponins were positively correlated with remodeling.

Markers of inflammatory response

C-reactive protein is an acute phase protein of hepatic origin. Myocardial ischemia is associated with the systemic inflammatory response with increased production of acute phase proteins including CRP, partly as a response to stimulation by interleukin-6, which is released from the infarct zone. Levels of CRP increase in the first hours of MI and peak approximately at day 2. Elevated CRP concentrations are associated with adverse clinical outcome after MI, larger infarct size, microvascular obstruction and higher mortality in patients with heart failure [8]. In the present analysis CRP was assessed in 12 publications. In 9 studies, it was positively correlated with remodeling. Several studies assessed high-sensitivity (hs) CRP, which was also positively associated with remodeling.

Soluble suppression of tumorigenicity-2 (sST2) is the soluble form of interleukin-1 receptor-like 1 and is a protein biomarker of cardiac stress. Serum levels of sST2 were reported to be higher in patients with heart failure. In patients with MI, higher concentrations of sST2 predicted mortality and occurrence of post-MI heart failure [5]. In the present analysis sST2 was assessed in 3 studies and in 2 it was positively correlated with remodeling.

Extracellular matrix turnover

Extracellular matrix (ECM) surrounds cardiomyocytes and forms a scaffold which maintains the LV shape and geometry. ECM rearrangement corresponds to a balance between degradation and synthesis of extracellular components, regulated by MMPs and TIMPs [9]. MMPs are members of zinc-dependent endopeptidases, which degrade several ECM proteins and thus modulate physiological and pathological processes including MI and congestive heart failure. MMPs consist of 25 enzymes which are endogenously inhibited by TIMPs, a family comprising 4 members (TIMP-1, -2, - 3 and -4) [10]. The ECM turnover during remodeling is regulated through the balance of MMPs and TIMPs, levels of both of which rise after MI. In the present analysis MMP-9 was the most frequent analyzed member of MMPs. It was assessed in 9 studies and in 7 a positive correlation with remodeling was reported. The second most commonly assessed biomarker from this group was MMP-3, which appeared in 4 studies and in 3 a positive correlation with remodeling was observed. The relationship between levels of TIMPs and remodeling was inconclusive in the present analysis.

Collagen synthesis begins in fibroblasts which produce procollagen. In the ECM, the amino-terminal and carboxy-terminal propeptides are separated by endopeptidases and released into the circulation. They can be used as markers of collagen synthesis. Collagen type

I and III are principal structural proteins found in the myocardium. PINP is a marker of type I collagen synthesis. It was reported to be associated with reverse remodeling and inversely correlated with LV volumes in patients undergoing resynchronization therapy [11]. In the present analysis PINP was assessed in 3 studies and in 1 it was negatively correlated with remodeling. In 2 studies, no significant association with remodeling was reported.

MicroRNAs

MicroRNAs are small noncoding RNA molecules with regulatory functions. They participate in various cardiovascular processes through post-transcriptional regulation of gene expression. MicroRNAs are related to the regulation of cardiomyocyte apoptosis and fibrosis [12]. In the present analysis microRNAs were tested in 6 studies; however, the most frequently assessed microRNA-21 appeared only in 2 studies and in 1 analysis a positive correlation with remodeling was reported; thus selecting a biomarker of remodeling from the microRNA family is limited.

Methods and time points of remodeling assessment

Remodeling is defined as molecular, cellular and interstitial changes resulting from myocardial ischemia [13]. Clinical assessment of LV remodeling is based on detection of increase of LV volumes. In the present analysis the most common cut-off value was a 20% increase in LVEDV. Cardiac magnetic resonance is considered to be a gold standard for remodeling assessment due to accurate and reproducible measurements of LV volumes [14]. CMR is a more precise method with reduced operator variability compared to echocardiography. In addition, CMR with late gadolinium enhancement has the ability to distinguish between reversible and irreversible myocardial injury. CMR may also provide more precise information about scar formation, transmural necrosis and microvascular obstruction [15–18]. In the present analysis the rate of studies utilizing CMR was 41% and increased in more recent publications. Despite this, echocardiography remains the fastest and most accessible method which is used not only in clinical practice but also in clinical trials. Transthoracic echocardiography is also recommended in all patients with acute MI to evaluate global and regional function of LV [7].

Remodeling is a time-dependent process, which can continue up to 6–12 months after MI with infarct extension occurring in weeks to months after reperfusion [19]. Earlier assessment might not reflect the full remodeling process. A frequently selected time point for remodeling evaluation is 6 months after MI. Time points of blood collection are also vital. In several analyzed studies, serial blood sampling during index hospitalization and follow-up was utilized, which is helpful in determining the strongest association with remodeling. However, we think that the most clinically useful is the relationship between remodeling and levels of biomarkers measured in the acute phase of MI. Nowadays, biomarker guided therapy in patients after MI is not a standard approach. On the other hand, identification of high risk individuals could allow implementation of follow-up with more frequent LV assessment after hospital discharge.

Future directions

Association of classic biomarkers including BNPs, cardiac troponin and CRP with post-MI remodeling is widely documented. These biomarkers are readily available, routinely assessed in MI patients and their measurement is relatively inexpensive. In the present analysis MMP-9 was frequently examined and positively correlated with remodeling. However, measurement of MMP-9 activity is challenging due to its complex *in vivo* regulation. MMPs are synthesized as inactive zymogens, and must be enzymatically activated by hydrolyzation of a propeptide domain. Their activity is further regulated by TIMPs. Typical methods such as western blot, ELISA or immunohistochemistry are reported to be not sufficient to accurately describe MMPs' *in vivo* activity [20]. The ideal biomarker should not only allow improvement of clinical decisions but also be easily detectable from blood. The main idea of biomarker testing is their wide availability and no inter/intra-operator variability. The present analysis shows that a relatively large number of different biomarkers were assessed. Due to the complex pathophysiology of remodeling, selecting one marker is challenging. What is more, several biomarkers including MMPs, TIMPs and microRNAs occur in many types; thus despite being tested in a relatively large amount of studies, individual biomarkers appeared in a limited number of reports. Perhaps at a recent stage of studies, single biomarker testing might be not sufficient for remodeling prediction. A combination of biomarkers from different groups, reflecting different pathways of remodeling, might be appropriate. Reinstadler *et al.* showed that combined biomarker testing including NT-proBNP, troponin T, CRP, lactate dehydrogenase and liver transaminases improved the predictive value for remodeling compared to single biomarker assessment [21].

Conflict of interest

The authors declare no conflict of interest.

References

1. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics-2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007; 115: e69-171.
2. McManus DD, Gore J, Yarzebski J, et al. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. Am J Med 2011; 124: 40-7.

3. Jernberg T, Johanson P, Held C, et al.; SWEDEHEART/RIKS-HIA. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. JAMA 2011; 305: 1677-84.
4. Bhatt AS, Ambrosy AP, Velazquez EJ. Adverse remodeling and reverse remodeling after myocardial infarction. Curr Cardiol Rep 2017; 19: 71.
5. Berezin AE, Berezin AA. Adverse cardiac remodelling after acute myocardial infarction: old and new biomarkers. Dis Markers 2020; 2020: 1215802.
6. Crilley JG, Farrer M. Left ventricular remodelling and brain natriuretic peptide after first myocardial infarction. Heart 2001; 86: 638-42.
7. Collet JP, Thiele H, Barbato E, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2020; ehaa575. https://doi.org/10.1093/eurheartj/ehaa575.
8. Anzai T, Yoshikawa T, Shiraki H, et al. C-reactive protein as a predictor of infarct expansion and cardiac rupture after a first Q-wave acute myocardial infarction. Circulation 1997; 96: 778-84.
9. Halade GV, Jin YF, Lindsey ML. Matrix metalloproteinase (MMP)-9: a proximal biomarker for cardiac remodeling and a distal biomarker for inflammation. Pharmacol Ther 2013; 139: 32-40.
10. DeLeon-Pennell KY, Meschiari CA, Jung M, Lindsey ML. Matrix metalloproteinases in myocardial infarction and heart failure. Prog Mol Biol Transl Sci 2017; 147: 75-100.
11. Petrovic I, Stankovic I, Milasinovic G, et al. The relationship of myocardial collagen metabolism and reverse remodeling after cardiac resynchronization therapy. J Med Biochem 2016; 35: 130-6.
12. Dutka M, Bobiński R, Korbecki J. The relevance of microRNA in post-infarction left ventricular remodelling and heart failure. Heart Fail Rev 2019; 24: 575-86.
13. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling-concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000; 35: 569-82.
14. Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol 2002; 90: 29-34.
15. Hoffmann R, von Bardeleben S, Kasprzak JD, et al. Analysis of regional left ventricular function by cineventriculography, cardiac magnetic resonance imaging, and unenhanced and contrast-enhanced echocardiography: a multicenter comparison of methods. J Am Coll Cardiol 2006; 47: 121-8.
16. Fieno DS, Kim RJ, Chen EL, et al. Contrast-enhanced magnetic resonance imaging of myocardium at risk: distinction between reversible and irreversible injury throughout infarct healing. J Am Coll Cardiol 2000; 36: 1985-91.
17. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 1999; 100: 1992-2002.
18. Tarantini G, Razzolini R, Cacciavillani L, et al. Influence of transmurality, infarct size, and severe microvascular obstruction on left ventricular remodeling and function after primary coronary angioplasty. Am J Cardiol 2006; 98: 1033-40.
19. Ganame J, Messalli G, Masci PG, et al. Time course of infarct healing and left ventricular remodelling in patients with reperfused ST segment elevation myocardial infarction using comprehensive magnetic resonance imaging. Eur Radiol 2011; 21: 693-701.
20. Hadler-Olsen E, Kanapathippillai P, Berg E, et al. Gelatin in situ zymography on fixed, paraffin-embedded tissue: zinc and ethanol fixation preserve enzyme activity. J Histochem Cytochem 2010; 58: 29-39.
21. Reinstadler SJ, Feistritzer HJ, Reindl M, et al. Combined biomarker testing for the prediction of left ventricular remodelling in ST-elevation myocardial infarction. Open Heart 2016; 3: e000485.
22. Jirmár R, Pelouch V, Widimský P, et al. Influence of primary coronary intervention on myocardial collagen metabolism and left ventricle remodeling predicted by collagen metabolism markers. Int Heart J 2005; 46: 949-59.
23. Matsunaga T, Abe N, Kameda K, et al. Circulating level of gelatinase activity predicts ventricular remodeling in patients with acute myocardial infarction. Int J Cardiol 2005; 105: 203-8.
24. Wagner DR, Delagardelle C, Ernens I, et al. Matrix metalloproteinase-9 is a marker of heart failure after acute myocardial infarction. J Card Fail 2006; 12: 66-72.
25. Hirayama A, Kusuoka H, Yamamoto H, et al. Usefulness of plasma brain natriuretic peptide concentration for predicting subsequent left ventricular remodeling after coronary angioplasty in patients with acute myocardial infarction. Am J Cardiol 2006; 98: 453-7.
26. Webb CS, Bonnema DD, Ahmed SH, et al. Specific temporal profile of matrix metalloproteinase release occurs in patients after myocardial infarction: relation to left ventricular remodeling. Circulation 2006; 114: 1020-7.
27. Orn S, Manhenke C, Squire IB, et al. Plasma MMP-2, MMP-9 and N-BNP in long-term survivors following complicated myocardial infarction: relation to cardiac magnetic resonance imaging measures of left ventricular structure and function. J Card Fail 2007; 13: 843-9.
28. Kelly D, Khan SQ, Thompson M, et al. Plasma tissue inhibitor of metalloproteinase-1 and matrix metalloproteinase-9: novel indicators of left ventricular remodelling and prognosis after acute myocardial infarction. Eur Heart J 2008; 29: 2116-24..
29. Kelly D, Squire IB, Khan SQ, et al. C-terminal provasopressin (copeptin) is associated with left ventricular dysfunction, remodeling, and clinical heart failure in survivors of myocardial infarction. J Card Fail 2008; 14: 739-45.
30. Kuribara J, Tada H, Kawai Y, et al. Levels of serum deoxyribonuclease I activity on admission in patients with acute myocardial infarction can be useful in predicting left ventricular enlargement due to remodeling. J Cardiol 2009; 53: 196-203.
31. Garcia-Alvarez A, Sitges M, Delgado V, et al. Relation of plasma brain natriuretic peptide levels on admission for ST-elevation myocardial infarction to left ventricular end-diastolic volume six months later measured by both echocardiography and cardiac magnetic resonance. Am J Cardiol 2009; 104: 878-82.
32. Weir RA, Chong KS, Dalzell JR, et al. Plasma apelin concentration is depressed following acute myocardial infarction in man. Eur J Heart Fail 2009; 11: 551-8.
33. Fertin M, Hennache B, Hamon M, et al. Usefulness of serial assessment of B-type natriuretic peptide, troponin I, and C-reactive protein to predict left ventricular remodeling after acute myocardial infarction (from the REVE-2 study). Am J Cardiol 2010; 106: 1410-6.

34. Weir RA, Murphy CA, Petrie CJ, et al. Monocyte chemoattractant protein-1: a dichotomous role in cardiac remodeling following acute myocardial infarction in man? Cytokine 2010; 50: 158-62.
35. Weir RA, Miller AM, Murphy GE, et al. Serum soluble ST2: a potential novel mediator in left ventricular and infarct remodeling after acute myocardial infarction. J Am Coll Cardiol 2010; 55: 243-50.
36. Weir RA, Balmain S, Steedman T, et al. Tissue plasminogen activator antigen predicts medium-term left ventricular end-systolic volume after acute myocardial infarction. J Thromb Thrombolysis 2010; 29: 421-8.
37. Kelly D, Khan SQ, Dhillon O, et al. Procalcitonin as a prognostic marker in patients with acute myocardial infarction. Biomarkers 2010; 15: 325-31.
38. Hallén J, Jensen JK, Fagerland MW, et al. Cardiac troponin I for the prediction of functional recovery and left ventricular remodeling following primary percutaneous coronary intervention for ST-elevation myocardial infarction. Heart 2010; 96: 1892-7.
39. Lamblin N, Bauters A, Fertin M, et al. Circulating levels of hepatocyte growth factor and left ventricular remodelling after acute myocardial infarction (from the REVE-2 study). Eur J Heart Fail 2011; 13: 1314-22.
40. Weir RA, Tsorlalis IK, Steedman T, et al. Aldosterone and cortisol predict medium-term left ventricular remodelling following myocardial infarction. Eur J Heart Fail 2011; 13: 1305-13.
41. Dominguez-Rodriguez A, Abreu-Gonzalez P, Avanzas P. Relation of growth-differentiation factor 15 to left ventricular remodeling in ST-segment elevation myocardial infarction. Am J Cardiol 2011; 108: 955-8.
42. Aoki S, Nakagomi A, Asai K, et al. Elevated peripheral blood mononuclear cell count is an independent predictor of left ventricular remodeling in patients with acute myocardial infarction. J Cardiol 2011; 57: 202-7.
43. Erkol A, Oduncu V, Pala S, et al. Plasma osteoprotegerin level on admission is associated with no-reflow phenomenon after primary angioplasty and subsequent left ventricular remodeling in patients with acute ST-segment elevation myocardial infarction. Atherosclerosis 2012; 221: 254-9.
44. Wyderka R, Wojakowski W, Jadczyk T, et al. Mobilization of CD34+CXCR4+ stem/progenitor cells and the parameters of left ventricular function and remodeling in 1-year follow-up of patients with acute myocardial infarction. Mediators Inflamm 2012; 2012: 564027.
45. Devaux Y, Vausort M, Azuaje F, et al. Low levels of vascular endothelial growth factor B predict left ventricular remodeling after acute myocardial infarction. J Card Fail 2012; 18: 330-7.
46. Fertin M, Bauters A, Pinet F, Bauters C. Circulating levels of soluble Fas ligand and left ventricular remodeling after acute myocardial infarction (from the REVE-2 study). J Cardiol 2012; 60: 93-7.
47. Urbano-Moral JA, Lopez-Haldon JE, Fernandez M, et al. Prognostic value of different serum biomarkers for left ventricular remodelling after ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. Heart 2012; 98: 1153-9.
48. Weir RA, Miller AM, Petrie CJ, et al. Interleukin-21: a biomarker of importance in predicting myocardial function following acute infarction? Cytokine 2012; 60: 220-5.
49. Devaux Y, Vausort M, McCann GP, et al. MicroRNA-150: a novel marker of left ventricular remodeling after acute myocardial infarction. Circ Cardiovasc Genet 2013; 6: 290-8.
50. Bauters C, Kumarswamy R, Holzmann A, et al. Circulating miR-133a and miR-423-5p fail as biomarkers for left ventricular remodeling after myocardial infarction. Int J Cardiol 2013; 168: 1837-40.
51. Mather AN, Fairbairn TA, Artis NJ, et al. Relationship of cardiac biomarkers and reversible and irreversible myocardial injury following acute myocardial infarction as determined by cardiovascular magnetic resonance. Int J Cardiol 2013; 166: 458-64.
52. Meng L, Wang J, Ding WH, et al. Plasma catestatin level in patients with acute myocardial infarction and its correlation with ventricular remodelling. Postgrad Med J 2013; 89: 193-6.
53. Weir RA, Petrie CJ, Murphy CA, et al. Galectin-3 and cardiac function in survivors of acute myocardial infarction. Circ Heart Fail 2013; 6: 492-8.
54. Eschalier R, Fertin M, Fay R, et al. Extracellular matrix turnover biomarkers predict long-term left ventricular remodeling after myocardial infarction: insights from the REVE-2 study. Circ Heart Fail 2013; 6: 1199-205.
55. Reinstadler SJ, Klug G, Feistritzer HJ, et al. Association of copeptin with myocardial infarct size and myocardial function after ST segment elevation myocardial infarction. Heart 2013; 99: 1525-9.
56. Kleczyński P, Legutko J, Rakowski T, et al. Predictive utility of NT-pro BNP for infarct size and left ventricle function after acute myocardial infarction in long-term follow-up. Dis Markers 2013; 34: 199-204.
57. Fertin M, Lemesle G, Turkieh A, et al. Serum MMP-8: a novel indicator of left ventricular remodeling and cardiac outcome in patients after acute myocardial infarction. PLoS One 2013; 8: e71280.
58. Lv P, Zhou M, He J, et al. Circulating miR-208b and miR-34a are associated with left ventricular remodeling after acute myocardial infarction. Int J Mol Sci 2014; 15: 5774-88.
59. Kumarswamy R, Bauters C, Volkmann I, et al. Circulating long noncoding RNA, LIPCAR, predicts survival in patients with heart failure. Circ Res 2014; 114: 1569-75.
60. Manhenke C, Ueland T, Jugdutt BI, et al. The relationship between markers of extracellular cardiac matrix turnover: infarct healing and left ventricular remodelling following primary PCI in patients with first-time STEMI. Eur Heart J 2014; 35: 395-402..
61. Liu X, Dong Y, Chen S, et al. Circulating microRNA-146a and microRNA-21 predict left ventricular remodeling after ST-elevation myocardial infarction. Cardiology 2015; 132: 233-41.
62. Abdel Hamid M, Bakhoum SW, Sharaf Y, et al. Circulating endothelial cells and endothelial function predict major adverse cardiac events and early adverse left ventricular remodeling in patients with st-segment elevation myocardial infarction. J Interv Cardiol 2016; 29: 89-98.
63. Türkoğlu C, Gür M, Şeker T, et al. The predictive value of M30 and oxidative stress for left ventricular remodeling in patients with anterior ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. Coron Artery Dis 2016; 27: 690-5.
64. Reindl M, Reinstadler SJ, Feistritzer HJ, et al. Fibroblast growth factor 23 as novel biomarker for early risk stratification after ST-elevation myocardial infarction. Heart 2017; 103: 856-62.
65. Grabmaier U, Clauss S, Gross L, et al. Diagnostic and prognostic value of miR-1 and miR-29b on adverse ventricular remodeling after acute myocardial infarction – The SITAGRAMI-miR analysis. Int J Cardiol 2017; 244: 30-6.

66. Hendriks T, Hartman MHT, Vlaar PJJ, et al. Predictors of left ventricular remodeling after ST-elevation myocardial infarction. Int J Cardiovasc Imaging 2017; 33: 1415-23.
67. Hsu JT, Chung CM, Chu CM, et al. Predictors of left ventricle remodeling: combined plasma B-type natriuretic peptide decreasing ratio and peak creatine kinase-MB. Int J Med Sci 2017; 14: 75-85.
68. Di Tano G, Caretta G, De Maria R, et al. Galectin-3 predicts left ventricular remodelling after anterior-wall myocardial infarction treated by primary percutaneous coronary intervention. Heart 2017; 103: 71-7.
69. Miñana G, Núñez J, Bayés-Genís A, et al. ST2 and left ventricular remodeling after ST-segment elevation myocardial infarction: a cardiac magnetic resonance study. Int J Cardiol 2018; 270: 336-42.
70. de Gonzalo-Calvo D, Cediel G, Bär C, et al. Circulating miR-1254 predicts ventricular remodeling in patients with ST-segment-elevation myocardial infarction: a cardiovascular magnetic resonance study. Sci Rep 2018; 8: 15115.
71. Orrem HL, Shetelig C, Ueland T, et al. Soluble IL-1 receptor 2 is associated with left ventricular remodelling in patients with ST-elevation myocardial infarction. Int J Cardiol 2018; 268: 187-92.
72. Padoan L, Beltrami AP, Stenner E, et al. Left ventricular adverse remodeling after myocardial infarction and its association with vitamin D levels. Int J Cardiol 2019; 277: 159-65.
73. Garcia G, Chao de la Barca JM, Mirebeau-Prunier D, et al. Metabolomic approach in STEMI-patients undergoing left ventricular remodeling. Int J Mol Sci 2019; 20: pii: E289. doi: 10.3390/ijms20020289.
74. Reindl M, Feistritzer HJ, Reinstadler SJ, et al. Thyroid-stimulating hormone and adverse left ventricular remodeling following ST-segment elevation myocardial infarction. Eur Heart J Acute Cardiovasc Care 2019; 8: 717-26.