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Emerging Paradigms in Cardiovascular Medicine: The Role of Biomarkers, Artificial Intelligence, and Gut Microbiota in Personalized Therapy — The Evolving Landscape of Cardiovascular Care

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ABSTRACT

Introduction: Cardiovascular diseases (CVDs) remain one of the leading causes of morbidity and mortality worldwide. While conventional diagnostic and therapeutic methods have made significant contributions, they may fall short in detecting the disease at early stages and in developing personalized treament strategies.
Objective: This review discusses three innovative approaches—biomarker-based analyses, artificial intelligence (AI)-assisted decision systems, and gut microbiota-focused applications—that have rapidly advanced in recent years and are expanding in their potential clinical applications.
Methods: With the advent of next-generation biomarkers (e.g., soluble urokinase-type plasminogen activator receptor [suPAR], suppression of tumorigenicity 2 [ST2], galectin-3, and growth differentiation factor-15 [GDF-15]), processes such as heart failure, myocardial injury, and vascular inflammation can now be assessed more sensitively and at earlier stages.
Results: AI algorithms accelerate and enhance diagnostic accuracy by analyzing imaging data, electrocardiogram (ECG) signals, and multivariate clinical parameters. Meanwhile, the influence of gut microbiota on cardiovascular pathophysiology is increasingly understood, with microbial metabolites such as trimethylamine-N-oxide (TMAO) shown to play a significant role in atherosclerotic processes.
Conclusion: A comprehensive evaluation of these three approaches offers new perspectives for the development of personalized cardiology practices and lays the groundwork for more effective strategies in diagnosis, monitoring, and treatment.

Keywords: Cardiovascular Diseases, Biomarker, Artificial Intelligence, Microbiota, Personalized Medicine.

INTRODUCTION

Cardiovascular diseases (CVDs) are among the leading causes of death worldwide and contribute significantly to the decline in quality of life. In 2021 alone, CVDs accounted for 20.5 million deaths, representing approximately one-third of global mortality (1). Currently, diagnostic and treatment approaches are undergoing a major transformation driven by technological advancements. Early detection and timely intervention are critically important for improving clinical outcomes and preventing disease progression (2). In this context, emerging fields such as biomarkers, artificial intelligence (AI) applications, and gut microbiota offer promising new perspectives in the management of CVDs. This review aims to comprehensively examine the current state, clinical application potential, and future contributions of these three key approaches.

1. Biomarkers: Innovations in Molecular and Digital Biology

1.1. Traditional Biomarkers

Cardiac troponins I (cTnI) and T (cTnT) are considered the gold-standard biomarkers for the diagnosis of myocardial injury (3). B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are essential markers for the diagnosis and prognostic evaluation of heart failure (4). Although creatine kinase-MB (CK-MB) was widely used in the past, its current clinical application is limited. However, CK-MB levels begin to rise in the serum approximately 4–9 hours after the onset of myocardial injury, peak within 24 hours, and typically return to the reference range within 48–72 hours. This kinetic profile

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allows CK-MB to contribute to clinical decision-making, particularly in determining the timing of acute myocardial injury (5).

1.2. Next-Generation Molecular Biomarkers

Fibrosis and inflammation-related biomarkers such as Suppression of Tumorigenicity 2 (ST2), Galectin-3, Growth Differentiation Factor-15 (GDF-15), and Soluble Urokinase-type Plasminogen Activator Receptor (suPAR) have emerged as novel and promising tools in the prognostic assessment of heart failure (HF).

ST2 is considered a marker of fibrotic and inflammatory processes and is particularly utilized in predicting HF prognosis. Recent meta-analyses have demonstrated that its soluble form, sST2, is a reliable indicator of myocardial fibrosis and cardiac remodeling, offering strong prognostic value for predicting cardiovascular events in both acute and chronic HF settings (6).

Galectin-3 (Gal-3) is a key biomarker of cardiac fibrosis. Elevated plasma Gal-3 levels have been strongly associated with adverse clinical outcomes and the process of cardiac remodeling, especially in patients with HF(7).

GDF-15, a cytokine belonging to the Transforming Growth Factor-beta (TGF-β) superfamily, increases in response to cellular stress, non-ischemic cardiomyopathy, and aging, particularly in myocardial tissue. Studies have shown that GDF-15 levels correlate strongly with myocardial fibrosis, as evidenced in biopsies obtained during ventricular assist device implantation or heart transplantation (8, 9).

Soluble urokinase-type plasminogen activator receptor (suPAR) is a soluble receptor that has emerged as a marker of systemic inflammation. Elevated suPAR levels have been associated with cardiovascular diseases, renal dysfunction, sepsis, and other inflammatory conditions in both the general population and patient cohorts. Accordingly, suPAR is regarded as a broad-spectrum prognostic biomarker (10).

MicroRNAs (miRNAs) play a crucial regulatory role in the molecular mechanisms underlying cardiovascular diseases. Particularly in atherosclerosis and arterial remodeling, miRNAs contribute to processes such as endothelial dysfunction, monocyte activation, vascular smooth muscle cell migration, platelet aggregation, and plaque formation, where they can exert both pathogenic and protective effects. Due to these versatile roles, miRNAs are considered promising diagnostic and therapeutic biomarkers and potential molecular targets (11).

High-sensitivity cardiac troponins (hs-cTnT/I) are advanced versions of classical troponins used to detect myocardial injury. Recent studies suggest that hs-cTn levels can be used not only for the diagnosis of acute myocardial infarction but also for identifying subclinical stages of cardiovascular disease. Even slight elevations in hs-cTnI and hs-cTnT levels have been shown to correlate with long-term cardiovascular risk (12).

1.3. Liquid Biopsy and Genetic Biomarkers

Within the scope of liquid biopsy applications, biomolecular approaches such as exosomes, extracellular microRNAs (miRNAs), and polygenic risk scores (PRS) are gaining increasing potential for the early diagnosis and personalized treatment planning of cardiovascular diseases (CVDs). Developed as alternatives to traditional invasive methods, liquid biopsies have become a valuable tool not only for diagnostic purposes but also for monitoring biomolecular changes throughout the disease course and guiding therapeutic decisions dynamically (13). The literature indicates that liquid biopsies are not limited to blood samples; disease-specific genetic material can also be obtained from various biological fluids such as urine (14), saliva (15), pleural effusions (16), cerebrospinal fluid (CSF) (17), and stool (18). This highlights the potential for developing broader-spectrum, non-invasive biomarkers in the future. Extracellular vesicles, miRNAs, and circulating DNA fragments obtained from liquid biopsy samples allow for earlier and more sensitive detection of CVD risk.

It is well known that protein-coding mRNA transcripts account for less than 3% of the entire genetic material, while the remaining majority consists of non-coding RNA molecules that play functional roles in maintaining tissue homeostasis and regulating pathophysiological processes. Among these, miRNAs

stand out due to their ability to modulate the expression of genes involved in lipid metabolism (19). Identifying the genes targeted by miRNAs in pathological processes such as dyslipidemia, atherosclerosis, and endothelial dysfunction—conditions closely linked to CVD—has brought forward their potential use as diagnostic biomarkers and therapeutic agents. Furthermore, polygenic risk scores (PRS) are powerful tools that predict an individual's susceptibility to disease based on genetic predisposition and are expected to be integrated into the future of personalized medicine. In polygenic diseases with strong heritability, such as coronary artery disease (CAD), the use of PRS not only allows for risk stratification early in life but also complements traditional clinical risk factors, providing a more refined clinical decision-support tool (20). This enables the early identification of high-risk individuals and the implementation of preventive strategies.

1.4. Artificial Intelligence-Based Digital Biomarkers

The increasing use of AI-supported biomarkers in cardiovascular risk prediction has brought about a significant transformation in clinical practice. One notable study in this field is the AI Vascular Age model, which estimates an individual's vascular age based on photoplethysmography (PPG) signals. The difference between the estimated vascular age and the chronological age serves as a significant risk indicator for major cardiovascular events and has been associated with an approximately 2.3 to 2.9-fold increased risk (21).

Photoplethysmography (PPG) is a non-invasive, low-cost, and user-friendly optical signal technology widely used to monitor various hemodynamic parameters, especially heart rate (22). In recent years, advances in sensor technology and big data analytics have enabled PPG signals to be used not only for monitoring blood oxygen saturation (SpO_2) (23) but also for integration into smartwatches and other wearable devices (24).

With the advancement of AI algorithms, PPG signals have evolved from simple heart rate tracking tools into promising digital biomarkers for the early diagnosis and monitoring of cardiovascular diseases, such as atrial fibrillation (25) and hypertension (26). In this context, the integration of PPG-based sensors with AI is gaining increasing interest in remote patient monitoring, preventive healthcare, and digital health solutions.

2. Artificial Intelligence: Diagnosis, Risk Prediction, and Clinical Decision Support

AI-assisted cardiac imaging analyses offer higher accuracy, speed, and objectivity compared to conventional methods (27).

2.1. Artificial Intelligence in Imaging Diagnosis

The analysis of cardiac imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), and echocardiography (ECHO) using AI accelerates clinical decision-making through automated classification and segmentation algorithms (28). In particular, deep learning-based systems can accurately detect atherosclerotic plaque stability, degrees of coronary artery stenosis, and ventricular dysfunction with high precision (27).

2.2. Risk Scoring and Early Warning Systems

AI-based models integrate multivariate clinical, laboratory, and genetic data to develop personalized risk scoring systems (29, 28). These systems enable rapid calculation of an individual's risk for myocardial infarction in the coming years within minutes (30, 29). AI-assisted electrocardiogram (ECG) analyses also show promise in detecting subclinical pathologies. Moreover, these models facilitate disease identification prior to clinical symptom onset, contributing to early intervention and the development of preventive strategies.

2.3. Clinical Decision Support Systems

AI systems have the capability to integrate with electronic health records (EHR) and provide physician-specific, patient-centered treatment plans (31). This functionality is particularly critical in optimizing drug combinations for patients with comorbid conditions to enhance therapeutic efficacy. AI-assisted

decision support systems contribute to preventing potential adverse events by predicting drug–drug interactions with high accuracy. Accordingly, AI applications have been reported to improve both the safety and personalization of pharmacological therapies (32). Additionally, these systems hold potential to guide drug development processes.

3. Microbiota and Microbial Metabolites: The Heart-Health Axis

3.1. Trimethylamine-N-Oxide and Atherosclerosis

Trimethylamine-N-oxide (TMAO) is produced through the oxidation of trimethylamine (TMA), which is generated by the gut microbiota from dietary precursors such as phosphatidylcholine, choline, and carnitine, via hepatic flavin-containing monooxygenases (FMO3). Elevated plasma TMAO levels have been significantly associated with increased mortality and major cardiovascular events, especially in patients with stable coronary artery disease (33). Experimental models of heart failure with preserved ejection fraction (HFpEF) have demonstrated a 54% increase in TMAO levels, which has been linked to compromised intestinal barrier integrity, systemic inflammation, and advanced heart failure (34).

3.2. Short-Chain Fatty Acids

Short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate, synthesized from fermentable dietary fibers by the gut microbiota, exhibit anti-inflammatory and vasoprotective effects on cardiovascular health. In particular, propionate may ameliorate coronary microvascular dysfunction by reducing endoplasmic reticulum stress triggered by oxidized low-density lipoprotein (LDL) (35). Studies conducted in heart failure patients have reported strong negative and positive correlations between SCFA levels and NT-proBNP, proinflammatory cytokines, and endothelial function (36). These findings suggest that SCFAs may serve as potential biomarkers and therapeutic targets for the preservation of cardiac function.

3.3. Microbiota Composition and Cardiovascular Diseases

Significant compositional alterations in the gut microbiota have been observed in individuals with cardiovascular diseases (CVD). Notably, increased abundance of Streptococcus and Proteobacteria species, alongside decreased levels of anti-inflammatory bacteria such as Faecalibacterium, may contribute to inflammatory cardiometabolic processes (37). Oscillibacter species are proposed to participate in cholesterol metabolism, potentially regulating serum lipid levels. Furthermore, dysbiotic changes associated with conditions such as heart failure and atrial fibrillation support the direct pathophysiological linkage between the microbiota and CVD (38).

4. Microbiota Modulation: Clinical Trials and Approaches

4.1. Probiotic and Prebiotic Interventions

Reducing cardiovascular disease (CVD) risk through modulation of the microbiota composition has been primarily targeted via probiotic and prebiotic applications. The administration of Lactobacillus plantarum 299v has been reported to improve endothelial function and reduce systemic inflammatory markers in patients with stable coronary artery disease, although it did not show a significant effect on TMAO levels (39). Dietary modifications also influence cardiometabolic health through the microbiota. Plant-based diets (e.g., vegan or low-meat regimens) have been shown to significantly reduce both TMAO and L-carnitine levels, positively affecting blood pressure and lipotoxic oxidized LDL levels (40). Pilot studies demonstrated that high-fiber diets suppress the activity of the cutC gene responsible for TMA production in the gut, thereby decreasing TMAO synthesis (41). These findings suggest that prebiotics may exert beneficial effects not only on gut health but also on the cardiovascular system.

4.2. Drug and Metabolite-Targeted Interventions

Based on the cardiovascular effects of microbial metabolites, novel therapeutic strategies targeting these pathways pharmacologically are under development. In particular, enzyme inhibitors that suppress TMAO biosynthesis represent promising agents for modulating the microbiota–heart axis in the future (42).

DISCUSSION

The temporal burden of cardiovascular diseases (CVD) and the analysis of associated risk factors have been conducted using complex modeling techniques (43). In recent years, the role of innovative approaches alongside traditional biomarkers in the diagnosis, risk prediction, and management of CVD has increasingly gained importance. Cardiac troponins I (cTnI) and T (cTnT) are internationally recognized as standard biomarkers for detecting myocardial injury, risk stratification in patients with suspected acute coronary syndrome, and diagnosis of myocardial infarction. Evidence-based clinical databases for high-sensitivity troponin assays are rapidly evolving (44). Brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) remain fundamental biomarkers for the diagnosis and monitoring of heart failure (45). On the other hand, biomarkers such as creatine kinase-MB (CK-MB) have been partly supplanted by troponins in terms of sensitivity and specificity for cardiac injury (46). However, classical biomarkers alone are insufficient to fully reflect disease pathophysiology; thus, investigation of the gut microbiota and microbial metabolites has gained prominence. In particular, trimethylamine-N-oxide (TMAO), derived from L-carnitine metabolism via the gut microbiota, emerges as a potential biomarker for cardiac and renal diseases (47). In atherosclerosis mouse models, plasma TMAO levels have been shown to correlate with atheroma burden, and dietary choline has been found to enhance foam cell formation and scavenger receptor expression in macrophages. Clinical studies have also demonstrated that elevated plasma choline and betaine levels accompanying high TMAO are significantly associated with poor prognosis and increased risk of major cardiac events (48). Additionally, short-chain fatty acids (SCFAs)—acetate, propionate, and butyrate—produced by microbial fermentation of dietary fibers exert beneficial effects on host metabolism and cardiovascular health maintenance (49).

Short-chain fatty acids (SCFAs), although primarily recognized as crucial energy sources for intestinal epithelial cells, also possess regulatory properties that influence host metabolism, immune homeostasis, and cellular proliferation (50). It has been established that metabolic alterations in hosts with prehypertension or hypertension are closely linked to dysbiosis of the gut microbiome (51). Changes in gut microbiota composition serve as significant indicators. Over the past decade, it has become evident that the gut microbiota plays a vital role in the development of metabolic diseases, including cardiovascular diseases. Numerous studies have suggested a relationship between cardiovascular diseases and the gut microbiome. For instance, patients with atherosclerotic stroke exhibit altered gut microbiota characterized by increased abundance of opportunistic pathogens such as Enterobacter, Oscillibacter, and Desulfovibrio, alongside a decrease in beneficial bacteria including Bacteroides, Prevotella, and Faecalibacterium (52). The gut microbiota composition in patients with heart failure shows significant depletion of short-chain fatty acid-producing bacteria (53). The influence of gut microbiota on blood pressure and vascular tone is supported by findings in germ-free rats receiving healthy microbiota transplants, which restored blood pressure and vascular contractility; this strongly confirms that blood pressure can be modulated by the gut microbiota (54). Regarding dietary interventions, plant-based and fiber-rich diets have been shown to limit trimethylamine (TMA) production and consequently reduce TMAO levels. This effect is associated with downregulation of the cutC gene expression, thereby suppressing microbial TMA production (55).

In parallel with these biological and microbial advancements, artificial intelligence (AI) applications are playing an increasingly prominent role across the continuum of cardiovascular medicine, from diagnosis to treatment. Notably, the analysis of cardiac computed tomography (CT), magnetic resonance imaging (MRI), and echocardiography (ECHO) images using deep learning algorithms enables faster, more consistent, and objective assessment of critical parameters such as plaque stability, degrees of coronary stenosis, ventricular function, and fibrosis levels (56). AI models are not limited to image processing alone; by integrating multimodal clinical data, they offer promising results in developing personalized cardiovascular risk scores. For instance, deep neural networks applied to electrocardiogram (ECG) data can accurately predict subclinical heart failure, atrial fibrillation risk, or sudden cardiac death risk (30). Moreover, AI-driven early warning systems developed for intensive care and emergency settings can predict critical events such as acute myocardial infarction, cardiogenic shock, or ventricular arrhythmias within minutes, thereby accelerating intervention and enhancing patient safety (57). AI platforms integrated with clinical decision support systems can analyze drug-drug interactions through electronic

health records, personalize treatment protocols, and automatically suggest prescriptions, thus supporting clinicians' decision-making and reducing error risks (31). Collectively, these findings demonstrate that cardiovascular biomarkers have evolved beyond molecular-level indicators to encompass interdisciplinary approaches involving microbiota and artificial intelligence, advancing toward a broader, more precise, and personalized paradigm in cardiovascular health.

CONCLUSION

TMAO, SCFAs, next-generation biomarkers (such as ST2, Galectin-3, AI vascular age), and advancements in gut microbiota represent revolutionary potential in the diagnosis and management of cardiovascular diseases (CVD). AI-supported analyses enable multi-layered data integration ranging from clinical information and imaging techniques to genomics and metabolomics, facilitating the development of proactive and personalized healthcare approaches. Microbiota modulation, through drug-diet combinations and pharmacological targets, forms the foundation of integrated strategies for the prevention and treatment of CVD. Consequently, the future management of cardiovascular diseases is evolving toward an interdisciplinary and holistic approach focused on molecular biology advancements, digital data analytics, and microbial balance. Concurrent evaluation of these three domains will pave the way for individualized, preventive, and proactive healthcare delivery, playing a critical role in reducing CVD morbidity and mortality.

Future Perspectives

The integration of biomarkers, artificial intelligence (AI), and microbiota fields enables the development of comprehensive systems at algorithmic, molecular, and clinical levels for the diagnosis and treatment of cardiovascular diseases (CVD). Microbiota-based individual biomarkers, especially metabolite profiles and bacterial ensembles, hold promise for incorporation into routine clinical practice in the near future. Additionally, AI-supported non-invasive digital markers such as the "AI-vascular age" have the potential to become critical tools for early risk stratification and disease monitoring. Epigenetic modifications and metaproteomic profiles at the molecular level offer novel therapeutic targets for personalized microbiota interventions. The preservation of cardiovascular health and disease management now involve complexities beyond traditional physical examinations and imaging techniques. The elucidation of molecular processes by biomarkers, AI's predictive analyses of clinical data, and microbiota-based approaches providing novel diagnostic and therapeutic targets will collectively enable early diagnosis, effective treatment, and improved patient outcomes through an integrated approach.

In summary, biomarkers reveal disease processes at the molecular level; AI analyzes clinical data to provide personalized risk assessments and therapeutic predictions; and microbiota offers novel and unique targets for both diagnosis and therapy. This interdisciplinary integration will pioneer the reshaping of paradigms in the future management of cardiovascular diseases and facilitate the development of personalized, proactive, and effective healthcare strategies.

DESCRIPTIONS

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