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Genomics and Epigenetics in Cardiovascular Diseases: From Personalized Medicine to Targeted Therapies

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Cardiovascular diseases (CVDs) are the leading global cause of death, creating significant socioeconomic and healthcare challenges. Advances in genomics and epigenetics offer new avenues for biomarker discovery, early diagnosis, and personalized therapies. Omics technologies, integrated with artificial intelligence, enhance the potential for CVD prevention and targeted treatment. This narrative review comprehensively searched PubMed, Scopus, Web of Science, and Google Scholar for studies published, using keywords related to genomics, epigenetics, omics, and CVDs. The review included original research, reviews, and clinical trials, and the extracted data were organized into thematic categories: biomarkers, single-nucleotide polymorphisms (SNPs), epigenetic regulation, personalized medicine, novel therapeutics, and clinical challenges. Evidence indicates that genomic and epigenetic biomarkers play a crucial role in predicting CVD risk. SNPs are strongly associated with hypertension, atherosclerosis, and heart failure. Deoxyribonucleic acid (DNA) methylation and histone modifications modulate key pathological pathways, while microRNAs and lncRNAs act as important regulators of cardiovascular gene expression. In therapeutics, pharmacogenomics enables tailoring of drug regimens to patients' genetic profiles. Furthermore, omics technologies and multi-omics integration powered by AI enhance precision cardiovascular medicine by identifying molecular networks and improving risk prediction models. Integration of genomics and epigenetics with omics technologies and artificial intelligence may improve the diagnosis, prevention, and personalized management of cardiovascular diseases; however, many of these approaches still require further clinical validation before widespread implementation. Despite challenges such as genetic diversity, high costs, and ethical concerns, the establishment of national biobanks and population-based genomic studies in countries like Iran represent valuable opportunities to advance toward precision cardiovascular medicine and improve public health outcomes.

Keywords: Genomics, Epigenetics, Cardiovascular Diseases, Personalized Medicine, Targeted Therapies

Introduction

Cardiovascular diseases (CVDs) encompass coronary artery disease, stroke, peripheral vascular disease, heart failure, and other disorders affecting the heart and vascular system. These conditions are recognized as one of the leading causes of mortality worldwide[1] . According to reports from the World Health Organization, approximately 17.9 million people die each year due to CVDs, accounting for nearly one-third of all global deaths[2]. Moreover, the global prevalence of CVDs has increased markedly over recent decades. Global predictive models suggest that between 2025 and 2050, the prevalence of CVDs will rise by nearly 90%, while crude (non-age-standardized) mortality is expected to increase by

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approximately 73.4% [3]. In Iran, CVDs also represent one of the most significant public health challenges. Ongoing lifestyle transitions, increasing rates of obesity, diabetes, and uncontrolled hypertension have contributed to a younger age of disease onset, while simultaneously imposing substantial economic and healthcare costs on patients and the health system. Although more precise national statistics may be updated with some delay, available evidence indicates a continuing upward trend in the burden of CVDs in the country [4].

Genetic factors, including mutations, single-nucleotide polymorphisms (SNPs), and cumulative genetic scores, are recognized as stable and measurable predictors of CVD risk. For example, recent studies have demonstrated that using polygenic risk scores (PRS) for coronary artery disease can significantly improve the sensitivity and accuracy of traditional clinical risk prediction models [3]. In addition, monogenic or single-gene genetics plays an important role in early-onset forms of disease, whereby certain individuals develop cardiovascular conditions at a younger age due to pathogenic variants in a single gene [5]. In contrast, epigenetics refers to regulatory mechanisms that influence gene expression without altering the underlying DNA sequence, including DNA methylation, histone modifications, and non-coding RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) [6]. These epigenetic modifications are strongly influenced by environmental factors such as diet, physical activity, oxidative stress, and exposure to pollutants. Notably, epigenetic alterations may precede structural or clinical changes, making them valuable candidates for early biomarkers of cardiovascular disease [7]. Traditional management of CVDs has primarily focused on controlling established risk factors, such as hypertension, dyslipidemia, and diabetes, and is generally designed for the population as a whole. Although these approaches have proven beneficial, substantial inter-individual variability in treatment response exists, largely attributable to genetic and epigenetic differences as well as population heterogeneity [8]. In contrast, personalized medicine aims to tailor preventive and therapeutic strategies based on each individual's genetic, biological, and environmental profile. Recent research indicates that integrating genomic data with epigenetic information, multi-omics biomarkers, and machine-learning models enables more accurate risk prediction, earlier diagnosis, and optimized therapeutic decision-making. This approach has the potential not only to enhance treatment efficacy but also to reduce adverse effects and improve the efficiency of healthcare resource utilization [9].

The aim of this narrative review is to comprehensively examine the role of genomics and epigenetics across three major domains related to CVDs. First, in the context of prevention, the review explores how genetic and epigenetic data can be used to identify high-risk individuals and to design targeted interventions that may prevent disease onset or progression. Second, in the area of early diagnosis, the focus is placed on identifying molecular and genetic biomarkers capable of detecting disease prior to the emergence of clinical symptoms, thereby enabling timely intervention. Finally, in the domain of targeted therapy, the review discusses how genetic and epigenetic information can guide the selection of appropriate drugs, dose optimization, and the development of individualized treatment strategies to improve clinical outcomes while minimizing adverse effects.

Methods

This study was designed as a narrative review aimed at synthesizing and critically analyzing current evidence on the role of genomics and epigenetics in CVDs, with particular emphasis on personalized medicine, precision cardiology, and targeted therapeutic strategies.

A structured literature search was conducted in major international scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify relevant studies published in English up to 2025. Search terms and Medical Subject Headings (MeSH) were used alone or in combination and included "genomics," "epigenetics," "cardiovascular diseases," "precision medicine," "pharmacogenomics," "genome-wide association studies (GWAS)," "DNA methylation," "histone modification," "microRNA," "long non-coding RNA," "multi-omics," "artificial intelligence," and "targeted therapy." Additional relevant studies were identified through manual screening of reference lists from selected articles.

Eligible studies included peer-reviewed original research articles, clinical trials, systematic reviews, meta-analyses, and high-quality narrative reviews addressing the role of genomic and epigenetic mechanisms in the prevention, diagnosis, risk prediction, pathophysiology, and treatment of CVDs. Studies unrelated to cardiovascular conditions, conference abstracts, editorials, duplicate publications, and non-peer-reviewed sources were excluded. Preference was given to recent studies, landmark investigations, large-scale cohort studies, multi-ethnic genomic analyses, and clinically relevant translational research.

The identified literature was reviewed and prioritized according to methodological rigor, scientific relevance, recency of evidence, and potential clinical applicability. Particular emphasis was placed on studies investigating genomic risk prediction, polygenic risk scores, epigenetic regulation, pharmacogenomics, omics technologies, artificial intelligence-based analytical approaches, and emerging targeted therapies in cardiovascular medicine.

Relevant information was extracted manually from the selected studies, including study objectives, methodologies, principal findings, and clinical implications. The extracted data were subsequently organized into thematic categories encompassing genetic biomarkers, epigenetic mechanisms, personalized medicine, pharmacogenomics, multi-omics integration, artificial intelligence applications, and novel therapeutic strategies. A qualitative narrative synthesis approach was then applied to integrate findings and highlight converging and diverging evidence across studies.

Given the narrative nature of this review, no formal risk-of-bias assessment or quantitative meta-analysis was performed. Nevertheless, efforts were made to ensure scientific rigor by prioritizing high-quality and clinically informative publications and by incorporating evidence from both foundational and recent studies in the field.

Although this review was narrative in design, efforts were made to minimize potential selection bias by using multiple databases, predefined search terms, broad eligibility criteria, and prioritization of high-quality, clinically relevant, and widely cited studies representing diverse populations and research approaches.

Genomics in CVDs

Genetic Biomarkers in Cardiovascular Disease Risk Prediction

Genetic biomarkers refer to indicators based on specific genetic variations or combinations of variants that can predict an individual's risk of developing CVDs prior to the onset of clinical manifestations. For instance, PRS for coronary artery disease has been shown to significantly improve predictive accuracy when incorporated into conventional clinical risk models [10]. A large multi-ancestry study introduced a novel global multi-ancestry polygenic score for coronary artery disease by integrating genome-wide association data from multiple continents. This study demonstrated that individuals within the highest percentile of the polygenic risk score distribution had an approximately threefold higher risk of developing coronary artery disease compared with those in the intermediate risk category [11]. Similarly, for cardiovascular traits such as blood pressure, extensive GWAS have identified hundreds of genetic loci associated with systolic and diastolic blood pressure. When combined into PRS, these loci enhance the prediction of hypertension susceptibility and may help identify individuals who are more likely to exhibit treatment resistance or early disease onset [12].

SNPs Associated with Hypertension, Atherosclerosis, and Heart Failure

SNPs in genes with diverse biological functions have been identified in numerous studies as either risk or protective factors for CVDs. One well-established example involves SNPs in the SLCO1B1 gene, which plays a critical role in statin transport and metabolism. Specific allelic variants of this gene have been associated with an increased risk of statin-induced myopathy, highlighting the clinical relevance of genetic variation in drug response [13]. In the context of hypertension, SNPs in key components of the renin–angiotensin–aldosterone system, including ACE, AGT, and AGTR1, have been shown to influence blood pressure levels as well as individual responses to angiotensin-converting enzyme inhibitors and angiotensin receptor blockers [13]. These findings underscore the contribution of genetic variability to both disease susceptibility and therapeutic outcomes. For heart failure, large-scale genome-wide association studies have identified multiple genetic loci associated with disease risk. Many of these loci exhibit pleiotropic effects and are also implicated in related conditions such as hypertension, diabetes mellitus, coronary artery disease, and chronic kidney disease, reflecting the complex and multifactorial nature of heart failure pathogenesis [14]. Atherosclerosis is similarly influenced by SNPs in genes involved in lipid metabolism, vascular inflammation, plasma protein synthesis, and oxidative stress responses. Notably, the 9p21 locus has emerged as one of the most robustly associated genomic regions with coronary artery disease across multiple populations and independent studies, emphasizing its central role in atherosclerotic disease susceptibility [11, 15].

The Role of Genomics in Early Diagnosis and Preventive Strategies

Early diagnosis through genomics refers to the identification of individuals with a high genetic risk for CVDs before the onset of clinical symptoms.

The application of PRS and models derived from genome-wide association studies enables the identification of high-risk individuals at younger ages, allowing for the implementation of lifestyle modifications and preventive pharmacological interventions [11, 16]. For example, studies using the global multi-ancestry polygenic score have demonstrated that individuals with high genetic risk for coronary artery disease exhibit a substantially increased likelihood of disease development. Importantly, evidence suggests that intensive management of lipid levels, blood pressure control, and the use of lipid-lowering therapies in these individuals can significantly delay disease onset and progression [11]. In addition, the use of genome-wide association data related to blood pressure has led to the identification of numerous novel genetic loci, thereby increasing the proportion of blood pressure variability explained by genetic factors. This enhanced understanding provides new opportunities for targeted preventive strategies and early intervention in individuals predisposed to hypertension [17]. In populations with diverse ethnic backgrounds and distinct genetic architectures, recalibration and population-specific validation of genomic risk prediction models are essential to improve risk estimation accuracy and ensure equitable clinical application across different demographic groups [18].

Pharmacogenomics: Genetic Variability in Responses to Cardiovascular Drugs

Pharmacogenomics examines how inter-individual genetic differences influence drug responses in terms of both therapeutic efficacy and the risk of adverse effects. Recent review articles have demonstrated that multiple genetic polymorphisms play a critical role in modulating responses to commonly prescribed cardiovascular medications. For example, the antiplatelet drug clopidogrel is significantly affected by genetic variation in the CYP2C19 gene. Individuals carrying loss-of-function alleles of this gene may exhibit reduced platelet inhibition, resulting in a diminished therapeutic response and an increased risk of ischemic events [13]. In the case of statins, SNPs in the SLCO1B1 gene, particularly the rs4149056 variant, are associated with impaired hepatic uptake of statins and elevated plasma drug concentrations, which in turn increase the risk of statin-induced myopathy. Similarly, anticoagulant therapy with warfarin is strongly influenced by genetic variation in VKORC1 and CYP2C9. Different genotypes of these genes are associated with variable dose requirements and differential risks of bleeding complications, underscoring the importance of genotype-guided dosing strategies. Responses to antihypertensive medications are also affected by genetic factors. For instance, polymorphisms in the ADRB1 and ADRB2 genes have been shown to influence patient responses to beta-blockers, with certain ADRB1 genotypes exhibiting greater blood pressure reduction than others. Overall, pharmacogenomics holds substantial promise for optimizing cardiovascular therapy by enabling the selection of the most appropriate drug and dosage for each individual, thereby improving efficacy and minimizing adverse effects. Among current cardiovascular genomic applications, pharmacogenomic testing for CYP2C19, VKORC1, CYP2C9, and SLCO1B1 variants represents one of the most clinically validated areas, with increasing incorporation into personalized therapeutic decision-making frameworks. Nevertheless, several challenges remain, including genetic heterogeneity across populations, the cost and accessibility of genetic testing

, and the need for robust clinical trials to demonstrate clear clinical benefit and cost-effectiveness in routine practice [13].

Epigenetics in CVDs

DNA Methylation and Its Impact on Vascular Injury and Atherosclerosis

DNA methylation is one of the principal epigenetic mechanisms and involves the addition of a methyl group to cytosine residues at CpG sites. This process can either repress or activate gene expression without altering the underlying DNA sequence [19]. Large-scale human studies have demonstrated that alterations in DNA methylation levels within genes related to endothelial function, inflammation, and lipid metabolism are associated with an increased risk of CVDs [20]. For example, one study reported that blood-based DNA methylation patterns at hundreds of CpG sites were able to predict the occurrence of coronary artery disease beyond traditional cardiovascular risk factors [21].

Furthermore, aberrant methylation in regulatory regions of genes such as SLC1A5, SLC9A1, and TNRC6C has been identified in association with coronary artery disease, indicating potential effects on glutamine metabolism, inflammatory responses, and endothelial cell function [22]. DNA methylation has also been implicated in the progression of atherosclerosis through localized changes within the vascular wall. In this context, genes involved in nitric oxide production, oxidative stress responses, and cholesterol regulation appear to be epigenetically modified, contributing to endothelial dysfunction and plaque development [23].

Histone Modifications and Cardiac Cellular Reprogramming

Histone modifications, including acetylation, methylation, phosphorylation, and demethylation, play a central role in regulating chromatin structure and, consequently, the accessibility of transcriptional machinery to target genes [24]. Through these mechanisms, histone modifications exert fine control over gene expression without altering the DNA sequence. For example, reduced activity of HDAC1/2, which leads to decreased acetylation of histone marks H3K9/14ac and H4K8ac, has been shown to downregulate the expression of the NPR1 gene in response to angiotensin II. This epigenetic alteration contributes to vascular dysfunction and the development of hypertension [25].

Evidence from experimental and clinical studies further indicates that heart failure and ischemia–reperfusion injury are associated with distinct patterns of histone modifications. Specifically, increased levels of H3K27 methylation, a hallmark of transcriptional repression, along with altered HDAC activity, have been observed in both animal models and human tissues affected by cardiac injury [26]. Beyond their effects on gene expression, these histone modifications play a crucial role in cardiac cellular reprogramming following myocardial infarction or ischemic damage. By influencing inflammatory responses, fibrotic processes, and tissue remodeling, epigenetic reprogramming contributes to the dynamic adaptation of the heart during injury and repair, ultimately affecting disease progression and functional recovery [27].

miRNAs and lncRNAs in the Regulation of Cardiovascular Gene Expression

Non-coding RNAs, including miRNAs and lncRNAs, play a crucial role in the post-transcriptional regulation of gene expression. These molecules can modulate transcriptional activity, messenger RNA (mRNA) stability, and translational efficiency, thereby exerting significant influence over cardiovascular cellular processes [28]. For example, miRNA-92a has been reported to be upregulated in cardiovascular disease and to exert deleterious effects on endothelial function, thereby promoting the progression of atherosclerosis [29]. In contrast, miRNA-126 and miRNA-144 have been shown to play protective roles in maintaining vascular integrity, regulating angiogenesis, and reducing inflammatory responses within the vascular wall [30].

With respect to lncRNAs, several members of this class have been shown to regulate chromatin architecture through interactions with histone-modifying complexes or by recruiting enzymes such as histone deacetylases or histone acetyltransferases. Through these mechanisms, lncRNAs influence the expression of genes essential for cardiac function, cellular survival, and tissue repair following cardiac injury [31]. Importantly, both miRNAs and lncRNAs are detectable in circulating blood, which makes them attractive candidates as minimally invasive biomarkers for disease diagnosis, prognostic stratification, and monitoring of therapeutic responses in CVDs [32].

Epigenetics and Environmental Factors in the Development and Progression of CVDs

Environmental factors play a pivotal role in inducing epigenetic modifications that contribute to the development and progression of CVDs. Dietary patterns rich or deficient in methylation-related nutrients, such as folate, vitamin B12, and methionine, can alter DNA methylation profiles, thereby influencing vascular function and inflammatory pathways [6]. These diet-induced epigenetic changes highlight the dynamic interaction between nutrition and gene regulation in cardiovascular health. Physical activity has been consistently shown to exert beneficial epigenetic effects. For instance, regular aerobic exercise can reduce DNA methylation in genes involved in oxidative stress regulation and enhance the expression of anti-inflammatory miRNAs and lncRNAs. These epigenetic adaptations contribute to improved endothelial function, reduced vascular inflammation, and a lower burden of cardiovascular risk factors [33]. Conversely, adverse environmental exposures such as air pollution, cigarette smoke, diets high in saturated fats or refined sugars, oxidative stress, and metabolic conditions such as diabetes are well-established contributors to detrimental epigenetic alterations. These factors have been associated with aberrant DNA methylation patterns, histone modifications, and dysregulated miRNA and lncRNA expression, all of which can accelerate vascular injury, promote atherosclerosis, and worsen the clinical course of CVDs [34].

Personalized Medicine and Clinical Applications

Personalized Medicine in the Prevention of CVDs (Screening Based on Genetic and Epigenetic Profiles)

Personalized medicine in the field of CVDs is based on the premise that comprehensive knowledge of an individual's genetic and epigenetic profile enables more accurate identification of at-risk individuals and more informed preventive decision-making. The use of PRS as a complementary tool to conventional clinical risk models has been shown to improve risk stratification and facilitate targeted preventive interventions. For example, individuals positioned in the upper percentiles of the polygenic risk score distribution demonstrate a substantially higher risk of coronary artery disease, even in the presence of similar traditional risk factors, and may therefore benefit from earlier or more intensive preventive strategies [11]. In parallel, epigenetic markers, including DNA methylation patterns, circulating miRNA signatures, and histone modification profiles, offer accessible early indicators of disease susceptibility, often detectable in peripheral blood samples before clinical manifestation. Consequently, integrating PRS with epigenetic biomarkers may improve the sensitivity and specificity of cardiovascular disease screening programs, although further validation in large and diverse clinical populations is still required [35].

The clinical implementation of genetic and epigenetic screening requires a robust framework encompassing validation across diverse populations, recalibration for ethnic and ancestry-specific subgroups, and the development of clear clinical pathways. Such pathways should define who should be tested, how results are communicated, and which preventive actions should follow. Without these structured approaches, the application of PRS in routine clinical practice may lead to misinterpretation, uncertainty, or suboptimal clinical decision-making [36].

Personalized Therapies Based on Patients' Genomic and Epigenetic Profiles

Personalized treatment in CVDs is based on three main approaches: (1) selection of the appropriate drug and dosage according to genetic makeup (pharmacogenomics), (2) targeting specific molecular pathways that are dysregulated in an individual patient, and (3) using epigenetic biomarkers to guide decisions regarding the timing and intensity of therapy. For example, evidence indicates that CYP2C19 genotyping can inform the selection and dosing of clopidogrel following percutaneous coronary intervention, while VKORC1 and CYP2C9 genotypes significantly influence warfarin dose requirements and bleeding risk. In selected patients, pharmacogenomic testing can therefore reduce adverse events and improve therapeutic efficacy [13]. Beyond pharmacotherapy, genomic analysis and the identification of monogenic mutations in patients with early-onset CVDs, such as inherited cardiomyopathies, enable cascade screening of family members and the timely implementation of secondary preventive measures or prophylactic interventions, including the implantation of cardioverter-defibrillators (ICDs) when indicated [5, 37].

Use of Bioinformatics and Artificial Intelligence for the Analysis of Genomic and Epigenetic Data

Genomic and epigenetic datasets are inherently large-scale and high-dimensional, making the extraction of clinically meaningful information dependent on advanced bioinformatics tools and machine learning/artificial intelligence (AI) algorithms.

Machine learning models have demonstrated the ability to identify complex patterns and interactions among genetic variants, epigenetic markers, and clinical parameters in experimental and translational studies, potentially supporting the development of improved PRS and multi-omics biomarkers [39]. Moreover, AI can be applied across multiple stages of analysis: first, for the filtering, prioritization, and interpretation of genetic variants; second, for the integration of multi-omics data to construct robust predictive biological models; and third, for clinical decision support systems that assist clinicians in selecting appropriate therapies, optimizing drug dosages, or recommending targeted preventive interventions [40]. On the other hand, the volume and complexity of omics data necessitate analytical approaches that extend beyond classical statistical methods; this is where AI and machine learning become essential. Machine learning models and deep neural networks are capable of extracting complex patterns and non-linear interactions among diverse omics components, generating improved PRS, and developing predictive models for disease risk or therapeutic response that outperform traditional clinical models. Successful applications include the prediction of acute heart failure events, stratification of patient subgroups with atherosclerosis, and the identification of multi-omics biomarkers for prognostic assessment [41].

Despite these promising applications, it is essential that AI-based models are transparent, interpretable, and rigorously validated using independent datasets and diverse populations. Such safeguards are necessary to minimize bias, enhance generalizability, and prevent clinical errors, thereby ensuring the safe and effective translation of AI-driven tools into routine cardiovascular care [42]. However, many artificial intelligence-based and multi-omics predictive models remain exploratory and require further external validation, reproducibility assessment, and prospective clinical evaluation before widespread clinical implementation.

Novel Targeted Therapies

Gene Therapy and Genome Editing in Inherited CVDs

Gene therapy and genome-editing technologies, such as CRISPR–Cas9, base editing, and prime editing, have opened new horizons for the treatment of genetically driven CVDs. These approaches enable the correction of pathogenic mutations or the inactivation of deleterious genes, thereby offering promising investigational approaches for disease-modifying therapies in selected inherited cardiovascular disorders, although most applications remain in preclinical or early clinical stages [43]. In preclinical studies and early-phase human trials, targeted editing of lipid-related genes, including PCSK9 and ANGPTL3, has been associated with substantial and sustained reductions in LDL cholesterol and other atherogenic lipid parameters. These findings suggest that a single, one-time intervention may confer long-term safety, the risk of off-target genomic alterations, and potential immunological consequences require extended follow-up and rigorous monitoring [44, 45]. In monogenic cardiovascular conditions, such as familial cardiomyopathies and inherited metabolic disorders, genome-editing strategies have demonstrated disease-correcting effects in animal models. Nonetheless, several technical and clinical challenges remain, including the development of safe and efficient

delivery systems (using viral vectors, lipid nanoparticles, or non-viral carriers) and the identification of optimal target cell populations (e.g., hepatocytes for lipid-related genes versus cardiomyocytes for certain cardiomyopathies). Addressing these challenges is critical for the successful translation of genome-editing therapies into routine cardiovascular clinical practice [46].

RNA-Based Therapies

RNA-based therapeutics have emerged as promising investigational tools for the selective targeting of disease-related genes without permanent modification of the DNA sequence [47]. In the context of CVDs, RNA-based agents have been developed to suppress the expression of PCSK9 or APOC3 for lipid lowering, and several of these molecules (e.g., anti-APOC3 or anti-ANGPTL3 ASO/siRNA therapies) have demonstrated marked reductions in triglyceride levels and LDL cholesterol in clinical trials [48]. Beyond lipid control, therapeutic RNAs are also being explored to target key pathogenic processes such as inflammation, fibrosis, and ischemic injury [49]. For instance, specific miRNAs that regulate the expression of fibrotic or apoptotic genes have been shown in experimental models to attenuate myocardial fibrosis and improve cardiac function [50]. Nevertheless, challenges related to efficient cellular delivery, molecular stability of RNA agents in the circulation, and the risk of immune or inflammatory responses must be addressed before these therapies can be widely implemented in clinical practice [51].

Epigenetic Drugs in the Treatment of CVDs

A substantial proportion of cardiovascular injury arises from epigenetic reprogramming, including alterations in DNA methylation and histone modifications [52]. Consequently, inhibitors of epigenetic regulatory enzymes, such as DNA methyltransferase inhibitors (DNMTis) and histone deacetylase (HDAC) inhibitors, have been investigated as potential therapeutic strategies to modulate fibrosis, inflammation, and pathological cardiac remodeling [53, 54]. Evidence from animal models indicates that DNMTis and certain HDAC inhibitors can attenuate cardiac fibrosis and improve myocardial contractile function [55]. However, many currently available epigenetic inhibitors exert broad systemic effects and are associated with significant adverse events. Therefore, the development of more selective agents, targeted or localized delivery strategies (e.g., myocardial-specific delivery), and combination approaches with established therapies are key priorities to enhance efficacy while minimizing toxicity. In parallel, the identification and validation of epigenetic biomarkers to select patients most likely to benefit from these interventions is essential for their successful translation into clinical practice [56].

Future of Combination Therapies

The future of targeted cardiovascular therapies is moving toward multi-omics integration, combining genomics, epigenomics, transcriptomics, proteomics, and metabolomics with clinical and imaging data to construct precise, patient-specific profiles. This approach enables the identification of unique molecular pathways in each patient and the selection of optimal combination therapies, such as genome editing or RNA-based therapeutics alongside epigenetic drugs and lifestyle interventions [57]. Advanced bioinformatics and AI play a central role in analyzing multidimensional datasets, prioritizing biomarkers, and designing personalized combination treatment strategies [40]. However, several challenges remain, including data standardization, quality control, privacy protection, costs, and the need to demonstrate efficacy and safety in rigorous clinical trials. Future clinical trial programs should focus on establishing clinical benefit, long-term safety monitoring, and cost-effectiveness assessment to enable the integration of these strategies into routine cardiovascular care [58].

Role of Omics Technologies in CVDs

Transcriptomics, including RNA sequencing (RNA-seq) and single-cell/spatial transcriptomics, enables quantification of gene expression and non-coding RNAs in cardiac tissues and cells, directly contributing to the identification of active molecular pathways across disease stages, from inflammation and atherosclerosis to post-ischemic remodeling [59]. Single-cell transcriptomic studies have uncovered novel cellular subpopulations, such as specialized endothelial cells or fibroblasts, which play critical roles in pathogenesis and therapeutic response [60]. Proteomics, using mass spectrometry and immunoassay-based platforms capable of quantifying thousands of proteins, serves as a bridge between gene expression and biological function, identifying circulating protein biomarkers for cardiovascular event prediction and patient stratification [61]. Integration of transcriptomic and proteomic data has been particularly valuable for uncovering regulatory pathways and novel drug targets [62].

Metabolomics, which measures small molecules including metabolites, lipids, and amino acids in plasma or cardiac tissue, provides insight into the links between nutritional status, metabolic disturbances, and cardiac pathophysiology. Specific metabolic profiles, such as accumulation of oxidized fatty acids, acylcarnitines, and microbiome-associated metabolites, have been associated with heart failure and myocardial infarction risk and can predict responses to dietary or lipid-lowering interventions. Moreover, metabolomics can identify nutrition-dependent targetable pathways amenable to dietary or pharmacological modulation [63, 64].

Since each omic layer represents only a part of the molecular network, understanding cardiovascular disease pathogenesis requires integration of multiple layers—genomics, epigenomics, transcriptomics, proteomics, metabolomics, and even exosomal/microbiome data [65]. Network-based and multi-omics integration approaches enable identification of key nodes and pathways, stratification of patients according to molecular mechanisms, and suggestion of combinatorial therapeutic targets [66]. Multi-omics integration studies in atherosclerosis and heart failure have demonstrated superior biomarker discovery compared with single-omic analyses and provided novel insights into overlapping pathways linking metabolism, inflammation, and cardiac structural changes [67].

Challenges and Future Perspectives

Despite significant advances in cardiovascular genomics and epigenetics, several challenges limit the broad applicability of findings. Genetic diversity across populations is a primary concern, as many PRS and reference databases have been developed predominantly in European cohorts; therefore, predictive accuracy may be reduced in Asian, African, and Middle Eastern populations [68]. The lack of comprehensive multi-ethnic datasets also impedes the identification of high-risk variants, limiting their clinical utility [69]. Moreover, epigenetic modifications are influenced by environmental and cultural factors, including diet, pollution, and lifestyle, meaning predictive models may lack practical relevance if local conditions are not considered [70].

Ethical considerations are also critical. Ensuring patient privacy and preventing misuse of genomic data by insurers or employers remain major concerns [71]. High costs associated with sequencing, data storage, and analysis pose additional barriers for implementing precision medicine widely, particularly in developing countries [72]. Insufficient education for patients and healthcare providers regarding the interpretation of genetic data can lead to misunderstanding and psychological distress. National guidelines are therefore essential for safe, equitable, and ethical use of genomic information [73].

Iran, with its high genetic and ethnic diversity, represents a valuable opportunity for genomics and epigenetics research. Establishing national biobanks containing blood, DNA, and clinical data can provide foundational infrastructure for future studies. Population-scale genomic projects could collect longitudinal data from healthy and diseased individuals, enabling the development of locally relevant PRS and epigenetic biomarkers. Investment in human resources in bioinformatics, medical genetics, and genetic epidemiology, along with international collaboration and integration with global genome initiatives, can strengthen Iran's scientific standing.

The future of cardiovascular medicine is increasingly moving toward precision cardiology, where integration of genomics, epigenomics, multi-omics technologies, and artificial intelligence may support more individualized prevention and treatment strategies. This approach enables targeted therapies, optimized drug response prediction, and personalized preventive interventions. With advances in gene-editing technologies, RNA-based therapeutics, and epigenetic drugs, the management of CVDs is poised to move beyond traditional paradigms. In Iran, the development of appropriate scientific and ethical infrastructure could facilitate meaningful progress toward precision cardiovascular medicine.

Conclusion

CVDs remain the leading cause of mortality worldwide, imposing a substantial burden on healthcare systems. Advances in genomics and epigenetics, combined with multi-omics technologies, have opened new avenues for the prevention, early diagnosis, and precision treatment of these conditions. The identification of genetic and epigenetic biomarkers, discovery of risk-associated polymorphisms, and development of pharmacogenomic tools have enabled clinicians to tailor therapies according to the molecular characteristics of individual patients. Epigenetic studies, including DNA methylation, histone modifications, and the roles of miRNAs, have highlighted how environmental factors and lifestyle can modulate disease progression through gene expression regulation. Moreover, integrating multi-omics data with AI analytics has facilitated the emergence of precision cardiovascular medicine, a model that not only improves risk prediction and drug selection but also supports the design of personalized preventive interventions. Nonetheless, challenges such as population genetic diversity, limited data availability, high costs, and ethical considerations remain critical. Future research and clinical practice in this field are expected to focus on data integration, development of national biobanks, and expansion of international collaborations. These efforts will be essential to fully realize the potential of personalized cardiovascular medicine and to enhance cardiovascular health outcomes globally.

Although significant progress has been achieved in cardiovascular genomics and epigenetics, many emerging multi-omics, artificial intelligence-based, and epigenetic therapeutic approaches remain investigational and require further large-scale clinical validation before routine implementation in cardiovascular practice.

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Authors declare no conflicts of interests.

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