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Review

Emerging Circulating Biomarkers for Enhanced Cardiovascular Risk Prediction

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ABSTRACT

Cardiovascular disease (CVD) continues to be the primary cause of mortality worldwide, underscoring the importance of identifying additional cardiovascular risk factors. The consensus is that lipid levels alone do not fully reflect the status of atherosclerosis, thus necessitating extensive research on cardiovascular biomarkers. This review encompasses a wide spectrum of methodologies for identifying novel risk factors or biomarkers for CVD. Inflammation, oxidative stress, plaque instability, cardiac remodeling, and fibrosis play pivotal roles in CVD pathogenesis. We introduce and discuss several promising biomarkers—namely, osteocalcin, angiogenin, lipoprotein-associated phospholipase A2, growth differentiation factor 15, galectin-3, growth stimulation expressed gene 2, and microRNAs, all of which have potential implications in the assessment and management of cardiovascular risk.

Keywords: Cardiovascular disease; Biomarker; Cardiovascular risk enhancers

INTRODUCTION

Despite significant progress in early detection and intervention, cardiovascular disease (CVD) remains the primary global cause of mortality. Ischemic heart disease and stroke account for 16% and 11% of the total deaths, respectively.[1] In this context, it is imperative to estimate an individual's future risk of CVD to determine who requires early intensive preventive care or treatment. Therefore, the identification of additional cardiovascular risk enhancers is of paramount importance.

Although atherosclerosis is acknowledged as the fundamental cause of CVD, the intricate mechanisms driving the development of atherosclerotic plaques remain unclear. They are the consequence of complex processes involving the interaction of accumulating lipids, oxidative stress, vascular inflammation, and immune responses.[2] It is acknowledged that lipid levels alone are inadequate to fully explain atherosclerosis.[3,4] Consequently, there has been a significant amount of research focused on cardiovascular biomarkers.[5] A wide array of approaches—including genetics, epigenetics, transcriptomics, proteomics, metabolomics, microbiomics, epidemiology, and imaging—has been employed in the search for novel risk factors or biomarkers for CVD. In this article, we provide a concise summary of

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Conflict of Interest

The authors have no conflicts of interest to declare.

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

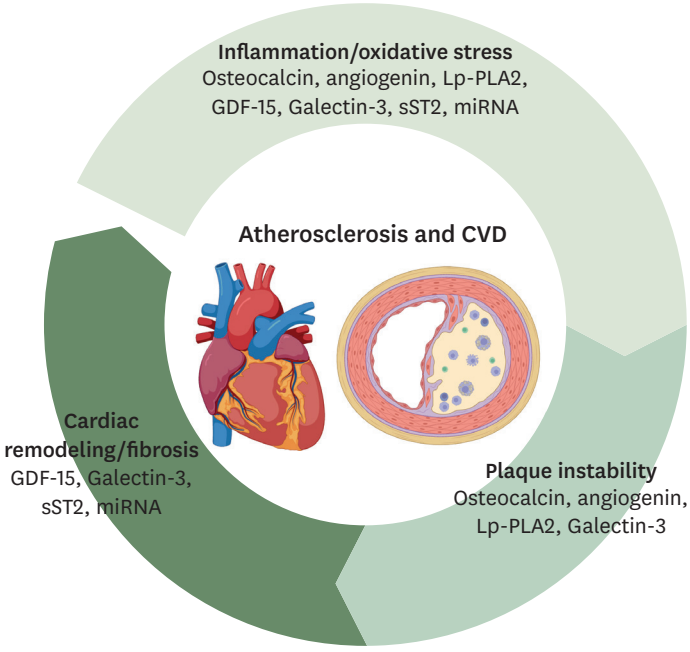

Fig. 1. Diverse functions of biomarkers in atherosclerosis pathophysiology and cardiovascular disease.
This figure provides a schematic representation of the progression of atherosclerosis and cardiovascular disease, highlighting the specific biomarkers discussed in this review. Osteocalcin, angiogenin, Lp-PLA2, GDF-15, Galectin-3, sST2, and miRNAs have been associated with inflammation and oxidative stress. Additionally, osteocalcin, angiogenin, Lp-PLA2, and Galectin-3 have been linked to plaque instability. Finally, GDF-15, Galectin-3, sST2, and miRNAs are involved in the progression of CVD.
Lp-PLA2, lipoprotein-associated phospholipase A2; GDF-15, growth differentiation factor 15; *ST2*, growth stimulation-expressed gene 2; CVD, cardiovascular disease.

potential novel biomarkers associated with diverse aspects of CVD, including inflammation, oxidative stress, plaque instability, cardiac remodeling, and fibrosis. Notably, we excluded well-established markers, such as brain natriuretic peptide (BNP), cardiac troponin, high-sensitivity C-reactive protein (hsCRP), and interleukin (IL)-6.

Our focus is predominantly on a broad range of CVDs, specifically coronary artery disease (CAD), acute coronary syndrome (ACS), acute myocardial infarction (AMI), and heart failure (HF).

The cardiovascular biomarkers reviewed in this article are summarized in **Fig. 1**.

OSTEOCALCIN (OC)

OC, also known as bone gamma-carboxyglutamic acid-containing protein, is a hormone primarily synthesized by osteoblasts. OC is initially synthesized as a precursor protein and later processed into its uncarboxylated form (uOC) as well as the carboxylated form (cOC), which facilitates calcium deposition in the bone matrix and inhibits bone resorption by osteoclasts. During the bone resorption process, cOC can revert to uOC and an undercarboxylated OC isoform (ucOC) following decarboxylation.[6] The differential impacts of OC isoforms on metabolism and atherosclerosis remain to be elucidated.[7-9]

Traditionally, OC has been acknowledged for its involvement in the regulation of bone mineralization by influencing the activity of chondrocytes and osteoblasts. However, beyond

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its bone-related functions, OC exerts diverse effects on glucose and lipid metabolism, contributing to aspects implicated in vascular calcification and atherosclerosis.[10,11]

OC has been identified as crucial in the process of vascular calcification. Triggered by oxidative stress, vascular smooth muscle cells may undergo a transformation into osteoblast-like cells, initiating osteogenic activities that elevate OC levels.[12] OC is recognized for its ability to inhibit apoptosis in endothelial cells triggered by free fatty acids, and this effect is mediated through the phosphatidylinositol 3-kinase/Akt signaling pathway.[13] On the other hand, OC can promote the proliferation of endothelial progenitor cells (EPCs), which are beneficial in the regeneration of vascular endothelium in patients with atherosclerosis.[14] Previous studies have suggested that EPCs can mitigate atherosclerotic alterations and may assist in distinguishing between clinically stable and unstable atherosclerotic disease.[15] A low count of EPCs has been associated with peripheral vascular disease and diabetes.[16]

OC has also been implicated in the regulation of glucose and lipid metabolism. Studies have shown that mice lacking OC can accumulate excessive visceral fat and exhibit reduced pancreatic beta-cell proliferation, resulting in conditions such as hyperglycemia, decreased insulin secretion, and insulin resistance.[17] Additionally, administration of OC to wild-type mice has been found to notably alleviate adverse effects on glucose metabolism and fat accumulation.[18] The suggested underlying mechanisms for this association involve the upregulation of adiponectin expression in adipocytes[17,18] and the specific role of the ucOC isoform in pancreatic beta cells and adipocytes.[19-21]

Reduced OC levels have been independently associated with a higher risk of future diabetes in Asians.[20,22] Additionally, lower OC levels have been correlated with the presence of atherosclerosis or atherosclerotic plaques in diverse populations, including individuals with type 2 diabetes mellitus.[23-26]

In contrast, the occurrence of carotid plaque markedly diminishes with higher OC levels, a relationship that persists even after accounting for conventional CVD risk factors in middle-aged and elderly males with normal glucose tolerance.[26]

Regarding the association with incident CVD or mortality outcomes in population-based studies, the results have been inconclusive. In the Health In Men Study, which included 3,542 community-dwelling elderly men, serum OC levels were shown to have a U-shaped association with all-cause and CVD-related mortality.[27] On the contrary, a different study that tracked 1,290 middle-aged and elderly men over 8.7 years observed no notable correlation between serum OC levels and the occurrence of CVD.[28]

Before serum OC can be considered a cardiovascular biomarker, several issues need to be addressed: the standardization of OC measurement, whether total serum OC or specific OC isoforms are more indicative, and the establishment of specific protocols are required.[29-31]

ANGIOGENIN

Angiogenin, an extracellular protein and a member of the ribonuclease superfamily (RNase 5), is recognized as among the strongest angiogenic factors.[32] It engages with endothelial cells and smooth muscle cells, instigating the generation of new blood vessels, thereby contributing

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to the destabilization of coronary plaques.[33] Angiogenin is implicated in a range of processes, including tumorigenesis, inflammation, tissue regeneration, and innate immunity.[33]

Angiogenesis is intimately associated with atherosclerosis.[34,35] Angiogenin works in conjunction with vascular endothelial growth factor to promote angiogenesis within the core of atherosclerotic plaques.[36] The resultant microvessels, which are fragile and unsupported by vascular smooth muscle cells, are susceptible to rupture, potentially leading to occlusive thrombosis and ACS.

Moreover, angiogenin can interact with proteases, such as the metalloproteinase family that mediates wound healing, and it can stimulate tissue plasminogen activator to generate plasmin, further contributing to plaque destabilization.[37,38] High levels of angiogenic factors, including angiogenin (≥400 ng/mL), have been proposed as potential indicators of plaque instability in ACS and as risk markers for future ACS events.[36] In a study comparing 107 patients with three-vessel CAD to 15 controls, those with CAD exhibited significantly higher angiogenin levels.[39] Furthermore, elevated angiogenin levels have been associated with advanced CAD, as indicated by higher Gensini scores (the Gensini scoring system quantifies angiographic atherosclerosis severity, and a score of 0 signifies the absence of atherosclerotic disease).[39]

The association between angiogenin levels and HF has also been documented. Jiang et al. reported a positive correlation between angiogenin and NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels.[40] Elevated angiogenin levels (≥426 ng/mL) were correlated with an increased risk of all-cause mortality in individuals with HF and preserved ejection fraction, as well as with poorer outcomes.[40] In a cohort of 109 men with congestive HF and 112 control patients, angiogenin concentrations were elevated in the congestive HF group relative to controls.[41] Angiogenin demonstrated a positive correlation with age, plasma glucose, insulin, and BNP levels. Elevated angiogenin levels were predictive of adverse events, including death, during the follow-up period.

LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 (LP-PLA2)

Lp-PLA2 is an enzyme that hydrolyzes platelet-activating factor and oxidized phospholipids in low-density lipoproteins (LDLs).[42] At present, Lp-PLA2 levels serve as a biomarker indicating vulnerability to atherosclerosis and vascular inflammation, aiding in the prediction of forthcoming cardiovascular events.[43] The enzyme is chiefly produced by macrophages and monocytes and is bound predominantly to LDL or high-density lipoprotein (HDL) cholesterol, with a small fraction unbound. Its expression is induced by oxidized LDL, apolipoprotein CIII, serum amyloid A, and leukocytes but downregulated by nitro-oleic acid.[44]

Lp-PLA2 has dual roles in inflammation, contingent on the type of lipoprotein it is associated with.[45] When bound to LDL, Lp-PLA2 has pro-atherogenic and pro-inflammatory effects; on the other hand, Lp-PLA2 associated with HDL exerts anti-inflammatory and anti-atherogenic actions.[45] Lp-PLA2 is predominantly bound to LDL in the circulation.

The involvement of LDL-associated Lp-PLA2 in the pathogenesis of atherosclerosis is as follows.[46] The hydrolysis of oxidized LDL initiates an inflammatory cascade, inducing chemotaxis of monocytes and leukocytes and promoting their entry into the sub-intimal areas of arterial walls, resulting in foam cell and fatty streak formation.[46-48] Muscle cells

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migrating to the intima contribute to stabilizing the atherosclerotic plaque by producing collagen and elastin.[47] Additionally, lysophosphatidylcholine, a byproduct of oxidized LDL, can enhance the production of reactive oxygen species. Cholesterol-lowering drugs and substances, such as statins, omega-3 fatty acids, and ezetimibe, can decrease both Lp-PLA2 activity and LDL cholesterol levels.[46] On the other hand, HDL-bound Lp-PLA2 reduces endothelial adhesiveness and macrophage recruitment.[47] In patients with metabolic syndrome, LDL-Lp-PLA2 levels are elevated, whereas HDL-Lp-PLA2 levels are diminished.[45] Previous studies have also indicated increased Lp-PLA2 levels in individuals with a history of CVD or HF.[47] These factors contribute to the recognition of Lp-PLA2 as a promising biomarker for atherosclerosis in asymptomatic patients.[46]

Epidemiological studies have reported a significant association between traditional cardiovascular risk factors and Lp-PLA2 levels in the general population.[49-52] Lp-PLA2 levels have been positively associated with the risk of coronary events in both the MONICA (MONItoring of trends and determinants in CArdiovascular disease) and Rotterdam studies, independent of non-HDL cholesterol levels.[53-55] In the Rancho Bernardo Study, which included 1,077 older adults followed for 16 years, increased Lp-PLA2 levels (≥488.5 ng/mL) were independently associated with coronary heart disease (CHD), even after adjusting for hsCRP levels.[55] A meta-analysis of 32 prospective studies with 79,036 participants found that both the activity and mass of Lp-PLA2 were significantly associated with the risk of CHD and vascular death, comparable to systolic blood pressure or non-HDL cholesterol.[49] Additionally, combining Lp-PLA2 (>200 ng/mL) with hsCRP (>3 mg/L) may aid in predicting the risk of CAD and stroke.[56]

However, several other prospective studies have reported contradictory findings.[57] In the Atherosclerosis Risk in Communities (ARIC) study, elevated Lp-PLA2 levels were linked to an increased 6-year risk of CHD only in subjects with LDL cholesterol levels below 130 mg/dL.[57] A recent Swedish cohort study found no association between Lp-PLA2 levels and a 12.8-year risk of CHD events.[58]

Moreover, data on the prognostic value of Lp-PLA2 levels in non-Caucasian populations are limited, suggesting a need for further research in this area.[59-61] Overall, Lp-PLA2 appears to be a marker of the processes contributing to plaque formation, but its clinical significance requires additional investigation.

GROWTH DIFFERENTIATION FACTOR 15 (GDF-15)

GDF-15 is a cytokine that belongs to the transforming growth factor β superfamily. It has been considered a strong biomarker for various comorbidities.[62,63] GDF-15 activation is associated with p53, which is involved in inflammation, oxidative stress, and oncogene activation.[62] Consequently, GDF-15 levels are elevated in macrophages within atherosclerotic plaques[64] and have been well-established as related to the risk of malignancy and malignancy-associated mortality.[62] In CVD, GDF-15 has emerged as a robust predictor for CVD, HF, and CVD-related mortality.[65]

Previous studies have demonstrated a GDF-15 level ≥1,200 ng/L to be a strong indication of 1-year mortality risk in 2081 patients with non-ST elevation myocardial infarction (non-STEMI),[66] and in 741 patients with STEMI.[67] In populations with stable angina pectoris (n=1,352) or ACS (n=877), GDF-15 >1,800 ng/L remained an independent predictor of 3.6-year

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Table 1. Studies evaluating the association of Lp-PLA2, GDF-15, and ST2 in various cardiovascular diseases

Variables	Population	CHD	Stroke	MACE	HF	Vascular death	All-cause mortality	References
Lp-PLA2	General population	✓	✓			✓		49,53,55,57
	Patients with CVD	✓				✓		49,54
GDF-15	General population				✓	✓	✓	65,70
	Patients with CVD			✓		✓	✓	66-69
	Patients with HF						✓	71
ST2	Patients with CVD			✓	✓		✓	72-74,78
	Patients with HF						✓	75-78

MACEs were determined as a composite of all-cause mortality, nonfatal events, such as acute coronary syndrome, or unplanned revascularization treatment.
Lp-PLA2, lipoprotein-associated phospholipase A2; GDF-15, growth differentiation factor 15; ST2, growth stimulation expressed gene 2; CHD, coronary heart disease; MACE, major adverse cardiovascular event; HF, heart failure.

CHD mortality, even after adjustments for cardiac troponin I and NT-proBNP.[68] Additionally, in a prospective study involving 3641 patients with CAD followed for a median of 6.4 years, elevated GDF-15 levels exceeding 1800 ng/L were linked to an increased risk of major adverse cardiovascular events (MACEs) and all-cause mortality.[69]

In a cohort from the Framingham Heart Study involving 3523 participants, GDF-15 was found to be associated with incident HF (hazard ratio [HR], 2.08), CVD death (HR, 1.96), and all-cause mortality (HR, 1.96).[70] Additionally, in 5010 patients with symptomatic HF, GDF-15 was shown to independently prognosticate mortality.[71] In **Table 1**,[49,53-55,57,65-78] a comparison of the clinical impact of GDF-15, Lp-PLA2, and ST2 was presented.

Despite its significance, the use of GDF-15 as a biomarker for CVD in the general population is challenging owing to its lack of cardiac specificity.[79]

GALECTIN-3

Galectin-3 is a member of the galectin family, which is involved in processes such as healing, fibrosis, immunity, inflammation, and malignancy. Intracellularly, galectin-3 is implicated in cellular growth, differentiation, and apoptosis, and extracellularly, it can stimulate the growth and differentiation of T and B cells.[80] Galectin-3 has diverse roles in various organs, including those within the cardiovascular, renal, hepatic, and pulmonary systems.[80,81] As a biomarker, galectin-3 has been identified as a marker of cardiac fibrosis, along with growth stimulation expressed gene 2 (ST2) and BNP.[82]

In the context of atherosclerosis, galectin-3 is known to be upregulated in unstable plaques, potentially attracting monocytes and exacerbating inflammation.[83] The ARIC study revealed a positive association between elevated galectin-3 levels and increased mean carotid intima-media thickness, as well as the presence of carotid plaque or shadowing.[84]

While there is less extensive evidence for CAD, galectin-3 (≥6.18 ng/mL) is significantly associated with both the presence and severity of CAD.[85] Wang et al.[86] reported an association between galectin-3 and myocardial infarction (MI) size, left ventricular hypertrophy, and potentially cardiovascular mortality.[82] A recent meta-analysis investigating the link between galectin-3 levels and the occurrence of MACEs following an MI revealed a significant negative association between galectin-3 and left ventricular ejection fraction (LVEF). Additionally, higher galectin-3 levels showed a significant predictive value for MACEs and all-cause mortality.[78]

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Galectin-3 can predict adverse cardiovascular outcomes such as increased severity and mortality in patients with chronic HF[82] and AMI.[87] In patients post-AMI, a decrease in galectin-3 levels at follow-up was associated with the absence of subsequent clinical endpoints, such as additional MI, percutaneous coronary intervention (PCI), coronary artery bypass grafting, stroke, hospitalization, or death.[88] An elevated galectin-3 concentration exceeding 9.2 ng/mL at discharge was associated with an increased risk of experiencing the composite endpoint during long-term follow-up.[88] In a population-based incident MI cohort with a mean follow-up of 5.4 years, patients in the highest tertile of galectin-3 had a 2.4-fold higher risk of death and a 2.3-fold higher risk of HF, independent of troponin T levels.[89] Consequently, in conjunction with soluble ST2 (sST2), galectin-3 has been recommended as a prognostic marker in patients with HF.[90]

Additionally, galectin-3 has been associated with right ventricular function, atrial fibrillation, and pulmonary hypertension.[82] Despite some inconsistent findings and the clinical implications of serial galectin-3 measurements, when combined with BNP, galectin-3 can differentiate patients with preserved left ventricular function based on their risk profile.[82]

For galectin-3 to be adopted as a biomarker, its utility in serial measurements and its diagnostic value for cardiac disorders must be substantiated.

GROWTH STIMULATION EXPRESSED GENE 2

Growth stimulation-expressed gene 2 (ST2), a receptor for IL-33, is a member of the IL-1 receptor family located on chromosome 2q12.1. It is also referred to as IL1RL-1, DER4, T1, and FIT-1.[91] It is important not to confuse this with products of the gene *ST2* (suppression of tumorigenicity-2; 11p14.3-p12), which are linked to several malignancies and have been reclassified as "serum stimulation-2."[92] Of the four ST2 isoforms, the transmembrane ST2 and sST2 are the most studied in relation to cardiac and inflammatory diseases.[92] When cells undergo damage and experience mechanical stress, the IL-33/ST2 system is triggered to increase its activity in both cardiomyocytes and fibroblasts. This activation initiates an anti-inflammatory pathway, potentially diminishing myocardial fibrosis and offering cardio-protective effects.[92-94] Conversely, sST2 can act as a decoy receptor, diminishing the availability of IL-33 to bind to transmembrane ST2.[93]

Increased sST2 concentrations are linked to an increased risk of MACEs, all-cause mortality, and HF in individuals with CAD. Elevated serum levels of sST2 have demonstrated a significant ability to predict upcoming MACEs in the ACS population.[95] In a study involving 379 patients undergoing PCI for STEMI, higher levels of sST2 (>11.6 ng/mL) were observed in the no-reflow group.[96]

In patients with HF, concentrations of sST2 have been demonstrated to be associated with future CVD incidence in ACS patients, as well as with the severity, myocardial stretch, and inflammation in individuals experiencing acute HF.[93] In chronic HF, elevated sST2 levels are found in patients with diabetes, indicative of left ventricular stiffness, and are associated with poorer clinical outcomes. Additionally, sST2 levels are elevated in individuals experiencing HF with reduced left ventricular function compared to those with preserved LVEF, and these concentrations are associated with prognosis.[93]

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Considering the extensive evidence highlighting the significance of sST2 in cardiac fibrosis and adverse cardiovascular outcomes, sST2 has been recommended as a prognostic biomarker in patients with HF.[90]

However, its use as a diagnostic biomarker is limited, as elevated sST2 levels have been observed in a variety of noncardiac disorders, including pulmonary and immune diseases.[95] Additionally, noncardiac secretion of sST2 from the colon and various hematopoietic cells has been documented.[97,98]

microRNAs

In the human genome, over two-thirds of genes are responsible for encoding RNAs that do not translate into proteins, collectively referred to as non-coding RNAs (ncRNAs).[99,100] A diverse array of ncRNAs has been identified over the years, encompassing long ncRNAs, circular RNAs, small nuclear RNAs, small nucleolar RNAs, ribosomal RNAs, heterogeneous nuclear RNAs, and transfer RNAs.[101] The biological roles of ncRNAs, which are pivotal in regulating gene expression and genome organization, have garnered considerable attention, with some being considered candidates for circulating biomarkers in CVD.[102] Among these, microRNAs (sometimes abbreviated miRNAs or miRs) have shown strong associations with CVD.

Ranging from 18–25 nucleotides in length, miRNAs primarily regulate gene expression by binding to the 3′ or 5′ untranslated regions of messenger RNA.[103,104] To date, 2654 miRNAs have been identified in humans.[105] Additionally, miRNAs are implicated in mediating inflammation, oxidative stress, apoptosis, cardiac remodeling, and fibrosis.[106] Prior research has indicated that altered expression levels of miRNAs are associated with the development of atherosclerosis and CVD.[107] In a clinical context, microRNAs hold promise as biomarkers for CVD screening, prediction, severity assessments, and prognostication, as illustrated in **Fig. 2** and **Table 2**.[108-126]

Numerous studies have underscored the importance of miRNA in predicting or diagnosing cardiovascular events.[108,127,128] Wang et al.[108] demonstrated that miRNA-208a offers high accuracy in identifying the presence of AMI, with its levels rising within one hour of occlusion in 90% of AMI patients tested, reaching 100% within four hours. Liu et al.[109] reported a notable increase in plasma levels of miR-1, miR-208, and miR-499 in patients with AMI compared to the control group. Receiver operating characteristic curve analyses showed miR-208 and miR-499 to be more reliable biomarkers for AMI screening than miRNA-1.[109] Furthermore, Liu et al.[110] suggested that combining miRNA-208a with miRNA-370 may offer more diagnostic accuracy for CAD than either miRNA alone. The analysis by Condrat et al.[129] highlighted the upregulation of miRNA-1, miRNA-133a, miR-208a/b, and miRNA-499 shortly after ACS.

Additionally, miRNA-1 and miRNA-133a play crucial roles in early cardiogenesis by influencing cardiac conductance, automaticity, and action potential in the heart. Notably, miRNA-1 exacerbates oxidative stress and increases apoptosis.[130-132] miRNA-133a is associated with positive effects on angiogenesis, inflammation, fibrosis, hypertrophy, apoptosis, and cardiac remodeling in infarcted cardiomyocytes.[133-136] miRNA-133a levels are elevated in patients with an occluded infarct-associated artery after MI.[112,121,137,138] Circulating levels of miRNA-1 and miRNA-133a rise earlier than creatine phosphokinase or cardiac troponin T following the onset of chest pain.[111]

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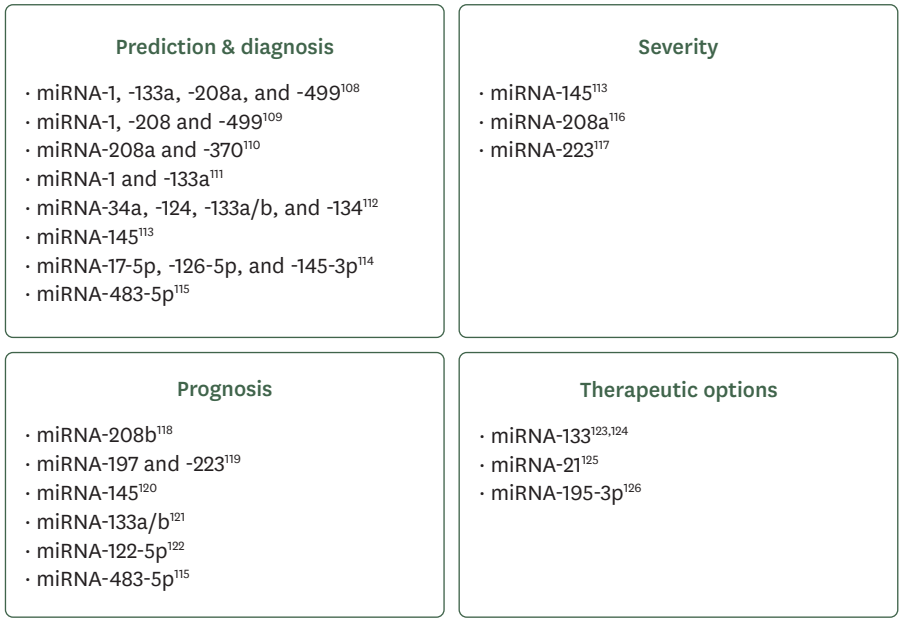

Fig. 2. Influence of miRNAs on various aspects of the pathogenesis of cardiovascular disease.
This figure categorizes miRNAs based on their roles in cardiovascular disease, including prediction and diagnosis, assessment of severity, determination of prognosis, and identification of therapeutic options.
miRNA, microRNA.

Chen et al. concluded that eight miRNAs (miRNA-1, miRNA-21, miRNA-126, miRNA-133, miRNA-145, miRNA-208, miRNA-223, and miRNA-499) have demonstrated significant clinical value as biomarkers for CAD.[128] Significantly, miRNA-126 is recognized for its role in inhibiting the formation of atherosclerotic lesions by suppressing the Notch1 inhibitor delta-like 1 homolog.[139] In an analysis of the circulating miR-17-5p, miR-126-5p, and miR-145-3p in 29 patients with AMI and 21 matched controls, plasma miR-17-5p, miR-126-5p, and miR-145-3p were significantly increased in AMI patients, and those levels showed considerable diagnostic efficiency for AMI.[114] Of 195 individuals who underwent coronary angiography for chest pain, the expression of miRNA-145 in plasma was downregulated in patients with CAD compared to the non-CAD group.[113]

Recently, serum miR-483-5p has garnered attention as a potential diagnostic marker for ACS and predictor of post-PCI adverse cardiac events. Higher levels of miR-483-5p have been identified in patients with ACS, with an association between miR-483-5p levels and the severity of the condition, as estimated by SYNTAX and Gensini scores, thereby differentiating AMI from ACS. Furthermore, miR-483-5p levels can predict the risk of MACEs after PCI.[115]

While the number of studies investigating diagnostic properties has been limited, a few studies on this topic have evaluated the severity of CVD. In patients with CAD, lower levels of miRNA-145 are associated with the severity of coronary lesions.[113] In two studies in China, Gensini scores reflecting the severity of coronary stenotic lesions were significantly associated with miRNA-208a and miR-223 expression in the analysis of individuals with and without CHD.[116,117] In patients with systolic dysfunction and cardiac remodeling, miRNA-122 upregulation has been demonstrated.[122]

Interestingly, miRNAs can serve as biomarkers for predicting cardiovascular-related prognoses. In a multicenter study of 1,155 patients presenting with acute chest pain, plasma

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Table 2. Comprehensive overview of research on microRNA implications in cardiovascular health, excluding meta-analyses

Function	miRNAs as candidates	Patients/disease	Findings	Year	Reference
Diagnosis	miRNA-1, miRNA-133a, miRNA-208a, miR-499	33 patients with AMI 33 non-AMI patients with chest pain	Plasma levels of all four miRNAs in patients with AMI were substantially higher than those from healthy people, patients with non-AMI coronary heart disease, and patients with other cardiovascular diseases.	2010	Wang et al.[108]
Diagnosis	miR-1, miR-208, miR-499	70 AMI patients 72 healthy controls	The expression of plasma miR-1, miR-208, and miR-499 were all significantly elevated in AMI patients compared with controls. From ROC analysis, the summary estimates of miR-1, miR-208, and miR-499 were 0.73, 0.80, and 0.83 for sensitivity, 0.82, 0.95, and 0.90 for specificity, and 0.84, 0.89, and 0.91 for AUC, respectively.	2015	Liu et al.[109]
Diagnosis	miR-208a, miR-370	95 CAD patients and 50 non-CAD control subjects	The plasma levels of miR-208a and miR-370 were significantly higher in the CAD group than in the control group. In ROC analysis, the largest AUC was associated with the combination of miRNA-208a and miRNA-370.	2016	Liu et al.[110]
Diagnosis	miRNA-1, miRNA-133a	29 patients with ACS 42 patients with non-ACS	Serum levels of miR-1 and miR-133a increased rapidly in patients with ACS. Serum miR-133a level was sensitive for myocardial injury compared with miR-1 level.	2011	Kuwabara et al.[111]
Diagnosis	miR-1, miR-16, miR-34a, miR-122, miR-124, miR-208b, miR-133a/b, miR-375, miR-499	43 patients with ACS	Patients with infarct-associated arterial occlusion had significantly higher levels of circulating miR-34a, miR-124, miR-133a/b, and miR-134.	2016	Gacon et al.[112]
Diagnosis	miR-145	167 patients with CAD 28 in the non-CAD group	Ln_miRNA-145 was significantly lower in CAD patients compared with the non-CAD group.	2015	Gao et al.[113]
Diagnosis	miR-17-5p, miR-126-5p, and miR-145-3p	29 patients with AMI and 21 matched control	The expression levels of plasma miR-17-5p, miR-126-5p, and miR-145-3p were significantly increased in AMI patients.	2019	Xue et al.[114]
Diagnosis	miR-483-5p	118 patients with ACS and 75 healthy controls	Serum miR-483-5p was effective in identifying ACS patients from healthy individuals (AUC=0.919) and AMI patients from ACS patients (AUC=0.867). A higher prevalence of MACEs was observed in patients with elevated miR-483-5p (p=0.01).	2023	Zhao et al.[115]
Severity	miR-145	167 patients with CAD 28 in the non-CAD group	Three-vessel disease, higher SYNTAX scores, and STEMI were significantly associated with lower Ln_miRNA-145.	2015	Gao et al.[113]
Severity	miR-208a	290 CHD patients and 110 subjects without CHD	Gensini score reflecting the severity of coronary stenotic lesions was significantly associated with miRNA-208a expression (r=0.853, p<0.001).	2017	Zhang et al.[116]
Severity	miR-223	300 CHD patients and 100 subjects	Gensini score was significantly associated with miR-223 expression (r=0.729, p<0.001).	2018	Guo et al.[117]
Prognosis	miR-208b	1155 patients with acute chest pain	Levels of miR-208b were higher in patients who died within 30 days.	2013	Devaux et al.[118]
Prognosis	miR-126, miR-197, miR-223	Large prospective cohort of 873 patients with CAD	Elevated levels of miRNA-197 and miRNA-223 reliably predicted future cardiovascular death. HRs (95% CI) per 1 SD of miRNA-197 and miRNA-223 were 1.77 (1.20–2.60) and 2.23 (1.20–4.14), respectively.	2015	Schulte et al.[119]
Prognosis	miR-145	246 patients with first STEMI who underwent PCI	Circulating miR-145 was a significant independent predictor of MACEs (HR [95% CI] was 7.17 [4.21–12.23]) and cardiac death (HR [95% CI] was 5.63 [1.99–15.91].	2015	Dong et al.[120]
Prognosis	miR-1, miR-133a/b and miR-208	47 patients who had died from MI	miRNA-133a/b levels were downregulated in patients with incident VF after MI.	2018	Bostjancic et al.[121]
Prognosis	miR-122-5p, miR-26a, miR-192, miR-483-5p, miR-720, miR-885-5p, and miR-1274	180 patients after Transcatheter aortic valve replacement	Aortic valve stenosis increased circulating miR-122-5p, which correlated with a lack of improvement of the left ventricular ejection fraction in patients after TAVR.	2022	Hosen et al.[122]
Prognosis	miR-483-5p	118 patients with ACS and 75 healthy controls	miR-483-5p was also an effective predictor of MACE occurrence (HR, 5.955; 95% CI, 1.928–18.389; p=0.002).	2023	Zhao et al.[115]
Therapeutic	miR-133	-	Increasing miR-133 levels using treatments such as carvedilol and hydrogen sulfide (H_2S) can protect cardiac remodeling.	2014 2012	Mishra et al.[123] Xu et al.[124]
Therapeutic	miR-21	Pig model of heart failure	Anti-miRNA-21 therapy led to reducing cardiac hypertrophy and fibrosis	2020	Hinkel et al.[125]
Therapeutic	miR-195-3p	AMI mouse models	Inhibiting miR-195-3p was found to suppress myofibroblast differentiation and collagen deposition, thereby providing protection to cardiac function.	2023	Carvalho et al.[126]

miRNA, microRNA; AMI, acute myocardial infarction; ROC, receiver operating characteristic; AUC, area under the curve; CAD, coronary artery disease; ACS, acute coronary syndrome; MACE, major adverse cardiovascular event; SYNTAX score, synergy between PCI with taxus and cardiac surgery score; STEMI, ST-segment elevation myocardial infarction; CHD, coronary heart disease; HR, hazard ratio; CI, confidence interval; SD, standard deviation; PCI, percutaneous coronary intervention; VF, ventricular fibrillation; TAVR, transcatheter aortic valve replacement.

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miRNA-208 levels were elevated in those with CAD and related to 30-day mortality after adjustment for age and sex.[118] In the large AtheroGene study cohort of 873 patients with CAD, elevated levels of miRNA-197 and miRNA-223 were reliable predictors of future cardiovascular death.[119] Dong et al.[120] demonstrated that miRNA-145 could predict the 1-year incidence of MACEs and cardiovascular death after AMI. In an analysis of 47 patients who died from MI, miRNA-133a/b levels were downregulated in patients with incident ventricular fibrillation after MI.[121] Additionally, there is an inverse correlation between miRNA-122 levels and the lack of improvement in LVEF following transcatheter aortic valve replacement.[122] miRNA-122 promotes endothelial cell apoptosis and reduces cardiomyocyte viability by inhibiting the anti-apoptotic protein Bcl-2 expression.[140] A recent study showed that miR-483-5p is also an effective predictor of MACE occurrence.[115]

With extensive evidence of their various impacts on CVD, miRNAs have been suggested as the basis of novel therapeutic strategies.[141] In the case of miR-133, which is known to suppress cardiac remodeling, there have been various approaches to increase miR-133 levels using treatments such as carvedilol, choline supplements, adiponectin, and hydrogen sulfide.[123,124,142] Recent studies using a pig model have shown that anti-miRNA-21 therapy improves cardiac function following ischemia–reperfusion injury, leading to reduced cardiac hypertrophy and fibrosis.[125] The role of miRNA-21 in cardiac fibrosis has been emphasized in a mouse model of pressure overload–induced disease; silencing of miRNA-21 has been shown to reduce hypertrophy and fibrosis, helping to restore impaired cardiac function.[143] Carvalho et al.[126] used MI mouse models to illustrate that MI induces elevated levels of miR-195-3p. Moreover, inhibiting miR-195-3p was found to suppress myofibroblast differentiation and collagen deposition, thereby protecting cardiac function.

However, despite numerous findings linking miRNAs with CVD, there are several challenges when considering miRNAs as cardiovascular biomarkers for public use. Given the heterogeneous nature of miRNA regulation across cell types, there is variability in the significance of miRNA levels in CVD.[108,127,128] Quantification of miRNAs is primarily performed by real-time quantitative polymerase chain reaction assays, which are expensive, time-consuming, and can be confounded by antiplatelet drugs or even a single injection of heparin.[144,145] Additionally, current miRNA assays exhibit lower sensitivity compared to protein-based biomarkers.[146]

CONCLUSIONS

This review highlights several biomarkers that can enhance the prediction of CVD risk when combined with established biomarkers or when used independently. A multi-omics approach appears promising for identifying individuals with the highest risk of cardiovascular events. We anticipate that these efforts will facilitate the integration of multidimensional molecular data throughout life, improving the precision of CVD risk prediction.

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