

Emerging Biomarkers in Cardiovascular Disease: Advances in Early Diagnosis and Novel Molecular Indicators

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Abstract

The global burden of cardiovascular disease (CVD) continues to rise, posing a major challenge to public health systems, particularly in low- and middle-income countries. Early diagnosis remains crucial for effective management and prevention of CVD-related morbidity and mortality. In this context, emerging biomarkers offer promising avenues for improving diagnostic precision and risk assessment. This review synthesizes recent findings from diverse medical and scientific sources to identify and evaluate novel biomarkers with diagnostic and prognostic potential in CVD. Biomolecules such as high-sensitivity cardiac troponins, natriuretic peptides, C-reactive protein, microRNAs, and novel omics-based markers have demonstrated significant utility in predicting disease onset and progression. These biomarkers provide molecular insights into underlying pathophysiological mechanisms, enabling earlier and more targeted intervention strategies. Additionally, integrating biomarker profiling with advanced bioinformatics and molecular diagnostics may further enhance personalized cardiovascular care. Overall, emerging biomarkers represent a transformative step toward redefining diagnostic frameworks and improving clinical outcomes in CVD management.

Keywords: Emerging biomarkers, Cardiovascular disease, Diagnostic markers, Cardiac troponins, MicroRNAs, Molecular diagnostics, Predictive medicine.

Introduction

Cardiovascular diseases (CVDs), including coronary artery disease (CAD), cerebrovascular disease (CD), and rheumatic heart disease (RHD), remain the leading non-communicable causes of morbidity and mortality worldwide. According to the World Health Organization, CVDs account for approximately 17.9 million deaths each year, representing about 31% of all global deaths, with coronary heart disease and stroke responsible for nearly 7.3 and 6.2 million fatalities, respectively. The mortality burden is projected to rise to 23.6 million deaths annually by 2030, primarily due to ischemic heart disease and cerebrovascular disorders. [1]

To counter this growing threat, the identification and utilization of reliable biomarkers have emerged as vital strategies for early diagnosis, prognosis, and disease monitoring. Cardiac biomarkers—biochemical molecules released into the bloodstream following myocardial injury or stress—provide critical insights into cardiac function and pathology. These molecular indicators, typically obtained through venous blood sampling, assist clinicians in evaluating cardiovascular risk, diagnosing acute coronary syndromes (ACS), and monitoring therapeutic outcomes.[2]

Despite significant advances, the availability of consistent and specific biomarkers for early-stage CVD detection remains limited. Therefore, exploring emerging biomarkers that exhibit strong diagnostic and prognostic value is essential for improving patient management and reducing global cardiovascular mortality [3].

Carbohydrate-Based Biomarkers

Glycogen Phosphorylase BB (GPBB)

The heart is particularly vulnerable to hypoxia caused by carbon monoxide (CO) exposure because of its high oxygen requirements. However, CO-related cardiac damage often goes unnoticed, as patients typically exhibit no distinct

symptoms or specific electrocardiogram (ECG) alterations. Therefore, there is an increasing need for early and specific biomarkers capable of detecting myocardial hypoxia.[4]

One promising candidate is the glycogen phosphorylase BB isoenzyme (GPBB), a relatively new cardiac biomarker that may enable the early identification of myocardial ischemia. Under conditions of low oxygen or glucose availability, GPBB plays a key role as the enzyme responsible for the initial, rate-limiting step in glycogen breakdown, converting it to glucose-1-phosphate.[5]

In humans, three isoforms of glycogen phosphorylase have been characterized: GPMM (found in skeletal muscle), GPLI (in the liver), and GPBB (in the brain and heart). Although markers such as myoglobin and ischemia-modified albumin (IMA) exhibit good sensitivity for ischemic events, they lack cardiac tissue specificity. In contrast, GPBB has demonstrated superior sensitivity and specificity for diagnosing acute coronary syndrome (ACS) within the first four hours following the onset of chest pain – reported at 81% and 93%, respectively.[6]

Studies indicate that GPBB is a valuable clinical biomarker for myocardial ischemia and can assist in diagnosing ACS. Despite the fact that GPBB levels may rise during pregnancy and are also detectable in the brain, making it not entirely cardiac-specific, plasma GPBB remains a useful surrogate marker for acute coronary syndromes in numerous investigations. Consequently, GPBB can serve as a secondary biomarker for the detection of acute myocardial infarction. [7,8]

Protein-Based Biomarkers

Aspartate Aminotransferase (AST)

Aspartate aminotransferase (AST), also known as a liver transaminase, is an intracellular enzyme that catalyzes transamination reactions between amino acids and keto acids. Although AST is predominantly located in hepatocytes and commonly used as a serum marker for liver injury, it is also found in the heart, skeletal muscles, brain, and kidneys. [9,10]

Historically, AST was the first enzyme identified as a potential cardiac biomarker in 1954. However, due to its lack of cardiac tissue specificity, it is not considered reliable for diagnosing acute myocardial infarction (AMI). Later developments introduced other enzymes such as creatine kinase (CK), which became a recognized indicator of muscle injury in 1959, and lactate dehydrogenase (LDH), which was applied to AMI diagnosis in 1960. By 1979, the World Health Organization (WHO) recommended a diagnostic panel combining CK, AST, and LDH for confirming AMI. [11]

LDH, or lactate dehydrogenase

Lactate dehydrogenase (LDH), an intracellular enzyme, which is readily available, catalyzes the transformation of pyruvic acid, the last byproduct of the glycolytic process, into lactate. As a sign of heart failure, LDH has been used to detect acute myocardial infarction since the 1960s. Five isozymes are produced by the two self-contained subunits that make up LDH. Every isozyme is expressed in a different organ:

Hepatocytes express LDH5, lung tissue contains LDH3, and cardiomyocytes express LDH1 [12, 13]. LDH is expressed by numerous organs, such as the kidney, liver, heart, lung, skeletal muscle, and erythrocytes. One of the five isoenzymes that make up LDH is present in nature.

It is currently not used to diagnose AMI, despite reports indicating an LDH1-to-LDH2 ratio greater than 1 is specific for AMI [14]. Nowadays, LDH is only utilized to distinguish between acute and subacute myocardial infarction (MI) in patients who have positive troponins and whose CK and CK-MB readings have returned to normal by the time they get to the hospital [15].

Carbonic anhydrase III (CA-III)

Carbonic anhydrases (CAs), the main protein components of red blood cells, are metalloproteins that include zinc, agents that quicken carbon dioxide's hydration and dehydration [16]. Numerous physiological processes, such as gluconeogenesis, acid-base homeostasis, adipogenesis, and

calcification, are carried out by CAs, which are present in a variety of tissues [17]. A distinct member of the CAs family, the CA-III protein is involved in a number of conditions, such as skeletal muscle damage, MI, and type-2 diabetes. The cytosolic enzyme CA-III protein is less active than carbon dioxide hydratase [18].

Creatine Kinase-MB (CK-MB)

CK-MB, an isoenzyme of creatine kinase, is predominantly expressed in cardiac muscle and released into circulation following myocardial cell necrosis. It has long been used as a biochemical marker for acute myocardial infarction (AMI). CK-MB typically rises 4–6 hours after myocardial injury, peaks within 24 hours, and normalizes in 48–72 hours. Despite its diagnostic value, CK-MB can also elevate in skeletal muscle injury and certain non-cardiac conditions, limiting its specificity. It remains useful when troponin assays are unavailable or when reinfarction is suspected. [19]

Cardiac Troponins (cTnI and cTnT)

Cardiac troponins are regulatory proteins that control cardiac muscle contraction and are highly specific to myocardial tissue. They are currently considered the gold standard for diagnosing AMI. Elevated levels of troponins indicate myocardial cell damage and correlate with infarct size and prognosis. High-sensitivity cardiac troponin (hs-cTn) assays allow detection of minute increases in circulating troponin concentrations, enabling diagnosis of myocardial injury even in the early stages or in chronic cardiac conditions such as heart failure. [20]

Hydroxybutyrate Dehydrogenase (HBDH)

HBDH, an isoenzyme of lactate dehydrogenase (LDH), was historically used in MI diagnosis before troponin testing became standard. Its elevation reflects tissue necrosis, including cardiac muscle injury. Although less specific than troponins, HBDH measurement can still support differential diagnosis of myocardial injury when used alongside other markers. [21]

Biomarkers of Neurohormonal Activation

Brain Natriuretic Peptide (BNP) and N-terminal pro-BNP (NT-proBNP)

BNP and its inactive fragment NT-proBNP are released from cardiac ventricles in response to increased wall stretch and volume overload. They are established markers for diagnosing and prognosticating heart failure (HF). Elevated BNP and NT-proBNP levels correlate with ventricular dysfunction, increased filling pressures, and mortality risk. Beyond HF, these peptides may also predict adverse outcomes in acute coronary syndromes and hypertensive heart disease. Their rapid measurement and high negative predictive value make them valuable in distinguishing cardiac from non-cardiac causes of dyspnea. [22]

Biomarkers of Inflammation and Immune Activation

C-Reactive Protein (CRP)

CRP is an acute-phase protein synthesized in the liver under the regulation of interleukin-6 (IL-6). High-sensitivity CRP (hs-CRP) assays can detect subclinical inflammation and have been shown to independently predict CVD risk. Elevated hs-CRP concentrations are associated with atherosclerotic plaque instability and increased risk of myocardial infarction, stroke, and cardiovascular mortality. CRP is thus a marker of systemic inflammation rather than direct myocardial injury. [23]

Interleukin-6 (IL-6)

IL-6 is a pleiotropic proinflammatory cytokine involved in endothelial activation, vascular inflammation, and atherogenesis. Elevated IL-6 levels correlate with CVD severity, plaque instability, and adverse cardiac remodeling after MI. IL-6 acts upstream of CRP synthesis, suggesting that IL-6 blockade could have therapeutic potential in attenuating inflammatory-driven cardiovascular events. [24]

Tumor Necrosis Factor-Alpha (TNF- α)

TNF- α contributes to the inflammatory cascade, promoting endothelial dysfunction, myocardial apoptosis, and

remodeling. Elevated TNF- α levels are observed in heart failure and coronary artery disease. While it is not a diagnostic marker, it provides mechanistic insight into inflammation-driven cardiac injury and may serve as a prognostic biomarker in chronic CVD and heart failure. [25]

Biomarkers of Oxidative Stress, Fibrosis, and Remodeling

Galectin-3

Galectin-3 is a β -galactoside-binding lectin secreted by activated macrophages that plays a key role in inflammation, fibrosis, and myocardial remodeling. Elevated plasma galectin-3 levels are associated with worsening heart failure and higher mortality. It has prognostic value independent of natriuretic peptides and can help identify patients at risk for progression of cardiac dysfunction. [26]

Pregnancy-Associated Plasma Protein-A (PAPP-A)

PAPP-A is a zinc-binding metalloproteinase that regulates insulin-like growth factor availability and is released by unstable atherosclerotic plaques. Elevated circulating PAPP-A levels have been linked to plaque rupture and acute coronary syndromes (ACS). It is considered a promising biomarker for early detection of plaque instability and subclinical atherosclerosis. [27]

Fibrinogen

Fibrinogen, a glycoprotein synthesized by the liver, plays a central role in coagulation and is an acute-phase reactant. Elevated plasma fibrinogen levels are associated with increased blood viscosity, platelet aggregation, and thrombus formation. High fibrinogen concentrations correlate with increased risk of myocardial infarction, stroke, and peripheral artery disease, making it a predictive biomarker of cardiovascular risk and inflammation. [28]

Biomarkers of Vasopressin Pathways and Stress Response

Copeptin

Copeptin is the C-terminal fragment of the vasopressin prohormone and is released in equimolar amounts with

arginine vasopressin (AVP). As AVP is unstable and difficult to measure, copeptin serves as a reliable surrogate marker. It rises rapidly after acute myocardial infarction and reflects endogenous stress responses, complementing cardiac troponin testing for early rule-out of AMI. Combined measurement of copeptin and troponin improves diagnostic accuracy in the emergency setting. [29]

Procalcitonin (PCT)

Procalcitonin, a precursor of calcitonin, is primarily a biomarker of bacterial infection and systemic inflammation but has recently been associated with adverse cardiovascular outcomes. Elevated PCT levels have been reported in heart failure, myocarditis, and post-infarction inflammation. It may reflect inflammatory activation secondary to myocardial injury rather than a direct cardiac biomarker, yet it can provide valuable prognostic information in patients with CVD and concurrent infection. [30]

Clinical Integration and Diagnostic Utility

The integration of emerging biomarkers into clinical practice requires demonstration of analytical validity, clinical validity, and clinical utility. Combining biomarkers that reflect different biological pathways—such as myocardial injury (troponin, CK-MB), neurohormonal activation (BNP/NT-proBNP, copeptin), inflammation (CRP, IL-6, TNF- α), and fibrosis (galectin-3, PAPP-A, fibrinogen)—can enhance diagnostic precision and prognostic assessment. Multi-marker strategies are particularly valuable in complex CVD phenotypes such as heart failure with preserved ejection fraction or microvascular angina, where single biomarkers may not suffice. [31]

Future Perspectives

Future biomarker development is likely to focus on multi-omics integration—combining genomic, proteomic, and metabolomic data with imaging and AI-based models to refine cardiovascular risk stratification. Emerging technologies such as high-sensitivity assays, machine learning-based pattern

recognition, and microRNA profiling will further enable precision cardiovascular medicine. Standardization, cost-effectiveness, and accessibility remain key challenges for widespread clinical adoption. [32]

Conclusion

Over the past decade, significant progress has been made in identifying promising biomarkers for cardiovascular disease (CVD) detection and management. Despite these advances, the pursuit of an ideal biomarker – one that is simultaneously predictive, diagnostic, and prognostic – remains ongoing. Emerging markers such as BNP, NT-proBNP, cardiac troponins, CRP, IL-6, TNF- α , galectin-3, copeptin, and PAPP-A have expanded the understanding of CVD pathophysiology by reflecting diverse mechanisms including myocardial stress, inflammation, and fibrosis.

An optimal biomarker should not only meet analytical and clinical validity standards but also provide actionable information to guide patient care. While several circulating molecules show strong potential, further validation through large-scale, multicenter studies is required before they can be fully integrated into clinical practice. The combination of traditional and emerging biomarkers in multi-marker strategies may improve early detection, risk stratification, and therapeutic monitoring.

Future research should focus on developing standardized, high-sensitivity analytical platforms and leveraging bioinformatics, artificial intelligence, and multi-omics technologies to discover and validate novel targets. With

continued innovation and collaboration, biomarker-driven precision medicine may transform cardiovascular care, offering earlier diagnosis, personalized treatment, and improved patient outcomes.

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