Scholars LITERATURE

International Journal of Integrative Cardiology

Review Article

DOI: https://doi.org/10.47275/2690-862X-148
Volume 7 Issue 1

A Systematic Review on Novel Biomarkers and Multiple-Marker Approach for Cardiovascular Diseases and their Clinical Applications

Gaddam Harshiini Reddy[1*], Akshina Reddi[2], Aashrita Divakar Gurram Sri[3] and Kalamalla Rohin Sai[4]

[1]Kakatiya Medical College, Warangal, Telangana, India

[2]NRI Medical College, NRI Institute of Medical Sciences, Visakhapatnam, Andhra Pradesh, India

[3]Kasturba Medical College, Manipal, Karnataka, India

[4]Apollo Medical College, Apollo Institute of Medical Sciences, Hyderabad, Telangana, India

Abstract

In spite of several efforts to prevent and treat atherosclerosis, cardiovascular disease (CVD) remains a major cause of morbidity and mortality worldwide, and its prevalence is expected to rise in the coming years. A marked reduction in mortality rates for coronary heart disease (CHD) has been observed in western countries over the last few decades, thanks to improvements in acute care and prevention strategies; however, both CVD prevalence and mortality have exponentially increased in low- and middle-income countries over the same period, likely due to globalization. World-wide, CVD cause the majority of deaths and disabilities. A primary prevention strategy for CVD relies on identifying high-risk individuals early on. The need for accurate risk stratification is evident here. Biomarkers that predict cardiovascular events are becoming more prevalent. In CVD management, biomarkers play a critical role in defining, prognosticating, and making decisions. Several promising biomarkers are reviewed here that provide diagnostic and prognostic information. It is possible to diagnose myocardial infarction (MI) in the early hours following symptoms by using the myocardial tissue-specific biomarker cardiac troponin, high-sensitivity cardiac troponin assays and heart-type fatty acid binding protein. The presence of inflammation markers such as growth differentiation factor-15, high-sensitivity C-reactive protein, fibrinogen, and uric acid can predict the risk of MI and death. Myeloperoxidase, matrix metalloproteinases, and plasma protein A associated with pregnancy predict the risk of acute coronary syndrome. The authors also explored papers mentioning some emerging areas, such as micro-RNA assessment. Each biomarker represents a different aspect of atherosclerosis development. Also, CVD is also a comorbidity for several chronic diseases, including type 2 diabetes mellitus (T2DM), chronic kidney disease, and chronic obstructive pulmonary disease. Therefore, biomarkers appear to be the most convenient option for screening and monitoring CVD patients. Ideally, a biomarker should be widely available, inexpensive, and reliable. This purpose has been served by several biomarkers over the past few decades, and several others are currently being developed. In specific populations, these biomarkers are used to predict cardiovascular risk. According to our knowledge, no biomarker for CVD is routinely used or scientifically validated in the general population and does not appear in cardiovascular risk scores. In order to spread knowledge about novel biomarkers that can be used to predict and/or manage cardiovascular risk, we proposed a review topic for analyzing previously published data systematically in order to draw robust conclusions regarding the potential use of biomarkers in CVD research.

Keywords: Cardiovascular disease, Prediction, Biomarker

[*]***Correspondence to:*** Gaddam Harshiini Reddy, Kakatiya Medical College, Warangal, Telangana, India.

Citation: Reddy GH, Reddi A, Sri ADG, Sai KR (2025) A Systematic Review on Novel Biomarkers and Multiple-Marker Approach for Cardiovascular Diseases and their Clinical Applications. Int J Integr Cardiol, Volume 7:1. 148. DOI: https://doi.org/10.47275/2690-862X-148

Received: November 19, 2024; **Accepted:** January 06, 2025; **Published:** January 09, 2025

Introduction

Globally, CVD causes the greatest number of deaths and disabilities. As a result of conventional CVD risk factors, such as hypertension, diabetes, smoking, and hypercholesterolemia, risk prediction models and therapies have been developed [1]. However, some patients with coronary disease have no traditional risk factors, and majority have only one. The limited predictive value of current risk-assessment models restricts the implementation of such strategies in a cost-effective manner [2, 3]. As a part of this review, we discuss ongoing research into novel risk biomarkers to enhance CVD risk-stratification metrics and improve prevention strategies. Biomarkers are measures of biological signs that can be quantified and reproduced [4-6]. The term refers to a characteristic that can be objectively measured and evaluated as an indication of a physiological process, a pathogenic process, or a response to a therapeutic intervention. There are three criteria that must be met for biomarkers to be useful: accuracy: that is, identifying individuals at risk; reliability: ensuring that results are stable when repeated; and therapeutic impact with early intervention [7]. Using the keywords "biomarker" and "CVD" or "acute coronary syndrome" or "MI" or "heart failure (HF)", we conducted a systematic search on PubMed, Web of Science, and Scopus without applying date restrictions. Biomarkers that are emerging and on the horizon were manually selected in the myocardial necrosis, inflammation, plaque instability, platelet activation, myocardial stress, and neurohormonal activation categories and those traditional proinflammatory molecules were excluded [8, 9] [Figure 1].

Biomarkers of MI

Cardiac troponin

In striated muscle, troponin is a complex of three globular

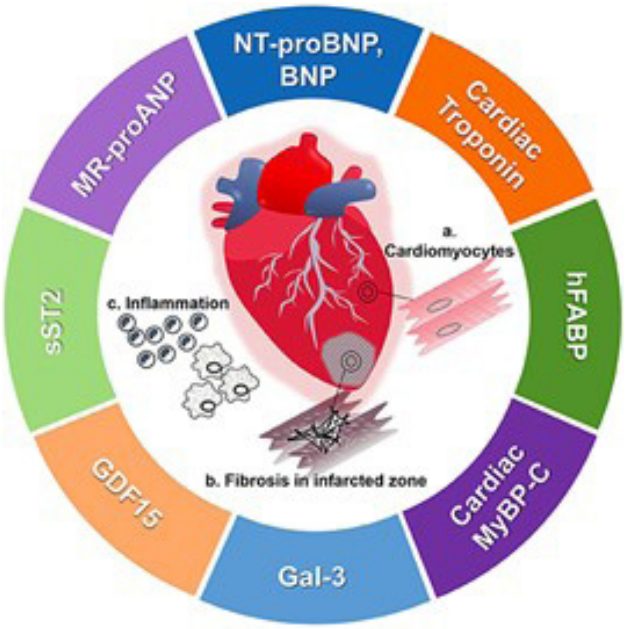

Figure 1: Protein biomarkers [10].

contractile regulatory proteins (troponin T, I, and C) which are positioned at regular intervals in the thin filament [11]. They inhibit contraction by blocking the interaction between actin and myosin. The cardiac troponin I protein (cTnI) and the cardiac troponin T protein (cTnT) are biomarkers of myocardial damage that are specific and sensitive [2, 12-16]. As skeletal muscles and cardiac muscles contain different cTnT and cTnI molecules, they can be used as cardiac biomarkers. In skeletal muscle and cardiac muscle, troponin C can be found in type 2 fibers; therefore, it is difficult to use it as a cardiac marker. cTnI and cTnT are released from necrotic myocardium during acute MI (AMI). In peripheral blood, cTn indicates cardiomyocyte damage and quantifies it [17]. Compared to creatine kinase (CK), CK-MB, and myoglobin, cardiac troponins are more sensitive and specific markers of cardiomyocyte injury. Myocardial ischemia can be diagnosed based on a dynamic elevation of cardiac troponin above the 99th percentile of healthy individuals. Due to delayed increases in circulating levels, conventional cTn assays are relatively insensitive at the time of AMI presentation, requiring serial sampling for 6 - 9 h in many cases [18-21].

High-sensitivity cardiac troponin: As a result of technological advancements, cTn assays have become more accurate in detecting and quantifying cardiomyocyte damage. Troponin assays have recently been improved to be more sensitive [22]. Due to the development of these hs-cTn assays, cTn has evolved from a marker used only in the acute diagnosis of disease to one that can detect ongoing myocardial injury in even seemingly healthy individuals. Hs-cTn and sensitive cTn assays differ from conventional cTn assays in that they detect cTn in a greater number of healthy people and they define "normal level" more precisely (the 99th percentile) [23-25]. The levels of cardiac troponin rise rapidly after the onset of AMI symptoms, usually within one hour if high-sensitivity assays are used, and they remain elevated for a variable period. Multiple large multicenter studies have consistently demonstrated that sensitive cTn and hs-cTn assays increase the accuracy of AMI diagnosis in emergency departments. In a recent study of patients with diabetes mellitus and stable coronary artery disease (CAD), high-sensitivity troponin was found to be associated with 5-year outcomes [26]. A significant, consistent association was found between baseline circulating cTnT concentrations and the risk of death, MI, stroke, and HF in patients with type 2 diabetes and stable CAD. As a result of these results, the hs-cTn assay is an excellent tool for assessing the risk of diabetes and CAD [3, 27-29].

Biomarkers of Inflammation

Fibrinogen

During the first half of the nineteenth century, fibrinogen was discovered and described as the first clotting factor. When acute inflammation occurs, fibrinogen levels can exceed 7 mg/mL, which is an acute phase protein synthesized in the liver. Additionally, it contributes to platelet aggregation, endothelial injury, viscosity of plasma, and thrombosis [30-34]. Incidence of CVD is increased by elevated fibrinogen levels. In a study, more than 154 thousand participants without known CVD from 31 research papers were assessed for their fibrinogen concentration and their risk of both major vascular and non-vascular outcomes. Results showed that fibrinogen concentrations were associated with CAD, strokes, and mortality [35]. An analysis of 53 prospective studies involving above two lakh participants without a history of CVD was conducted in the ERFC study, which revealed that CRP or fibrinogen concentrations significantly improved cardiovascular event prediction, when 300 people are screened for CRP or fibrinogen levels over a 5 year period, one additional cardiovascular event could be prevented [36]. Asymptomatic low-risk individuals are not allowed to be measured for fibrinogen in ESC guidelines for CVD prevention in clinical practice.

High sensitivity C-reactive protein and uric acid

As an innate immune response protein, CRP belongs to the pentraxin family. There has been extensive research on CRP in association with CVD and it is itself implicated in atherothrombosis pathogenesis [2, 37]. A correlation was found between CRP and cardiovascular events, independent of other cardiovascular risk factors, in the Women's Health Study and Physicians' Health Study, conducted in healthy women and men, respectively. CRP levels below 5mg/L will be stratified into low, intermediate, and high-risk patients. Patients classified as intermediate or high risk will benefit from aggressive treatment [38]. Additionally, higher CRP levels during percutaneous coronary intervention (PCI) are associated with higher 10-year mortality and MI rates. According to ESC guidelines, hsCRP may be measured in patients with unusual or moderate cardiovascular risks as part of a refined risk assessment. Despite its direct association with cardiovascular events, hsCRP is unlikely to cause CVD, even though recent research has confirmed CRP's predictive capability [39-44].

Purine metabolism in human's results in the production of Uric Acid (UA). Increasing UA levels and inactivating uricase are believed to have provided evolutionary advantages by protecting against oxidative damage. Increasing oxidative stress, promoting endothelial dysfunction, and enhancing inflammation are all associated with hyperuricemia, even below the clinical threshold for hyperuricemia [45]. UA has been independently associated with cardiovascular mortality in recent studies. The results are, however, still conflicting. There has been no independent association between UA and CVD in numerous epidemiological studies, including prospective, retrospective, cross-sectional, and meta-analyses. A study of 90 thousand Taiwanese showed that hyperuricemia was an independent risk factor of cardiovascular death over an eight-year period [46]. The Mendelian Randomization study reported that an increased UA concentration has a modest association with sudden cardiac death regardless of traditional risk factors. There is a causal relationship between high UA and adverse cardiovascular outcomes, especially sudden cardiac death. Those with prevalent type 2 diabetes, hypertension, or CAD history have also

shown positive associations [47].

Biomarkers of Plaque Instability/Rupture

Myeloperoxidase

A member of the heme peroxidase family, MPO is produced by polymorphonuclear leukocytes, neutrophils, and monocytes during inflammatory conditions. A macrophage expressing MPO can activate MMP, inhibit TIMP, and induce LDL oxidation by releasing hypochlorous acid, oxidizing ApoA-I, and reducing cholesterol efflux. Plaques are considered to be ruptured and formed by MPO [48]. According to Yunoki and co-authors, MPO levels are significantly inversely related to paraoxonase-1 levels bound to high density lipoprotein, which suggests that a mismatch between antioxidants and pro-oxidants may lead to coronary plaque instability, especially in patients with stable and unstable angina pectoris. It was first reported in 2022 that MPO levels were associated with CAD risk. A multimarker approach was employed to stratify patients with ACS based on circulating MPO concentrations in the CAPTURE trial, conducted by Baldus and co-authors. According to Nicholls and co-authors, MPO concentrations are predictive of cardiovascular events up to 16 hours after chest pain [49]. Although leukocyte activation and MPO release occur initially, it seems that MPO can only be used for risk stratification in the early stages of chest pain. In summary, some findings in papers published do not provide evidence that MPO directly causes adverse clinical outcomes, thus MPO cannot be used to identify patients at MI risk. There are still studies needed to determine MPO's actual role, and its routine measurement is not recommended in any clinical setting.

Pregnancy-associated plasma protein

PAPP-A belongs to the metzincin superfamily of matrix metalloproteinases, which bind zinc. In pregnant women, the placenta produces this hormone. It can contribute to atherogenesis and plaque instability by stimulating insulin-derived growth factor-1 activation [50].

Based on two preliminary studies, patients with suspected ACS were found to have recurrent ischemic events when their PAPP-A concentration increased, independent of TnI. The increased risk of cardiovascular events among patients with stable and unstable CAD has been associated with elevated levels of PAPP-A in clinical studies. An analysis of 3782 patients with ACS paired with a contemporary sensitive assay for cTnI found a significant association between PAPP-A and cardiovascular death [51-53]. ACS risk stratification can therefore be performed with the help of circulating PAPP-A biomarkers. For the first time, a 3-vessel virtual histology (VH)-intravascular ultrasound (IVUS) study found a link between high PAPP-A levels and high 3-vessel thin-cap fibroatheroma burden in CAD patients. As a result, PAPP-A may be useful as a serum biomarker for predicting increased plaque instability and thin-cap fibroatheroma burden in the coronary arteries [54].

Matrix metalloproteinases

MMPs are a family of endopeptidases produced by inflammatory and tumor cells as zymogens and then activated by proteinases. Intimal thickening is a process that stabilizes plaques and destroys extracellular matrix, which causes plaque rupture [55]. Atherosclerotic plaque rupture and clinical events are caused by degrading fibrillar collagen, degrading denatured collagen MMP-2, MMP-8, and MMP-9, which degenerate structural components of the plaque matrix. The activity of tissue inhibitors of MMP is inhibited by these antagonists. Despite their association with cardiovascular death, HF, or both, TIMP-1 and MMP-9 do not seem to be associated with recurrent MI [56]. As a predictor of all-cause mortality in the post-ACS population, MMP-2 is also elevates following a MI. The presence of elevated MMP-2 activity in plaques is associated with an increased risk of subsequent ischemic cerebrovascular events. As opposed to MMP-2, MMP-8 is associated with an unstable plaque phenotype in the carotid artery. There is a correlation between high MMP-8 levels in carotid plaques and a systemic cardiovascular outcome [57].

Markers of Platelet Activation

Secretory phospholipase A2 and lipoprotein-associated phospholipase A2

In this family of enzymes, sPLA2 consists of 10 disulfide-rich isoenzymes with low molecular mass, the largest group. These are sPLA2-IB, -IIA, -IIC, -IID, -IIE, -IIF, -III, -V, -X, and -XIIA, and these isoenzymes play a variety of roles in biology. Among the sPLA2s, sPLA2-IIA, sPLA2-V, and sPLA2-X have been identified in atherosclerotic lesions and in regions with ischemic heart disease [58]. Atherosclerosis and inflammation may be enhanced by this enzyme by retaining lipoprotein with vascular proteoglycans, activating platelets through the proteinoid pathway, and facilitating oxidation of LDL. Higher circulating levels of sPLA2-IIA and increased sPLA2 activity have been associated with an increased risk of incident and recurrent cardiovascular events (cardiovascular death, AMI, and stroke) [59-61]. In patients with ACS, varespladib did not significantly reduce the risk of recurrent cardiovascular events, and it significantly increased the risk of MI. The clinical value of measuring sPLA2 levels is unclear which needs to be determined in further studies.

The Lp-PLA2 enzyme belongs to the superfamily of phospholipases A2. Monocytes and macrophages are mainly responsible for producing it [62-64]. Lp-PLA2 modifies the surface of LDL particles during phospholipid hydrolysis, which increases their susceptibility to oxidation. A cascade of inflammatory factors is triggered when Lp-PLA2 and lyso-phosphatidylcholine are released in response to LDL oxidation. In the sub-intimal space, lysophosphatidylcholine and oxidized fatty acids accumulate, contributing to the formation of plaque lipid cores and macrophage foam cells [2, 65, 66]. It is suggested that Lp-PLA2 activity contributes to the formation of vulnerable plaques and the development of ACS. It has been shown that elevated Lp-PLA2 levels are associated with an increased cardiovascular risk regardless of other covariates, however, the additional clinical utility of this biomarker is unknown. An Lp-PLA2 inhibitor has not shown any clinical benefit in stable or unstable CAD patients in two large-scale randomized trials [68-69]. It appears that this biomarker may be less useful for predicting cardiovascular risk based on these results. Thus, further studies are needed to determine whether Lp-PLA2 is causally related to CVD.

Biomarkers of Neurohormonal Activation

Mid-regional-proadrenomedullin (MR-proADM) and Copeptin

Adrenomedullin (ADM) was initially discovered in pheochromocytoma cells of the adrenal medulla, a 52-amino acid ringed peptide with C-terminal amidation. In response to physical stretch and specific cytokines, ADM acts as a potent vasodilator in the adrenal medulla, vascular endothelial cells, and the heart. As a result of pressure and volume overload, ADM levels in the heart will increase [70]. As ADM has a short half-life and binds to proteins, it is difficult to measure plasma levels. Measurements of MR-proADM, which is more stable and manufactured one-to-one with active ADM, can indirectly quantify this peptide. Zhang et al. [71] demonstrated that MR-proADM has a strong prognostic value for patients with HF after an AMI and is superior to NT-proBNP in risk prediction [71]. MR-proADM was

the only biomarker that significantly predicted cardiovascular death in unselected older emergency department patients. In addition, MR-proADM has an adverse effect on carotid intima-media thickness and brachial pulse pressure. Thus, MR-proADM may serve as a prognostic biomarker for subclinical CAD and early atherosclerotic plaque development. There is also a strong association between elevated MR-proADM plasma concentrations and classical cardiovascular risk factors as well as CAD. According to Haaf and co-authors, MR-proADM does not provide any clinical value in early diagnosis of AMI, but it does provide prognostic value for all-cause mortality. In spite of its promise to predict short-term prognosis, more data are needed before MR-proADM can be considered a prime-time clinical tool [3].

As with AVP, copeptin is a glycosylated 39-amino-acid peptide that is derived from pre-provasopressin (pre-proAVP). In contrast to AVP, copeptin is stable in plasma and has a half-life of days. It has been established that copeptin is a reliable biomarker for heart disease and a predictor of mortality instead of AVP. As an activator of the hypothalamus-pituitary-adrenal axis, copeptin is thought to be a novel hallmark. As a result, copeptin has received significant attention in clinical practice as a marker of cardiovascular events (including AHF, AMI, and stroke) and extracardiac conditions (including sepsis). Recently, Meuwese et al. [72] found that copeptin could predict CAD development and cardiovascular mortality in both diabetics and non-diabetics. There was a > 70% increase in death rates from CAD among subjects in the top quartile versus those in the bottom quartile. According to Boeckel, and co-authors, patients with an AMI exhibit a significant increase in copeptin, but not a direct release into the coronary circulation. It is therefore still unclear whether the heart contributes to the release of copeptin into the blood [72].

Biomarkers of Myocardial Dysfunction or Stress

Galectin-3 (Gal-3) and soluble decoy receptor (ST2)

An activated cardiac macrophage secretes Gal-3, a lectin-family glycoprotein-binding protein of 26 kDa. Atherogenesis is facilitated by its enhancement of phagocytosis, and it reverses the switch from inducible-nitric oxide synthase to arginase within plaques. Sawicki et al. [73] reported that plasma Gal-3 predicts cardiovascular death in high-risk coronary angiography patients. Inflammatory cascades following cardiac injury and pathways regulating cardiac contraction are also possible functions of Gal-3. Gal-3 is a useful biomarker for the diagnosis and prognosis of HF in patients with preserved ejection fraction, along with studies showing that galectin-3 expression is up-regulated in HF patients. CHF and AHF are both associated with elevated Gal-3 levels. In addition, Gal-3 was approved by the Food and Drug Administration in 2010 for use in risk stratification for HF. Gal-3 is not the only instrument that can be used to determine the prognosis of HF [73].

The ST2 receptor family consists of two types: a transmembrane receptor (ST2L) and a ST2. T-helper 2 (Th2) associated cytokines are produced as a result of its downstream effects, which include activation of Th2 cells. Higher plasma sST2 concentrations in patients with AMI, AHF, and CHF have been associated with an increased risk of mortality and nonfatal adverse cardiac events, such as worsening HF, recurrent MI, and stroke. Dieplinger and coauthors found increased sST2 provided complementary prognostic information to hs-cTnT and NT-proBNP for stable CAD patients. An analysis of a low-risk population found that sST2 is associated with higher all-cause and cardiovascular mortality. For patients with suspected or proven ACS, the appropriate ST2 upper reference limit remains unclear. Based on MERLIN-TIMI 36 data, the conventional value of 35 ng/mL might be acceptable, but whether gender-based thresholds are necessary remains unclear [74].

Neuregulin-1 (NRG-1) and Endothelin-1

Endothelial cells release NRG-1, a paracrine growth factor that binds to the ErbB receptors on nearby cardiac myocytes to promote cell growth, survival, and maintenance. A total of 15 different protein products have been identified as encoded by the NRG-1 gene. A majority of NRG-1 proteins are found in the heart, the most abundant of which is NRG-1 beta. Paracrine action of NRG-1 ligand is mediated by ErbB tyrosine kinase receptors. Oxidative stress, ischemia, and exercise are some of the cardiovascular stimuli that activate NRG-1 expression. Therefore, the NRG-1/ErbB4 paracrine signaling system is involved in cardiac adaptation to various types of physiologic stress [75].

A higher level of NRG-1 correlated with advanced stages of HF and a worse prognosis for HF patients with CAD. The circulating level of NRG-1 was inversely correlated with severity of CAD in an observational cohort of patients referred for PCI with stable CAD, and high in patients with positive stress tests for ischemia. Patients with HF also have poor outcomes when their serum levels of NRG are elevated. Similar to NT-proBNP, elevated serum NRG levels may be an inadequate physiologic response to cardiovascular damage, and exogenous NRG administration may be beneficial. A myocardial NRG-1 response to ischemia is consistent with these findings. NRG-1 may be a useful biomarker for CVD. Further study is needed [Figure 2].

Future perspectives

CVD is still one of the leading causes of morbidity and mortality worldwide, despite several efforts to prevent and treat it. As a result of improvements in acute care and prevention strategies, mortality rates for CHD have the prevalence and mortality of CVD have exponentially increased in low- and middle-income countries, likely as a result of globalization. The topic obtained a great success, since we reviewed good number of articles published. The Research Topics of the published articles covered many of the most important and prevalent CVD, from HF to light chain cardiac amyloidosis, pulmonary hypertension, AMI, etc. The biochemistry and roles of emerging novel biomarkers in relation to future cardiovascular events in individuals with and without CAD and their clear clinical utility have not yet been fully clarified. Due to this, it is difficult to draw specific conclusions from the current evidence about how a biomarker could affect the prognosis. Biomarkers can be combined to increase the accuracy of certain tests, but the optimal combination to diagnose or prognosis needs to be determined. Cardiovascular risk stratification is provided by GDF-15 and ST2 in patients with stable CAD or acute coronary syndrome. Evaluations of hsCRP, fibrinogen, or MPO may provide information beyond traditional risk factors for CVD. Moreover, the European guidelines consider

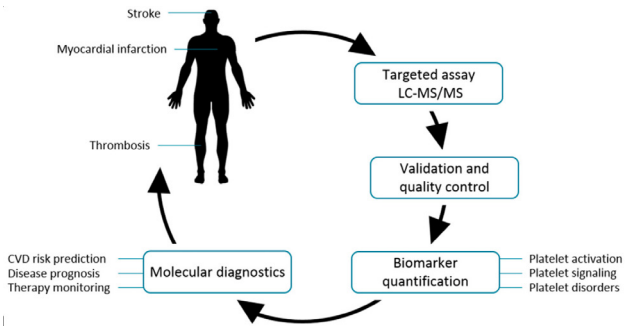

Figure 2: Potential CVD biomarkers by targeted proteomics [76].

NT-proBNP as equally useful for diagnosing HF as MR-proANP. All biomarkers work in conjunction with other clinical information such as history, physical examination, laboratory findings, and radiographic findings. While biomarkers have significantly improved our delivery of care, it is important to remember that they are only one part of the picture. Rather than being solely used as diagnostic aids, they must be interpreted within their clinical context. CAD has a multifactorial pathogenesis, which makes detailed risk stratification challenging. To better stratify risk, additional research is needed to identify new biomarkers and to determine if a multi-marker strategy of established and novel biomarkers is feasible. It is still early days for powerful new discovery platforms, such as genomics, proteomics, metabolomics, and lipidomic, but there is great potential for rapid development. It will be crucial to translate these discoveries into clinical practice in order to reduce the burden of CVD on the population.

Acknowledgements

None.

Conflict of Interest

None.

References

1. Davidson SM, Boulanger CM, Aikawa E, Badimon L, Barile L, et al. (2022) Methods for the identification and characterization of extracellular vesicles in cardiovascular studies: from exosomes to microvesicles. Cardiovasc Res 119: 45–63. https://doi.org/10.1093/cvr/cvac031
2. Kim SJ, Mesquita FCP, Hochman-Mendez C (2023) New biomarkers for cardiovascular disease. Tex Heart Inst J 50: e238178. https://doi.org/10.14503/THIJ-23-8178
3. Wang J, Tan GJ, Han LN, Bai YY, He M, et al. (2017) Novel biomarkers for cardiovascular risk predicion. J Geriatr Cardiol 14: 135-150. https://doi.org/10.11909/j.issn.1671-5411.2017.02.008
4. Piepoli MF, Corra U, Dendale P, Frederix I, Prescott E, et al. (2017) Challenges in secondary prevention after acute myocardial infarction: a call for action. Eur Heart J Acute Cardiovasc Care 6: 299–310. https://doi.org/10.1177/2048872616689773
5. Jenca D, Melenovsky V, Stehlik J, Staněk V, Kettner J, et al. (2021) Heart failure after myocardial infarction: incidence and predictors. ESC Heart Fail 8: 222–237. https://doi.org/10.1002/ehf2.13144
6. Dhingra R, Vasan RS (2017) Biomarkers in cardiovascular disease: statistical assessment and section on key novel heart failure biomarkers. Trends Cardiovasc Med 27: 123–133. https://doi.org/10.1016/j.tcm.2016.07.005
7. Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, et al. (2009) Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation 119: 2408–2416. https://doi.org/10.1161/CIRCULATIONAHA.109.192278
8. Wong YK, Tse HF (2021) Circulating biomarkers for cardiovascular disease risk prediction in patients with cardiovascular disease. Front Cardiovasc Med 8: 1-12. https://doi.org/10.3389/fcvm.2021.713191
9. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, et al. (2021) 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Rev Esp Cardiol 74: 544. https://doi.org/10.1016/j.rec.2021.05.002
10. Shrivastava A, Haase T, Zeller T, Schulte C (2020) Biomarkers for heart failure prognosis: proteins, genetic scores and non-coding RNAs. Front Cardiovasc Med 7: 601364. https://doi.org/10.3389/fcvm.2020.601364
11. Morrissey J, Mesquita FCP, Chacon-Alberty L, HochmanMendez C (2022) Mining the mesenchymal stromal cell secretome in patients with chronic left ventricular dysfunction. Cells 11: 2092. https://doi.org/10.3390/cells11132092
12. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, et al. (2018) Fourth universal definition of myocardial infarction (2018). Circulation 138: e618–e651. https://doi.org/10.1161/CIR.0000000000000617
13. Chaulin AM (2022) The importance of cardiac troponin metabolism in the laboratory diagnosis of myocardial infarction (comprehensive review). Biomed Res Int 2022: 6454467. https://doi.org/10.1155/2022/6454467
14. Chaulin AM (2022) False-positive causes in serum cardiac troponin levels. J Clin Med Res 14: 80–87. https://doi.org/10.14740/jocmr4664
15. Deranek AE, Baldo AP, Lynn ML, Schwartz SD, Tardiff JC (2022) Structure and dynamics of the flexible cardiac troponin t linker domain in a fully reconstituted thin filament. Biochemistry 61: 1229–1242. https://doi.org/10.1021/acs.biochem.2c00091
16. Kimenai DM, Janssen E, Eggers KM, Lindahl B, den Ruijter HM, et al. (2018) Sex-specific versus overall clinical decision limits for cardiac troponin I and T for the diagnosis of acute myocardial infarction: a systematic review. Clin Chem 64: 1034–1043. https://doi.org/10.1373/clinchem.2018.286781
17. Giannitsis E, Mueller-Hennessen M, Zeller T, Schuebler A, Aurich M, et al. (2020) Gender-specific reference values for high-sensitivity cardiac troponin T and I in well-phenotyped healthy individuals and validity of high-sensitivity assay designation. Clin Biochem 78: 18–24. https://doi.org/10.1016/j.clinbiochem.2019.11.013
18. Mitsis A, Kadoglou NPE, Lambadiari V, Alexiou S, Theodoropoulos KC, et al. (2022) Prognostic role of inflammatory cytokines and novel adipokines in acute myocardial infarction: an updated and comprehensive review. Cytokine 153: 155848. https://doi.org/10.1016/j.cyto.2022.155848
19. Lacy P, Stow JL (2011) Cytokine release from innate immune cells: association with diverse membrane trafficking pathways. Blood. 118: 9–18. https://doi.org/10.1182/blood-2010-08-265892
20. Ueland T, Gullestad L, Nymo SH, Yndestad A, Aukrust P, et al. (2015) Inflammatory cytokines as biomarkers in heart failure. Clin Chim Acta 443: 71–77. https://doi.org/10.1016/j.cca.2014.09.001
21. Kumar G, Dey SK, Kundu S (2020) Functional implications of vascular endothelium in regulation of endothelial nitric oxide synthesis to control blood pressure and cardiac functions. Life Sci 259: 118377. https://doi.org/10.1016/j.lfs.2020.118377
22. Schmitter D, Cotter G, Voors AA (2014) Clinical use of novel biomarkers in heart failure: towards personalized medicine. Heart Fail Rev 19: 369–381. https://doi.org/10.1007/s10741-013-9396-5
23. Canoui-Poitrine F, Luc G, Mallat Z, Machez E, Bingham A, et al. (2011) Systemic chemokine levels, coronary heart disease, and ischemic stroke events: the PRIME study. Neurology 77: 1165–1173. https://doi.org/10.1212/WNL.0b013e31822dc7c8
24. Rothenbacher D, Muller-Scholze S, Herder C, Koenig W, Kolb H (2006) Differential expression of chemokines, risk of stable coronary heart disease, and correlation with established cardiovascular risk markers. Arterioscler Thromb Vasc Biol 26: 194–199. https://doi.org/10.1161/01.ATV.0000191633.52585.14
25. Julian-Villaverde FJ, Serrano-Ponz M, Ramalle-Gomara E, Martinez A, Ochoa-Callejero L (2022) CCL5 levels predict stroke volume growth in acute ischemic stroke and significantly diminish in hemorrhagic stroke patients. Int J Mol Sci 23: 9967. https://doi.org/10.3390/ijms23179967
26. Matsuzaka Y, Yashiro R (2022) Advances in purification, modification, and application of extracellular vesicles for novel clinical treatments. Membranes 12: 1244. https://doi.org/10.3390/membranes12121244
27. Song M, Bai H, Zhang P, Zhou X, Ying B (2023) Promising applications of human-derived saliva biomarker testing in clinical diagnostics. Int J Oral Sci 15: 1-17. https://doi.org/10.1038/s41368-022-00209-w
28. Sharma S, Zuniga F, Rice GE, Perrin LC, Hooper JD, et al. (2017) Tumor-derived exosomes in ovarian cancer—liquid biopsies for early detection and real-time monitoring of cancer progression. Oncotarget 8: 104687–104703. https://doi.org/10.18632/oncotarget.22191
29. Lo Cicero A, Stahl PD, Raposo G (2015) Extracellular vesicles shuffling intercellular messages: for good or for bad. Curr Opin Cell Biol 35: 69–77. https://doi.org/10.1016/j.ceb.2015.04.013
30. Xu Y, Hu Y, Xu S, Liu F, Gao Y (2021) Exosomal microRNAs as potential biomarkers and therapeutic agents for acute ischemic stroke: new expectations. Front Neurol 12: 747380. https://doi.org/10.3389/fneur.2021.747380
31. Yi X, Chen J, Huang D, Feng S, Yang T, et al. (2022) Current perspectives on clinical use of exosomes as novel biomarkers for cancer diagnosis. Front Oncol 12: 966981. https://doi.org/10.3389/fonc.2022.966981
32. Narang P, Shah M, Beljanski V (2022) Exosomal RNAs in diagnosis and therapies. Noncoding RNA Res 7: 7–15. https://doi.org/10.1016/j.ncrna.2022.01.001
33. Zhang Z, Salisbury D, Sallam T (2018) Long noncoding RNAs in atherosclerosis:

JACC review topic of the week. J Am Coll Cardiol 72: 2380–2390. https://doi.org/10.1016/j.jacc.2018.08.2161

34. Ollen-Bittle N, Roseborough AD, Wang W, Wu JD, Whitehead SN (2022) Mechanisms and biomarker potential of extracellular vesicles in stroke. Biology 11: 1231. https://doi.org/10.3390/biology11081231
35. Chen Y, Song Y, Huang J, Qu M, Zhang Y, et al. (2017) Increased circulating exosomal miRNA-223 is associated with acute ischemic stroke. Front Neurol 8: 57. https://doi.org/10.3389/fneur.2017.00057
36. Yaghoubi S, Najminejad H, Dabaghian M, Karimi MH, Abdollahpour-Alitappeh M, et al. (2020) How hypoxia regulate exosomes in ischemic diseases and cancer microenvironment? IUBMB Life 72: 1286–1305. https://doi.org/10.1002/iub.2275
37. Gidlöf O, van der Brug M, Ohman J, Gilje P, Olde B, et al. (2013) Platelets activated during myocardial infarction release functional miRNA, which can be taken up by endothelial cells and regulate ICAM1 expression. Blood 121: 3908–3917. https://doi.org/10.1182/blood-2012-10-461798
38. Garcia A, Dunoyer-Geindre S, Zapilko V, Nolli S, Reny JL, Fontana P (2019) Functional validation of microRNA-126-3p as a platelet reactivity regulator using human haematopoietic stem cells. Thromb Haemost 119: 254–263. https://doi.org/10.1055%2Fs-0038-1676802
39. Hromadka M, Motovska Z, Hlinomaz O, Kala P, Tousek F, et al. (2021) MiR-126-3p and MiR-223-3p as biomarkers for prediction of thrombotic risk in patients with acute myocardial infarction and primary angioplasty. J Pers Med 11: 508. https://doi.org/10.3390/jpm11060508
40. Grabmaier U, Clauss S, Gross L, Klier I, Franz WM, et al. (2017) 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 244: 30–36. https://doi.org/10.1016/j.ijcard.2017.06.054
41. Sassi Y, Avramopoulos P, Ramanujam D, Grüter L, Werfel S, et al. (2017) Cardiac myocyte miR-29 promotes pathological remodeling of the heart by activating Wnt signaling. Nat Commun 8: 1614. https://doi.org/10.1038/s41467-017-01737-4
42. Surina S, Fontanella RA, Scisciola L, Marfella R, Paolisso G, et al. (2021) miR-21 in human cardiomyopathies. Front Cardiovasc Med 8: 767064. https://doi.org/10.3389/fcvm.2021.767064
43. Wang GK, Zhu JQ, Zhang JT, Li Q, Li Y, et al. (2010) Circulating microRNA: a novel potential biomarker for early diagnosis of acute myocardial infarction in humans. Eur Heart J 31: 659–666. https://doi.org/10.1093/eurheartj/ehq013
44. Huang XH, Li JL, Li XY, Wang SX, Jiao ZH, et al. (2021) miR-208a in cardiac hypertrophy and remodeling. Front Cardiovasc Med 8: 773314. https://doi.org/10.3389/fcvm.2021.773314
45. Zhang L, Chen X, Su T, Li H, Huang Q, et al. (2015) Circulating miR-499 are novel and sensitive biomarker of acute myocardial infarction. J Thorac Dis 7: 303–308. https://doi.org/10.3978%2Fj.issn.2072-1439.2015.02.05
46. JFO Sullivan, Neylon A, McGorrian C, Blake GJ (2016) miRNA-93-5p and other miRNAs as predictors of coronary artery disease and STEMI. Int J Cardiol 224: 310–316. https://doi.org/10.1016/j.ijcard.2016.09.016
47. Bei Y, Lu D, Bär C, Chatterjee S, Costa A, et al. (2022) miR-486 attenuates cardiac ischemia/reperfusion injury and mediates the beneficial effect of exercise for myocardial protection. Mol Ther 30: 1675–1691. https://doi.org/10.1016/j.ymthe.2022.01.031
48. Zhang MW, Shen YJ, Shi J, Yu JG (2021) MiR-223-3p in cardiovascular diseases: a biomarker and potential therapeutic target. Front Cardiovasc Med 7: 610561. https://doi.org/10.3389/fcvm.2020.610561
49. Bai R, Yang Q, Xi R, Li L, Shi D, et al. (2017) miR-941 as a promising biomarker for acute coronary syndrome. BMC Cardiovasc Disord 17: 227. https://doi.org/10.1186/s12872-017-0653-8
50. Lin J, Jiang J, Zhou R, Li X, Ye J (2019) MicroRNA-451b participates in coronary heart disease by targeting VEGFA. Open Med 15: 1–7. https://doi.org/10.1515/med-2020-0001
51. Ghafouri-Fard S, Gholipour M, Taheri M (2021) Role of microRNAs in the pathogenesis of coronary artery disease. Front Cardiovasc Med 8: 632392. https://doi.org/10.3389/fcvm.2021.632392
52. Hosen MR, Goody PR, Zietzer A, Xiang X, Niepmann ST, et al. (2022) Circulating microRNA-122-5p is associated with a lack of improvement in left ventricular function after transcatheter aortic valve replacement and regulates viability of cardiomyocytes through extracellular vesicles. Circulation 146: 1836–1854. https://doi.org/10.1161/CIRCULATIONAHA.122.060258
53. Zhong Z, Hou J, Zhang Q, Zhong W, Li B, et al. (2018) Circulating microRNA expression profiling and bioinformatics analysis of dysregulated microRNAs of patients with coronary artery disease. Medicine 97: e11428. https://doi.org/10.1097%2FMD.0000000000011428
54. Xue S, Liu D, Zhu W, Su Z, Zhang L, et al. (2019) Circulating MiR-17-5p, MiR-126-5p and MiR-145-3p are novel biomarkers for diagnosis of acute myocardial infarction. Front Physiol 10: 123. https://doi.org/10.3389/fphys.2019.00123
55. Li N, Zhou H, Tang Q (2018) miR-133: a suppressor of cardiac remodeling? Front Pharmacol 9: 903. https://doi.org/10.3389/fphar.2018.00903
56. Dai R, Liu Y, Zhou Y, et al. (2020) Potential of circulating proangiogenic microRNA expressions as biomarkers for rapid angiographic stenotic progression and restenosis risks in coronary artery disease patients underwent percutaneous coronary intervention. J Clin Lab Anal 34: e23013. https://doi.org/10.1002/jcla.23013
57. Zhang YN, Vernooij F, Ibrahim I, Ooi S, Gijsberts CM, et al. (2016) Extracellular vesicle proteins associated with systemic vascular events correlate with heart failure: an observational study in a dyspnoea cohort. PLoS One 11: e0148073. https://doi.org/10.1371/journal.pone.0148073
58. Verbree-Willemsen L, Zhang YN, Ibrahim I, Ooi SB, Wang JW, et al. (2020) Extracellular vesicle cystatin C and CD14 are associated with both renal dysfunction and heart failure. ESC Heart Fail 7: 2240–2249. https://doi.org/10.1002/ehf2.12699
59. Chen X, Luo Q (2022) Potential clinical applications of exosomes in the diagnosis, treatment, and prognosis of cardiovascular diseases: a narrative review. Ann Transl Med 10: 372. https://doi.org/10.21037%2Fatm-22-619
60. de Freitas RCC, Hirata RDC, Hirata MH, Aikawa E (2021) Circulating extracellular vesicles as biomarkers and drug delivery vehicles in cardiovascular diseases. Biomolecules 11: 388. https://doi.org/10.3390/biom11030388
61. Ellis BW, Ronan G, Ren X, Bahcecioglu G, Senapati S, et al. (2022) Human heart anoxia and reperfusion tissue (HEART) model for the rapid study of exosome bound miRNA expression as biomarkers for myocardial infarction. Small 18: e2201330. https://doi.org/10.1002/smll.202201330
62. Ahmad T, Fiuzat M, Pencina MJ, Geller NL, Zannad F, et al. (2014) Charting a roadmap for heart failure biomarker studies. JACC Heart Fail 2: 477–488. https://doi.org/10.1016/j.jchf.2014.02.005
63. Li J, Cao T, Wei Y, Zhang N, Zhou Z, et al. (2021) A review of novel cardiac biomarkers in acute or chronic cardiovascular diseases: the role of soluble ST2 (sST2), lipoprotein-associated phospholipase A2 (Lp-PLA2), myeloperoxidase (MPO), and procalcitonin (PCT) Dis Markers 2021: 6258865. https://doi.org/10.1155/2021/6258865
64. Lund J, Qin QP, Ilva T, Pettersson K, Voipio-Pulkki LM, et al. (2003) Circulating pregnancy-associated plasma protein a predicts outcome in patients with acute coronary syndrome but no troponin I elevation. Circulation 108: 1924–1926. https://doi.org/10.1161/01.cir.0000096054.18485.07
65. Heeschen C, Dimmeler S, Hamm CW, Fichtlscherer S, Simoons ML, et al. (2005) Pregnancy-associated plasma protein-a levels in patients with acute coronary syndromes: comparison with markers of systemic inflammation, platelet activation, and myocardial necrosis. J Am Coll Cardiol 45: 229–237. https://doi.org/10.1016/j.jacc.2004.09.060
66. Lund J, Qin QP, Ilva T, Nikus K, Eskola M, et al. (2006) Pregnancy-associated plasma protein a: a biomarker in acute ST-elevation myocardial infarction (stemi). Ann Med 38: 221–228. https://doi.org/10.1080/07853890500525883
67. Bonaca MP, Scirica BM, Sabatine MS, Jarolim P, Murphy SA, et al. (2012) Prospective evaluation of pregnancy-associated plasma protein-a and outcomes in patients with acute coronary syndromes. J Am Coll Cardiol 60: 332–338. https://doi.org/10.1016/j.jacc.2012.04.023
68. Wu XF, Yang M, Qu AJ, Mintz GS, Yang Y, et al. (2016) Level of pregnancy-associated plasma protein-a correlates with coronary thin-cap fibroatheroma burden in patients with coronary artery disease: novel findings from 3-vessel virtual histology intravascular ultrasound assessment. Medicine 95: e2563. https://doi.org/10.1097/md.0000000000002563
69. Nicholls SJ, Hazen SL (2005) Myeloperoxidase and cardiovascular disease. Arterioscler Thromb Vasc Biol 250: 1102–1111. https://doi.org/10.1161/01.atv.0000163262.83456.6d
70. Yunoki K, Naruko T, Inaba M, Inoue T, Nakagawa M, et al. (2013) Gender-specific correlation between plasma myeloperoxidase levels and serum high-density lipoprotein-associated paraoxonase-1 levels in patients with stable and unstable coronary artery disease. Atherosclerosis 231: 308–314. https://doi.org/10.1016/j.atherosclerosis.2013.08.037

71. Zhang R, Brennan ML, Fu X, Aviles RJ, Pearce GL, et al. (2001) Association between myeloperoxidase levels and risk of coronary artery disease. JAMA 286: 2136–2142. https://doi.org/10.1001/jama.286.17.2136

72. Meuwese MC, Stroes ES, Hazen SL, van Miert JN, Kuivenhoven JA, et al. (2007) Serum myeloperoxidase levels are associated with the future risk of coronary artery disease in apparently healthy individuals: the epic-norfolk prospective population study. J Am Coll Cardiol 50: 159–165. https://doi.org/10.1016/j.jacc.2007.03.033

73. Sawicki M, Sypniewska G, Kozinski M, Gruszka M, Krintus M, et al. (2011) Diagnostic efficacy of myeloperoxidase for the detection of acute coronary syndromes. Eur J Clin Invest 41: 667–671. https://doi.org/10.1111/j.1365-2362.2010.02457.x

74. Tang WH, Tong W, Troughton RW, Martin MG, Shrestha K, et al. (2007) Prognostic value and echocardiographic determinants of plasma myeloperoxidase levels in chronic heart failure. J Am Coll Cardiol 49: 2364–2370. https://doi.org/10.1016/j.jacc.2007.02.053

75. Cavusoglu E, Ruwende C, Eng C, Chopra V, Yanamadala S, et al. (2007) Usefulness of baseline plasma myeloperoxidase levels as an independent predictor of myocardial infarction at two years in patients presenting with acute coronary syndrome. Am J Cardiol 99: 1364–1368. https://doi.org/10.1016/j.amjcard.2006.12.060

76. Malchow S, Loosse C, Sickmann A, Lorenz C (2017) Quantification of cardiovascular disease biomarkers in human platelets by targeted mass spectrometry. Proteomes 5: 31. https://doi.org/10.3390/proteomes5040031