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Biomarkers in Cardiovascular Disease: Evolution, Clinical Utility and Future Directions.

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ABSTRACT:

Introduction: Cardiovascular diseases (CVDs) are the major reason for deaths worldwide, making early, precise, and cost-effective diagnosis an important requirement. In the last seven decades, cardiac biomarker development has transformed cardiovascular medicine by allowing timely disease identification, categorization, and monitoring. This review traces their historical evolution, current clinical applications, and future prospects.

Objectives: This review aims to comprehensively review the historical evolution, current clinical applications, and future prospects of cardiac biomarkers in cardiovascular disease management.

Methods: A comprehensive review of the literature was conducted to evaluate established and emerging cardiac biomarkers. The analysis includes early enzymatic markers, cardiac-specific biomarkers, natriuretic peptides, inflammatory and oxidative stress markers, and newly investigated molecular candidates relevant to myocardial injury, heart failure, and atherosclerosis.

Results: Early enzymatic markers such as aspartate aminotransferase, lactate dehydrogenase, creatine kinase, and CK-MB provided initial biochemical insights into myocardial infarction (MI), although their limited cardiac specificity restricted clinical utility. The introduction of cardiac troponins in the 1990s marked a major breakthrough, establishing them as the gold standard for diagnosing acute MI due to their superior sensitivity and specificity. Natriuretic peptides, particularly BNP and NT-proBNP, have become essential for diagnosis, risk stratification, and monitoring of heart failure. Emerging biomarkers, including early injury markers (myoglobin, heart-type fatty acid binding protein), stress markers (copeptin, cardiac myosin-binding protein C), inflammatory mediators (interleukin-6, tumor necrosis factor-α, high-sensitivity C-reactive protein, matrix metalloproteinase-9), oxidative stress markers (myeloperoxidase, oxidized LDL), and novel candidates like soluble ST2, growth differentiation factor-15, interferon-γ, provide deeper insight into the multifactorial pathophysiology of CVD. However, challenges such as assay variability, inconsistent predictive accuracy, and limited validation across diverse populations remain. Evidence increasingly supports multi-marker panel approaches over reliance on single biomarkers.

Conclusions: This review concludes that cardiac biomarkers, both established and emerging, are indispensable in reshaping cardiovascular care. Future research must prioritize large-scale validation, assay standardization, and clinical integration of multi-marker strategies to optimize outcomes in CVD management.

1. Introduction

Cardiovascular diseases (CVDs) are the major reason for adult deaths worldwide. According to a 2008 report by the WHO, nearly 17.3 million people succumbed to cardiovascular disease that year, which was around 30% of all deaths worldwide. Of these, about 7.3 million succumbed to coronary heart disease, and 6.2 million to stroke. Standard means of diagnosis include ECG, chest X-rays, cardiac catheterization, computed tomographic heart scans, and blood examinations. While initial treatment of myocardial ischemia aims at prevention of necrosis, its effectiveness relies heavily on timely diagnosis. Biomarkers are crucial in enhancing the diagnostic accuracy for diseases, and also for risk stratification and prognosis [1]. Arson and colleagues defined biomarker as a biological measure that serves as a stand-in for, and ideally forecasts, a clinically meaningful endpoint or an intermediate outcome that is harder to measure directly [2]. They're measurable biological variables that assess health or disease states, significantly influencing clinical outcomes. Optimal biomarkers are connected to clinical endpoints in disease-focused observational and clinical studies, and in some cases, they may act as surrogate endpoints. In addition, biomarkers ought to function independently of existing risk factors and be clearly associated with the disease they signify [3]. Cardiac biomarkers have become crucial in

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cardiology practice, but there is still much to learn that could benefit patients. Although the search for new and better markers for heart disorders is justified, most of it in the last decade has had limited clinical influence [4]. As CVD serves as the primary reason for mortality, identification of conventional factors like high cholesterol, blood pressure, diabetes, and smoking have improved primary prevention but the fatality rates persist [5]. Around 20% of those experiencing coronary disease lack traditional risk factors and 40% have only one. The cost-effective implementation of these strategies is hindered by the limited predictive accuracy of existing risk assessment models [6]. Recent scientific advancements have uncovered a wide array of new biomarkers linked to cardiovascular risks.

Table 1: Biomarkers for specific cardiovascular conditions

Condition	Key Biomarker	Clinical Relevance
Myocardial Infarction Heart Failure	Troponins, CK-MB, Myoglobin BNP, NT-Pro BNP	Diagnosis of MI, risk stratification. Severity assessment, prognosis.
Inflammation	CRP, IL-6, TNF-α	Indicators of systemic inflammation and cardiovascular risk.
Atherosclerosis	Ox-LDL, MPO, Interleukin-6, TNF-α	Inflammation markers, plaque instability.

myocardial infarction, heart failure, troponin, natriuretic peptides, inflammation, atherosclerosis, oxidative stress, novel biomarkers, and risk stratification. The selected literature was critically examined and organized into thematic sections reflecting the historical evolution of biomarker development, followed by disease-specific classification, including biomarkers related to myocardial infarction, heart failure, inflammation, atherosclerosis, and oxidative stress. Both established markers and emerging molecular candidates were analysed with respect to their diagnostic accuracy, prognostic relevance, pathophysiological significance, and clinical applicability. Studies were included based on scientific credibility, clinical relevance, and contribution to understanding the mechanistic and translational aspects of cardiovascular biomarker development. The collected evidence was synthesized to provide a comprehensive overview of past advancements, current clinical practice, and future directions in multi-biomarker strategies for cardiovascular disease management.

2. Objectives

Inflammation markers, plaque instability. prevention, diagnosing and managing AMI, and diagnosing and assessing the possibility of heart failure (HF). 6 decades earlier, in 1954, Karmen et al. first discovered that aspartate aminotransferase, earlier named glutamate oxaloacetate transaminase, is released as a result of cardiac cell death, which could be traced in the serum, aiding for AMI This review aims to comprehensively examine the historical evolution, clinical utility, and future directions of cardiac biomarkers in cardiovascular diseases, with emphasis on their diagnostic, prognostic, and risk stratification roles across myocardial infarction, heart failure, inflammation, atherosclerosis, and oxidative stress, and to evaluate the potential of emerging multi- biomarker strategies in improving precision-based cardiovascular care.

3. Methods

This study was designed as a structured narrative review to comprehensively evaluate the evolution, classification, and clinical utility of cardiac biomarkers in cardiovascular diseases. A detailed literature search was conducted using electronic databases including PubMed, PubMed Central, and Google Scholar. Relevant peer-reviewed original research articles, clinical trials, meta-analyses, and review papers published in English were retrieved using combinations of keywords such as cardiac biomarkers, evaluation. This marked the onset of enzyme based approaches in cardiology. The year 1955 marked lactate dehydrogenase (LDH) as the first reported AMI biomarker [7]. Though these markers were increased during AMI, they lacked cardiac specificity. Later, a direct enzyme based method for evaluating α-hydroxybutyrate dehydrogenase activity was established to enhance cardiac specificity. In the 1970s [8], Rosalki developed a reliable enzyme based approach for quantifying creatine kinase (CK) activity, establishing CK as the primary indicator for identifying muscle injury. CK served as the primary diagnostic tool for AMI for about 2 decades. The introduction of immunoinhibition methods for measuring CKMB activity on automated analyzers made this test popular. Although CK is less cardiac-specific, it is more specific than LDH for diagnosing AMI, particularly in individuals having comorbidities such as muscle or liver disease. In 1978, the first method to detect myoglobin, which increases post AMI damage in the serum, was developed. Today, in the high-

sensitivity cardiac troponin era, myoglobin testing is not currently advised as the initial indicator for myocardial necrosis. Eventually, advancements in electrophoresis enabled the identification of cardiac-related isoenzymes present in creatine kinase as well as lactate dehydrogenase (LDH). However, their deployment was limited because of poor specificity and a high likelihood of false-positive outcomes, which raised the demand for a more cardiac- specific biomarker. Emerging candidates such as cardiac myosin-binding protein C (cMyC), heart fatty acid-binding protein, ischemia-modified albumin, growth-differentiation factor-15, coeptin, F2 isoprostanes have since been investigated [9]. Initial studies on biomarkers like soluble

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ST2, growth differentiation factor-15, CD-40, interleukin-6, as well as mi-RNA suggest considerable potential for future application in cardiovascular diagnostics biomarkers. However, additional studies will be necessary to prove their effectiveness in investigating potential risks involved in cardiovascular disease progression. Additionally, they currently lack the robust analytical validation required for widespread adoption in clinical practice. Further research is essential to determine their utility in diagnosis [10].

Table 2: Evolution of cardiac biomarkers over time.

S.No.	Time Period	Biomarker
1	1954	Aspartate aminotransferase
2	1955	Lactate dehydrogenase
4	1970	Creatine kinase
4	1978	Myoglobin

3.1 Classification of cardiac biomarkers with respect to their disease states

3.21 Biomarkers related to myocardial infarction

AMI, commonly called heart attack, usually happens when the flow of blood to a region of the heart is distorted, which eventually leads to the loss of cardiac tissue. It usually occurs due to the presence of clots in the epicardial artery that supplies the particular region of the heart. Although it is now established that not every AMI case is related to blood clots, every living tissue, including heart muscle, must match the supply versus demand ratio. A disproportion in this fraction, for instance, very fast heart rate which increases the oxygen demand or low blood blood pressure which limits the supply can cause injury to the heart muscles even without a clot. Throughout much of the 20th century,

contribution of thrombosis to acute myocardial infarction remained controversial, until research in the 1970s conclusively responsible for almost all infarctions cases seen in autopsies and major infarction cases diagnosed in clinical settings. The buildup of arterial plaque and associated inflammatory response represent the leading mechanism responsible for thrombus formation. Dysfunction of the endothelium represents the central pathological feature of atherosclerosis. It represents a persistent inflammatory condition that targets the innermost layer of medium and large arteries and engages multiple cellular components, including endothelial cells, monocytes, macrophages, T- lymphocytes, smooth muscle cells as well as lipids and platelets [11].

Aspartate aminotransferase

In 1954, researchers found that aspartate aminotransferase, earlier called glutamate oxaloacetate transaminase, is secreted into the bloodstream from necrotic cardiac myocytes and may help in diagnosing AMI. This marked the first biomarker deployment for AMI diagnosis, although AST is no longer deployed presently owing to its lack of heart specificity. This discovery, however, initiated the era of enzyme-based diagnostics in cardiology. Just one year later, lactate dehydrogenase was recognized as another valuable biomarker for identification of AMI [12].

Lactate dehydrogenase

Lactate dehydrogenase (LDH) is found in multiple organs, like skeletal muscles, with the highest concentrations in the kidneys, heart, liver, lungs, and red blood cells. Lactate dehydrogenase comprises five isozymes, where LDH1 is predominant in the heart, though it lacks high specificity for cardiac tissue. LDH may also be secreted from erythrocytes, kidneys, brain, skeletal muscles, stomach, and pancreas. Its levels can rise in certain types of tumors, such as seminomas and dysgerminomas. LDH levels elevate within six to twelve hours following the onset of chest pain, peaking over one to three days and returning to normal within eight days to almost two weeks. An LDH1:LDH2 ratio greater than 1 is AMI specific, but this marker is not currently used for AMI diagnosis. Nowadays, LDH plays a role to distinguish acute and sub-acute myocardial infarction in individuals who arrive at the hospital later during the condition, where troponin concentrations remain elevated, however, creatine kinase (CK) and CK-MB levels have normalized.

Creatine kinase and creatine kinase-MB

Myocardial injury leads to increased levels of total CK and CK-MB. After AMI, the levels of TCK and CK-MB in plasma can stay elevated in the serum for up to 72 hours [13].

Several conditions can lead to false-positive CK-MB test results. These include malignancies like breast cancer and prostate cancers, pulmonary embolism, use of aspirin, inflammation of the heart muscles (myocarditis and pericarditis), underactive thyroid (hypothyroidism), chronic kidney disease, vigorous physical activity, trauma or injury to the heart (including surgery or contusions), and inflammatory muscle disorders like muscular dystrophy. Additional contributors may encompass muscle injuries, rhabdomyolysis, conditions affecting connective tissues, such as systemic lupus erythematosus, elevated body temperature (hyperthermia), Reye's syndrome, the postpartum period, excessive alcohol intake, acute gallbladder inflammation (cholecystitis), prolonged abnormal heart rhythms (arrhythmias), seizures, electrical injuries, repeated cardioversion, and intramuscular injections. These factors should be carefully considered when interpreting CK-MB levels for detecting AMI. Damage to skeletal muscles, particularly those rich in "red" muscle fibers, can cause CK-MB levels to rise beyond the normal range seen in acute myocardial infarction (AMI). Such

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elevations could be seen after strenuous physical activity.

Troponins

Troponins are proteins regulating muscle contraction. The heart contains troponin subunits cTnI, cTnT, and cTnC that are crucial for the proper contraction of myocardium. These subunits are encoded by distinct genes, setting them apart from troponin found in skeletal muscle. As per the fourth universally accepted definition of myocardial infarction, there must be an increase and decrease in level of troponin, with the minimum measurement exceeding 99th percentile, having clear proof of myocardial ischemia. Type 1 myocardial infarction is the commonest form of ACS seen in the department of emergency. It is triggered by atheromatous plaque rupture, leading to formation of thrombus and its embolization, which obstructs the coronary artery and causes tissue necrosis. Type 2 myocardial infarction is caused by insufficient supply of oxygen to the muscles of the heart. Other forms of MI are uncommon. In myocardial infarction, troponin levels change rapidly, but patients might seek medical attention much later than the initial chest pain. Levels of cardiac troponin I remain upregulated for as long as 5 days, and cardiac troponin T can remain elevated up to 10 days. However, two troponin measurements taken 2–3 hours apart may not show a significant difference. Troponin testing in general practice is discouraged because troponin levels alone cannot definitively exclude the possibility of ACS. Comprehensive risk-based classification, requiring multiple measurements, is necessary for accurate diagnosis [14].

Myoglobin

Myoglobin is proteinaceous in nature and forms a bond with iron and oxygen and is profoundly present in cardiac muscles and animal skeletal muscles. The protein exists solely in muscular tissue. However, its entry into the bloodstream can be due to muscle damage. Although it lacks specificity, it is a sensitive marker for AMI. Myoglobin promptly enters the circulation from cardiac muscles during injury followed by its rapid elimination by the kidneys in nearly 24 hours. Following myocardial cell injury, myoglobin enters the circulation rapidly, with levels increasing within the first hour and achieving peak values in 4 to 6 hours [15]. Levels of myoglobin can start peaking in half an hour post the initiation of a sudden event owing to its rapid kinetics. This makes it a valuable marker for early identification and/or elimination of the possibility of cardiac injury. Due to its poor specificity, negative myoglobin values are more clinically significant than positive ones. Therefore, in diagnosing AMI, it's essential to consider creatine kinase-MB, cardiac troponin T, ECG results, and clinical findings. However, myoglobin remains useful for assessing the size of the infarct and monitoring reperfusion.

Heart-type fatty acid binding protein

HFABP is known for its stability and its low molecular mass, which ranges between 14 to 15 kDA. It occurs plentifully in the cytoplasmic region of cardiomyocytes. The combination of its molecular size and water solubility facilitates its movement into the blood stream, where it is detectable within 90 minutes post symptom onset and peaks at six hours. The base level is then reached approximately a day later. Although heart type fatty acid binding protein shows similar kinetics as other early biomarkers of acute myocardial infarction (AMI) like myoglobin, soluble CD40 ligand, ischemia-modified albumin, pregnancy-associated plasma protein A, and myeloperoxidase, it is regarded as heart specific muscle tissue. This high specificity makes HFABP a valuable marker intended for usage concurrently with standard cTn tests. Additionally, rapid bedside chromatographic assays and fully automated turbidimetric immunoassays are available for H-FABP, allowing for quick measurement and short turnaround times. However, a 2010 meta-analysis by Bruins Slot et al. examining how HFABP evaluation contributes for individuals having unconfirmed acute myocardial infarction, drew a conclusion that H-FABP alone doesn't satisfy the criteria for making an early and safe diagnostic assessment [16].

Coeptin

Coeptin contains 39-amino acids and is present on the C-terminal of pro-AV. It serves as an initial indicator of acute myocardial infarction and appears in the bloodstream alongside vasopressin during acute events. Due to its distinct pathophysiology and complementary time course to troponin I, Coeptin might be valuable for timely identification of acute myocardial infarction. Coeptin peaks quickly within an hour following the initial appearance of symptoms of acute myocardial infarction, returning to baseline in approximately 3 days in early presenters. However, emerging evidence shows that coeptin levels rise in serum under various conditions, including infections of the lower respiratory tract, sepsis, stroke, and also after AMI. This suggests that coeptin might serve as a useful, albeit non-specific, biomarker. Using coeptin in combination with troponin I (TnI) enhances the AMI diagnosis in those presenting soon after symptom onset as coeptin operates differently from markers linked to pathological processes. Adding coeptin to cardiac troponin I increases sensitivity and negative predictive value, making the two markers complementary for early AMI diagnosis. A dual marker strategy of TnI plus coeptin, instead of TnI plus CK-MB, could improve the process of confirmation and exclusion of AMI in people showing up soon after initial symptom onset in the emergency department [17].

3.22 Biomarkers for heart failure

HF is a disorder arising from defects in cardiac structure or function that limits the potential of the heart to fill with blood or pump it efficiently. The major underlying reason for HF is diminished function of the left ventricular myocardium; however, dysfunctions in the three layers of the heart, its valves, and large vessels can too have a part in heart failure, either individually or in combination. Key mechanisms driving heart failure include increased hemodynamic load, dysfunction triggered by ischemia, remodeling of the ventricles, and

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amplified neurohormonal activity, abnormal calcium handling in heart muscle cells, imbalanced extracellular matrix turnover, accelerated cell death, and genetic mutations [18].

Natriuretic peptides

Natriuretic peptides function as neurohormonal regulators of body fluids, facilitating sodium loss and urine production. They also reduce vasoconstriction by lowering the production of angiotensin II and norepinephrine. The class primarily consists of ANP, BNP, CNP and urodilatin [19 20]. BNP was initially discovered in the porcine brain, leading to its name, brain natriuretic peptide. Later research revealed that it is secreted by the myocardial cells of the left ventricle as a result of elevated pressure or volume. Upon release, proBNP splits in C-terminal BNP which is in active form and N terminal-proBNP, which then enters the circulation. Since proBNP is predominantly synthesised and secreted from the ventricular myocardium as a result of hemodynamic changes, it provides a more accurate reflection of ventricular dysfunction compared to other natriuretic peptides. BNP concentrations show a close correlation with the severity of HF. The concentration of BNP increases as the severity of heart failure progresses, which is classified as per the New York Heart Association functional classification. This makes BNP highly valuable for prediction of a patient's condition and developing treatment strategies. The effectiveness of a clinical evaluation tool is determined by the power of prediction, which plays a key role in guiding treatment decisions. BNP independently predicts the incidence and mortality rates following MI and heart failure. Among all prognostic factors, BNP is regarded as a highly important maker for forecasting the risk of heart failure outcomes. It is regarded as an essential prognostic indicator that warrants inclusion in upcoming clinical studies. Multiple studies have demonstrated the strong diagnostic utility of B-type natriuretic peptide and N-terminal-pro B type natriuretic peptide in assessment of heart failure. In routine clinical settings, they are considered reliable tests for excluding disease in the emergency department and OPD. However, these markers should not be used as stand-alone diagnostic tools but should always be interpreted alongside the patient’s clinical symptoms. Furthermore, as key prognostic indicators, BNP and NT-proBNP are expected to be instrumental in guiding diagnostic and therapeutic decisions for heart failure [21]. Similar to B-type natriuretic peptide and N-Terminal-pro B- type natriuretic peptide, midregional-pro atrial natriuretic peptide is also a marker of prognosis to determine untoward clinical events in individuals with acute worsening of HF. Researchers from the GISSI-HF study demonstrated the prognostic significance of midregional-pro atrial natriuretic peptide in predicting death rate. In the PRIDE study, elevated levels of MR-proANP were shown to be prognostic and helped reclassify the risk of fatality at 1 year and 4 years. In the BACH trial, mideregional-pro atrial natriuretic peptide levels were estimated in 1,641 individuals with acute dyspnea. The study demonstrated that midregional-pro atrial natriuretic peptide, using a threshold of 120 pmol/L, performed comparably to B-type natriuretic peptide at 100 pg/mL, in the diagnosis of acute HF, showing no inferiority in diagnostic accuracy. Additionally, MR-proANP exhibited augmented diagnostic performance in the grey zone of B- type natriuretic peptide (100-500 pg/mL) and in patients with obesity. Heining and colleagues also found that mideregional-pro atrial natriuretic peptide levels exhibited a significant increase in heart failure patients than those with other causes of dyspnea [22].

3.23 Biomarkers for inflammation and atherosclerosis

Inflammation refers to a series of immune system responses triggered by various stimuli, which do not always pose a risk. Such triggers may involve infectious agents such as bacteria, viruses, and parasites, along with trauma, burns and radiation, tissue injury, and immune mediated processes like allergies. The main objective of the inflammatory process is to eliminate the triggering factor, clear damaged tissue, and support tissue repair and regeneration. While acute inflammation is generally protective and self-limiting, persistent low-grade inflammation plays an important role in the onset and advancement of several chronic disorders. This sustained inflammatory state is frequently accompanied by oxidative stress and is strongly linked with conditions like obese state, metabolic syndrome, T2DM, atherosclerosis and other cardiovascular disorders. Additionally, CKD and autoimmune conditions, like inflammatory bowel diseases such as Crohn's disease (CD) and ulcerative colitis (UC), are also associated with these conditions [23].

Atherosclerosis, the precursor of cardiovascular diseases, is the chronic inflammatory state of large vessels [24], however, up until recently, it was viewed as a condition involving the passive build-up of cholesterol in the sub endothelial space, in spite of the evidence gathered by Virchow almost 100 years ago. This view has since been superseded by extensive insights from foundational research and patient-based studies showing that every stage of atherogenesis, dysfunction of endothelial to foam cell initiation, maturation, and rupture of plaque is facilitated by cytokines, interleukins, and inflammatory cells [25]. Identifying traditional atherosclerosis markers, like low- density lipoprotein, high-density lipoprotein, and triglycerides,may lack predictive accuracy in populations with intermediate or non-traditional cardiovascular risk. In such cases, non-traditional atherosclerosis biomarkers can offer more precise management. A biomarker with high clinical value should exhibit high sensitivity, consistent results, and be applicable in clinical practice at a low cost. Atherosclerosis biomarkers are specific to different stages of the disease and include inflammatory biomarkers, markers associated with plaque instability, acute phase proteins, ischemia, tissue breakdown, and impaired cardiac function [26].

C-reactive protein and high sensitivity-C-reactive protein

The C-reactive protein is the member of pentraxin class of proteins [27]. Maximum CRP is synthesised in the liver as an acute phase protein due to circulating cytokines, particularly IL-6. Levels of CRP increase due to non-chronic infections, inflammatory states, and state of injury. Under such

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circumstances, CRP concentrations quickly elevate, typically exceeding 10 mg/L. There's also a simultaneous increase in erythrocyte sedimentation rates (ESR). High- sensitivity assay methods like immunonephelometry, immunoturbidimetry, high-sensitivity enzyme-linked immunosorbent assay, and resonant acoustic profiling can assess C-reactive protein within 0.01 to 10 mg/L. Such assays enable detection of subtle systemic inflammatory activity in the absence of obvious immune mediated diseases. While numerous non-interventional researches have reported robust links between C-reactive protein, atherosclerotic burden, and cardiovascular risk, CRP alone does not act as a causal factor in atherothrombosis. The JUPITER trial emphasized the importance of measuring hs- CRP for risk stratification, focusing on evaluating the effectiveness of statin therapy in lowering major CVD events in individuals with near normal low-density lipoprotein but elevated high-sensitivity C-reactive protein concentrations. Involving 17,802 healthy individuals, the study compared 20 milligrams of Rosuvastatin to a placebo. The study was stopped before time post 1.9 years follow up as rosuvastatin diluted the primary composite endpoint, including myocardial infarction, stroke, cardiovascular death, arterial revascularization, and unstable angina. Rosuvastatin reduced low-density lipoprotein levels up to fifty percent and high sensitivity C-reactive protein levels up to thirty seven percent. However, the trial left unresolved whether the benefits were due to lipid-lowering or inflammation suppression alone, or both. The CANTOS trial seeks to further clarify these questions which investigated whether targeted inhibition of IL-1β through canakinumab can cause reduction in cardiovascular events in high-risk, post MI individuals having elevated hs-CRP concentrations.

The Reynolds risk score

The Reynolds risk score was engineered to anticipate an individual's 10-year risk of CVDs in healthy women, using data from approximately 25,000 U.S. female health professionals. It includes factors like age, systolic blood pressure, HbA1c for diabetic patients, smoking of cigarettes, total cholesterol and high-density lipoprotein cholesterol, high sensitivity C-reactive protein, and family history of premature myocardial infarction. Unlike traditional risk models like the FRS, the Reynolds score incorporates hsCRP and parental history of premature CHD. The score has also been successfully adapted for use in healthy, non-diabetic men, showing improved cardiovascular risk prediction compared to the FRS [28].

Interleukin-6

Interleukin-6 is a highly significant and versatile interleukin. Along with TNF-alpha, it is categorized as a pro- inflammatory cytokine. Interleukin-6 is mainly synthesized by monocytes and macrophages. Its concentrations tend to rise with age and are linked to higher death rates in individuals over 65, regardless of whether the cause is cardiovascular or non-cardiovascular. IL-6 levels rise in individuals with CAD and serve as an inflammatory marker associated with risk of CVD. It also plays a role in plaque formation, plaque instability, promoting matrix metalloproteinases, TNF-alpha, and MCP-1 expression. In FRISC-II and Fragmin study, upregulated IL-6 levels (>5 ng/L) were linked to increased mortality at 6 and 12 months, regardless of troponin and hs-CRP levels [29].

Tumor necrosis factor- α

TNF-alpha belongs to an expanding family of peptide mediators that includes at least 19 cytokines, such as lymphotoxin-α, Fas ligand, and CD40 ligand. It is a key cytokine involved in activating effector pathways in diseased inflammatory tissues as well as vessels compromised by atherosclerosis. It has a part in growth and formation of atherosclerotic plaques too. TNF-α blocks the eNOS function, boosts the synthesis of ROS, and slows the EDHF activity. These processes impair vasodilation and cause vascular endothelial damage due to inflammation. TNF-α is considered a biomarker for increased cardiovascular risk, and studies show that its concentration in the blood rises with age. Elderly individuals with elevated TNF-α levels are often diagnosed with atherosclerosis. Tumor necrosis factor-α is also found to be linked to myocardial dysfunction and remodeling following acute coronary events. In the CARE study, high TNF-α levels were linked with elevated recurrent coronary event risk after an MI, compared to controls.

Matrix metalloproteinase-9

Metalloproteinases represent a broad class of enzymes containing Zinc and require Calcium for their activity. Matrix metalloproteinase-9 is implicated in inflammatory activity and the disruption of atherosclerotic plaque integrity. It promotes the infiltration of monocytes beneath the endothelium lining of blood vessels. Elevated matrix metalloproteinase-9 in the circulation has been linked to increased lipid core dimensions and heightened plaque vulnerability. Individuals having unstable angina and non- ST-elevation MI (NSTEMI) show elevated MMP-9 levels. Furthermore, a higher concentration of MMP-9 is linked with increased susceptibility to MI or stroke, irrespective of its consideration as a strong and independent cardiovascular risk factor.

Interferon- γ

Interferon-γ, the only constituent of interferon family (type II), is synthesized by T cells and macrophages. It is crucial for atherogenesis and induces the production of other cytokines and influences multiple stages of atherosclerosis. IFN-γ primarily activates the Janus kinase/signal transducer and activator of transcription (JAk/STAT) pathway, causing oxidative stress, formation of foam cells, multiplication and migration of smooth muscle cells, upregulated expression of platelet-derived growth factor, and plaque destabilization. This causes onset and advancement of CVD. Due to its critical role in advancing CVD, IFN-γ's signaling pathways are under investigation as potential drivers of atherosclerosis. IFN-γ targeted strategies may enable novel treatment options for CVD prevention and treatment, with several therapies currently under exploration focusing on this

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cytokine [30].

3.24 Biomarkers for oxidative stress

Oxidative stress refers to a lack of balance between the production of reactive oxygen species and the body's antioxidant defense system [31]. ROS carry out several physiological functions, including cellular signaling, and are formed as secondary by-products during oxidative metabolic processes. Exogenous stimuli causing stress like UV radiation, ionizing radiation, pollutants, heavy metals, and certain xenobiotics (like chemotherapy drugs) predominantly elevate reactive oxygen species synthesis. This excessive reactive oxygen species generation disrupts the balance and causes oxidative stress, leading to damage of cells and tissues [32]. In pathological conditions, such as atherosclerosis or hypertension, reactive oxygen synthesis surpasses the system's natural antioxidant defense mechanism, leading to cell death. Oxidative stress contributes greatly towards cardiovascular issues, including MI, ischemia, reperfusion injury, and heart failure [33].

Myleoperoxidase

MPO (myeloperoxidase) contributes to cardiovascular disease (CVD) development by promoting inflammation and oxidative stress mechanisms. It's released from neutrophils and monocytes during inflammation. Superoxide produced by neutrophils can participate in oxidative reactions or be transformed into Hydrogen Peroxide through the action of Superoxide Dismutase. Myeloperoxidase then utilizes hydrogen peroxide to give rise to powerful oxidants such as hypochlorous acid, hydroxyl radicals, nitrogen dioxide, and peroxynitrite. The compounds produced are capable of oxidizing LDL as well as HDL. Additionally, oxidation of protein-based products like di-tyrosine and 3-chlorotyrosine, which are induced by MPO-derived oxidants, have been found in atherosclerotic lesions. While MPO is primarily associated with inflammation, its role in producing potent oxidants found in atherosclerotic plaques has led to it being recognized as a marker for oxidative stress in numerous studies. The first trial in this area examined 604 individuals showing up with chest pain in an emergency ward, following them for 30 days and six months. It was found that baseline MPO levels were considerably elevated in the 34 patients who succumbed within a six months period in comparison to those who survived. Multivariate analysis revealed that increased MPO levels significantly predicted a heightened vulnerability for heart attack, revascularization, and major adverse coronary events at one month and semi-annual timepoints. Additionally, 4 other studies on acute coronary syndrome patients, all cohort and non-controlled, revealed that MPO levels were linked to cardiovascular outcomes such as death rate, life threatening and non life threatening myocardial infarction, and re-occuring ischemia related events. The MPO and heightened AMI vulnerability correlation in patients with pain in the chest may be attributed to activation of neutrophil triggered by vasospasm or thrombosis. However, the connection between the levels of myeloperoxidase and coronary artery disease risk in stable patients remains unclear [34].

Oxidised low-density lipoprotein

Oxidized low density lipoprotein is instrumental for formation and development of atherosclerotic plaques. The oxidation of native LDL occurs inside the sub-endothelium by superoxide, myeloperoxidase (MPO), 15-lipoxygenase, and peroxynitrite. This process results in the formation of either type of low-density lipoprotein, which is, minimally modified-low density lipoprotein or fully modified-low density lipoprotein. Minimally modified low-density lipoprotein is capable of binding to native low-density lipoprotein receptors, but fully modified low-density lipoprotein is recognized by scavenger receptors, like CD- 36 and SR-A, on macrophages. Over time, macrophages accumulate Ox-LDL, turning into lipid-laden foam cells due to their inability to properly dispose of it. These foam cells contribute to fatty streak formation, with smooth muscle cells migrating to the subendothelial layer, proliferating, and absorbing modified lipoproteins, furthering the development of atherosclerosis. While oxidised low-density lipoprotein is commonly found in atherosclerotic lesions, no direct witness exists that proves it causes cardiovascular disease initiation and progression. 16 out of 26 studies measuring oxidised low-density lipoprotein found that it serves the purpose of standalone predictor of cardiovascular diseases. Some researches using the same cohort reported different findings, likely due to variations in study duration, antibody type, or focus on primary versus secondary CVD. Notably, larger studies contributed to varied outcomes, where some suggest Ox-LDL as predictive and others not. Issues such as patient characteristics, antibody detection methods, and differences in disease conditions (e.g., diabetes, hypertension) may explain the inconsistent results. Furthermore, studies also reported conflicting outcomes regarding whether increased autoantibodies to Ox-LDL predict higher or lower cardiovascular risk. These inconsistencies highlight issues regarding the reliability of Ox-LDL as a consistent predictor of CVD.

4. Discussion

The progressive evolution of cardiac biomarkers has predominantly advanced the diagnosis of CVDs and its management. Traditional enzymatic biomarkers such as AST, LDH, and CK provided the foundation for biochemical detection of myocardial infarction but were hampered by poor specificity and overlap with non-cardiac conditions. The advent of cardiac-specific troponins in the 1990s marked a major breakthrough, offering unmatched sensitivity and specificity for detecting myocardial necrosis, and they remain the gold standard in acute coronary syndrome diagnosis. Similarly, natriuretic peptides, particularly B-type natriuretic peptide and N-terminal pro- B-type natriuretic peptide, have exhibited indispensable for evaluating heart failure and understanding its prognosis.

Emerging biomarkers extend the diagnostic landscape by reflecting additional dimensions of CVD pathophysiology, including inflammation, oxidative stress, endothelial

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dysfunction, and plaque instability. Inflammatory mediators such as interleukin-6, tumor necrosis factor-α, and high sensitivity C-reactive protein highlight the contribution of chronic low-grade inflammation to atherosclerosis, while oxidative stress markers such as MPO and Ox-LDL provide insight into vascular damage and lipid oxidation. Novel candidates like H-FABP, copeptin, cMyC, sST2, GDF-15, and MMP-9 offer promising avenues for early detection, prognosis, and personalized risk assessment, though their clinical adoption remains limited due to challenges in assay standardization, reproducibility, and validation across diverse populations.

A key limitation of current approaches is the reliance on single biomarkers, which may not completely explore the multifactorial and evolving character of CVD. Multi-marker strategies that integrate traditional and novel biomarkers appear more promising, as they provide a comprehensive assessment of disease mechanisms and patient risk profiles. However, large-scale prospective studies are needed to determine their incremental value and establish clear clinical utility.

5. Conclusion

Cardiac biomarkers have transformed the clinical approach to cardiovascular diseases by enhancing early diagnosis, refining risk stratification, and guiding therapeutic decisions. While troponins and natriuretic peptides remain the cornerstones of practice, emerging biomarkers reflecting inflammation, oxidative stress, and vascular injury broaden the understanding of CVD pathogenesis and offer potential for improved precision medicine. Nonetheless, challenges such as assay variability, limited reproducibility, and uncertain predictive value hinder their widespread implementation. The integration of biomarker panels, rather than reliance on single markers, represents the future direction of cardiovascular diagnostics. Moving forward, efforts must focus on standardization, validation across large and diverse cohorts, and incorporation into routine clinical workflows. With these advancements, cardiac biomarkers may play a crucial role in improving outcomes and redefining approaches for diagnosis and management of cardiovascular diseases.

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