

Unlocking Cardiovascular Health: The Synergy of Genetics, Pharmacotherapy, Comorbidities, and Herbal Medicine

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ABSTRACT

Cardiovascular Diseases (CVDs) are still a leading cause of morbidity and mortality worldwide, which has led to increased research in personalized approaches to therapy, new drug targets, and more understanding of comorbidities. The importance of the CYP2C19 polymorphisms and their role in the metabolism of the cardiovascular drug clopidogrel to establish whether there is an opportunity for precision medicine: genetic testing using PCR-based assays can identify patients with loss-of-function alleles. It also explains the significance of PCSK9 inhibitor therapies, which are increasingly mainstream in the treatment of hyperlipidemia in the form of available lipid-lowering options for statin-intolerant patients. We also highlight SGLT2 inhibitors, which software explores a role in heart failure management alongside their role in diabetes. Ultimately, this approach goes beyond a glycemic control strategy but includes renal and cardiovascular protection. Importantly, various comorbidities, including diabetes, Chronic Kidney Disease (CKD), and obesity-related hypertension, increase cardiovascular risk and must be considered in therapy. We discuss the existing pharmacologic management strategies for managing the dual risks of diabetes and CVD, the reciprocal relationship between CKD and CVD, and the underlying hypertension associated with obesity. Finally, we touch on the emerging field of cardio-oncology, as concern for cardiovascular toxicity due to treatment of cancer is just beginning, and treatment strategies to mitigate this area of risk are being developed. Variants in noncoding RNAs and genetic and epigenetic variables have a major role in the onset and advancement of cardiovascular disease. The use of herbal remedies and advancements in biomarker-based early identification offer the possibility of preventive and individualized cardiovascular therapy. This review summarizes the evolving landscape of cardiovascular therapy, including genetic components, new therapeutic agents, and the management of comorbidities, to improve patient quality and outcomes.

Keywords: Cardiometabolic Comorbidities, Cardiovascular Disease, PCSK9 Inhibitors, Precision Cardiology, SGLT2 Inhibitors.

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INTRODUCTION

Cardiovascular Disease (CVD) refers to a variety of disorders affecting the heart and blood arteries.¹ These problems include coronary artery disease, stroke, heart failure, and arrhythmias.² CVD is the largest cause of death worldwide, with heart attacks and strokes accounting for the majority of fatalities.³ Risk

factors include smoking, high blood pressure, high cholesterol, a poor diet, a lack of exercise, and obesity.⁴ Biological (age, sex), behavioural (diet, exercise, smoking, and alcohol consumption), environmental (pollutants, toxins, & infectious agents), and genetic (single gene, multiple gene mutations) factors all have an impact on diseases.^{5,6}

CVD is a leading cause of illness and mortality worldwide. Accounting for a sizable proportion of fatalities and impairments. CVDs alone killed 20.5 million people in 2021, accounting for over one-third of all deaths worldwide.⁷ More than 80% of all deaths from CVD now occur in low- and middle-income countries, where areas such as South Asia are seeing an earlier onset and spread to rural lands. Whereas some amount of decline in deaths from



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heart attacks has been witnessed in high-income countries, more chronic conditions, such as heart failure and atrial fibrillation, seem to be happening.⁸ CVD's high prevalence and cost highlight the need for further research into its pathogenesis, treatments, and management.⁹ Although there are numerous etiologies for heart disease, abnormal inflammatory processes appear to represent a common link between different kinds of CVD.¹⁰ The management of CVD has seen a rapid transformation in the past few decades due to the tremendous expansion in the disciplines of pharmacology, diagnostics, and therapies.¹¹ While SGLT2 inhibitors and GLP-1 receptor agonists target both metabolic and cardiovascular risk, novel lipid-lowering medicines¹² such as PCSK9 inhibition and drugs targeted at lipoprotein and inflammation, are revolutionizing prevention.¹³ Wearable technology, high-sensitivity biomarkers, and AI-assisted imaging are examples of diagnostic advancements that provide early diagnosis and ongoing disease process monitoring.¹⁴ Regenerative medicine ideas like tissue engineering and stem cells may also be used to achieve therapeutic advancements, which otherwise hold out a lot of promise for precision and customized cardiology.¹⁵

The growing worldwide impact of cardiovascular disease, together with complex metabolic, genetic, and environmental connections, makes precision medicine essential for future cardiovascular care.¹⁶ The medical field experiences a transformational shift because of pharmacological developments and genomic advancements, along with diagnostic progress and enhanced therapeutic methods, leading to customized patient care.¹⁷ This paper examines essential developments in cardiovascular treatment by examining pharmacogenomics together with new drug targets and cardiovascular risk management for common comorbidity patterns.

Pharmacogenomics

Pharmacogenomics (PGx) is the study of genomic diversity in medication response, which can affect both pharmacokinetic and pharmacodynamic aspects.¹⁸ Pharmacokinetics refers to the body's influence on a drug, which is classified as effects on absorption, distribution, metabolism, and excretion. Pharmacodynamics reflect the drug's influence on the body.¹⁹ Pharmacokinetics and pharmacodynamics are both factors that determine efficacy, effectiveness, and toxicity. Many medications are processed in the liver by Cytochrome P450 (CYP) enzymes.²⁰ Due to the wide-ranging relevance of PGx to genomic and pharmacology subspecialists, as well as to areas like thrombosis and coagulation, interventional cardiology, heart failure, arrhythmias, clinical trials, and policy/regulatory activity within cardiovascular medicine, this position statement aims to address these issues from a broad perspective.²¹ In addition to discussing general genomic techniques in cardiovascular medicine and the possible use of genomics in clinical trials, the following sections also discuss evidence for particular drug-gene pairings. The emphasis is on the translational elements that practitioners who

are not genomically trained are most likely to come upon in their daily work.

Role of CYP2C19 polymorphisms in cardiovascular drug metabolism

The Cytochrome P450 (CYP) superfamily includes significant phase I drug-metabolizing enzymes that oxidize about 90% of the pharmacological medicines used today.²² CYP1A2, 2A6, 2C9, 2C19, 2E1, 2D6, and 3A4.1 are responsible for more than 90% of drug oxidation in humans.²³ CYP2C9 is one of the most important CYPs, accounting for roughly 20% of P450-mediated drug oxidation processes. Non-functional alleles in the CYP2C9 gene are rather rare.²⁴ CYP2C19 belongs to the family of cytochrome P450 enzymes. Most commonly found in the liver.²⁵ Accountable for the metabolism of a wide range of medications, including prodrugs that need to be activated, such as clopidogrel.²⁶ CYP2C19 polymorphisms have a significant impact on the metabolism of various cardiovascular medications.²⁷ Variations (Table 1) in the CYP2C19 gene can modify enzyme activity, compromising medication efficacy and safety.²⁸

The effectiveness of clopidogrel in cardiovascular patients, especially those undergoing procedures like Percutaneous Coronary Intervention (PCI), is greatly impacted by CYP2C19 gene variations.²⁹ Variants that exhibit Loss-of-Function (LoF), like CYP2C192 and CYP2C193, decrease or stop the activity of the enzyme. One LoF allele is associated with intermediate metabolism, whereas two LoF alleles are associated with poor metabolism. Clopidogrel's conversion to its active form is decreased in both groups, which lowers platelet inhibition and increases the risk of serious adverse cardiovascular events.³⁰ Clinical practice advises CYP2C19 variation genotyping to direct antiplatelet treatment. Alternative antiplatelet medications may be preferred for patients who have been diagnosed as poor metabolizers to lower the chance of treatment failure.³¹ Poor metabolizers contain two loss-of-function alleles, which result in decreased or missing CYP2C19 enzyme activity. Platelet inhibition decreases as clopidogrel's conversion to its active metabolite is reduced, and a markedly increased risk of serious adverse cardiac and cerebrovascular events, particularly in high-risk situations such as Acute Myocardial Infarction (AMI).³²

Other Medications for Heart Disease: Dual antiplatelet therapy uses affected Proton Pump Inhibitors (PPIs), such as omeprazole.³³ converted by CYP2C19. Drug exposure may be higher in poor metabolizers, which would improve acid suppression but increase adverse effects.³⁴ In co-therapy settings, Vorapaxar and Citalopram (QT prolongation) have an impact but are less direct.³⁵ CYP2C19 genetic variations can change how well enzymes work, which in turn affects how effective certain cardiovascular medications are. These genetic differences are particularly important when making decisions about antiplatelet therapy for patients at high

risk. By including CYP2C19 genotyping in clinical practice, we can ensure safer and more effective personalized treatments.³⁶

Genetic and Epigenetic Factors in Cardiovascular Disease

The basis for early-onset CVD is likely due to a genetic basis. There is a genetic basis for early-onset CVD, as more and more research assesses the part that genetics plays in CVD development. There are clearly definable (Mendelian) forms of hereditary CVD like Familial Hypercholesterolemia (FH) and Hypertrophic Cardiomyopathy (HCM). FH and HCM are obvious examples of hereditary CVD that are due to a single genetic change (mutation) in a single gene (e.g., LDLR, APOB, PCSK9, MYH7, etc.) on each chromosome, which can lead to a serious illness at a young age through a disruption of lipid metabolism, a disruption of the myocardium, or a disruption of vascular tissue integrity in pathology. For numerous genes, mutations in coding (protein) genes can be due to polygenic contributions, particularly to susceptibility. Therefore, Polygenic Risk Scores (PRS) can indicate cumulative risk to an individual through inheriting certain genetic variants. More recently, advancements in genome and exome sequencing have made early diagnosis and prediction more accessible for hereditary CVD, while personalizing methods of treatment, including selection of an appropriate therapy such as a PCSK9 antagonist if appropriate. These developments raise significant ethical dilemmas such as the ownership and use of genetic data, informed consent, and inexplicable access to 'genetic medicine'.³⁷

Genetic Variants of Noncoding RNAs and their Role in Cardiovascular Disease

A major emphasis on the role of noncoding RNAs (ncRNAs) has emerged from large-scale projects providing functional annotation of the human genome (e.g. ENCODE, FANTOM). Historically, ncRNAs were often dismissed as "genomic noise". However, specific research areas investigating microRNAs (miRNAs) and Long Noncoding RNAs (lncRNAs) have emerged to be important gene expression regulators and independent evidence is mounting with respect to the important role ncRNAs have in human disease and specifically cardiovascular disease. Since ncRNAs and their target sequences are coded under the same genome, ncRNAs are susceptible to established genetic principles. Common genetic variation infrequently influences the expression, structure or function of ncRNA, thus affecting the regulatory relationship with its target genes. More recently, studies have identified many polymorphisms in ncRNAs or polymorphisms in binding sites for ncRNAs in target genes associated with susceptibility or resistance to cardiovascular phenotypes (e.g. atherosclerosis, myocardial infarction, heart failure). The goal of this review will be to summarize current evidence of the functional significance of these genetic variations

in ncRNAs with regard to pathogenesis and risk classification of cardiovascular disease.³⁸

Sudden Cardiac Death (SCD) is still one of the leading causes of mortality around the world, and there are important age-dependent differences in its etiologies. For example, Coronary Artery Disease (CAD) is the most prevalent cause of SCD in older adults, while inherited cardiomyopathies and channelopathies tend to cause the majority of SCD in individuals younger than 35 years old. Although previously thought to be monogenic, new studies have demonstrated that inherited cardiomyopathies and channelopathies involve polygenic inheritance and environmental factors. As such, knowledge of the genetic architecture of SCD is useful to identify individuals at risk, as well as to better understand and even prevent underlying mechanisms if possible. Ongoing progress in genetics is allowing for better risk stratification and ultimately better tailored prevention and therapy. This review examines the genetic risk factors and clinical implications of CAD in older patients and inherited cardiomyopathies and channelopathies in young individuals, to draw the two together for improved outcomes in each group.³⁹

PCSK9 inhibitors for hyperlipidaemia: Evolution and efficacy

The development of PCSK9 inhibition begins with pioneering genetic findings that defined PCSK9's role in managing LDL cholesterol levels and its consequences on cardiovascular health.⁴⁰ Statins are the first-line treatment for lowering LDL-C. There is still an unmet medical need for individuals who are statin intolerant, unable to take an appropriate dose, or do not achieve approved LDL-C values with a single statin treatment. For this reason, a combination of lipid-lowering drugs is frequently employed.⁴¹ Proprotein Convertase Subtilisin/Kexin type 9 inhibitors (PCSK9) are monoclonal antibodies able to specifically bind circulating PCSK9 protein, thus blocking its interaction with the LDLR. Therefore, the PCSK9-mediated degradation of LDLR is prevented with the consequent increased availability of the receptor at the cell surface.⁴² Monoclonal antibodies against PCSK9, evolocumab, and alirocumab exclusively bind to the LDLR binding site of PCSK9 to reduce LDL-C levels.⁴³ The first method inhibits PCSK9 from binding to LDL-R. Adnectins, also known as monobodies or monoclonal antibodies, are instances of this strategy. Evolocumab, alirocumab, and bococizumab are instances of monoclonal antibody therapeutic medicines.⁴⁴ These bind to PCSK9's catalytic and prodomains, inhibiting its interaction with the LDL-R and neutralizing its activity. Studies have shown maximum reduction of circulating unbound PCSK9 within 4-8 hours following injection of the monoclonal antibody.⁴⁵ With LDL-C decreases of roughly 65% in healthy individuals and roughly 60-80% in hypercholesterolemia patients. Similar to monoclonal antibodies, adnectins exhibit low toxicity and high target specificity.⁴⁶ The second approach is the nucleic acid drugs of PCSK9 inhibitors which are mainly ASOs, designed to

target PCSK9 mRNA and thereby inhibit intracellular protein translation and PCSK9 protein synthesis through the mechanism of occupying or cutting the targeted mRNA by RNase H1.⁴⁷ The third approach is that the PCSK9 protein's binding surface is relatively smooth and open, tiny compounds like Adnectin and BMS-962476 have a small contact area, and little hydrophobic force is produced. When natural macromolecular ligands come into interaction with it, they might dissociate even if it is attached to the PCSK9 protein. Alirocumab and evolocumab are the two PCSK9 inhibitors currently available on the market. It has been demonstrated that alirocumab, but not evolocumab, reduced mortality risk by 17% when compared to control.⁴⁸ However, the cost of these two PCSK9 inhibitor medications is between \$14,100 and \$14,600 annually.⁴⁹ PCSK9 inhibitors were administered to 141 individuals in this real-world cohort (90 receiving alirocumab and 51 receiving evolocumab; median age 58; 41% female); the majority of these patients also got statins and/or ezetimibe.⁵⁰ Both medications resulted in significant and long-lasting LDL-C reductions across a median 18-month follow-up, ranging from 47 to 50% from baseline. Patients with preexisting CVD and those taking statin therapy concurrently experienced somewhat larger absolute reductions. In general, PCSK9 inhibitors were well tolerated, which is in line with results from larger observational studies.⁵¹ It also includes future directions in the development of other PCSK9-targeting treatments, such as oral formulations, the most sophisticated of which is MK-0616 (A new oral macrocyclic peptide) has been spurred by the efficacy of PCSK9 inhibition using monoclonal antibody injections.⁵² With only twice-yearly dosage, Inclisiran, a gene-silencing medication that prevents the manufacture of hepatic PCSK9, reduces LDL-C to a level similar to that of monoclonal antibodies, increasing convenience and adherence. Alternative approaches, such as peptide-based anti-PCSK9 vaccinations and oral small-molecule inhibitors, are under preclinical development because injectable medicines are so expensive.⁵³

SGLT2 inhibitors in heart failure: Beyond glycaemic control

Many Sodium Glucose co-Transporter 2 (SGLT2) inhibitors, which work by preventing glucose reabsorption in the kidney's proximal tubule, have been created to treat hyperglycaemia in type 2 diabetes.⁵⁴ It has been proposed that the positive benefits of SGLT2 inhibitors in the context of heart failure are connected to the enhanced cardiac energetics and blood pressure-lowering effect of SGLT2 inhibition.⁵⁵ The European Medicines Agency and the US Food and Drug Administration have approved the four SGLT2 inhibitors that are often used in clinical treatment: ertugliflozin, canagliflozin, dapagliflozin, and Empagliflozin (EMPA).⁵⁶ The first approach is that SGLT2 inhibitors have been linked to weight loss in addition to decreasing glucose. They also function as osmotic diuretics, which lower Blood Pressure (BP) mainly reduce the risk of cardiac failure.⁵⁷ Enhancing cardiac

energetics and efficiency has been suggested as the mechanism by which SGLT2 inhibitors can help treat heart failure. Adipose tissue fatty acids are mobilized by SGLT2 inhibitors, leading to a rise in circulating ketone levels.⁵⁸ The liver uses these fatty acids for ketogenesis. Even in the absence of diabetes, circulating ketone levels may rise with SGLT2 inhibitor therapy.⁵⁹ As a "thrifty" heart fuel, these ketones have been suggested to enhance cardiac energetics and cardiac efficiency. Another approach is the SGLT2 inhibitor involved in cardiac remodelling. By reversing the cardiac remodelling observed in heart failure, SGLT2 inhibition may lessen the stress on the left ventricle and improve cardiac function (Table 2).⁶⁰

Diabetes and multimorbidity management

CVD is the primary cause of death in cases of diabetes. Type 2 Diabetes Mellitus (T2DM) greatly increases this risk. According to research, the risk of heart problems is two to four times higher for those with type 2 diabetes than for those without the condition. Heart issues claim the lives of many of these people.^{61,62} Numerous body functions are connected to diabetes and heart disease. Persistent high blood sugar levels can lead to chronic low-grade inflammation, endothelial problems, and oxidative stress. These elements worsen and encourage the development of atherosclerosis.^{63,64} Lipid imbalances brought on by diabetes, such as increased triglycerides, smaller or denser LDL particles, and decreased HDL cholesterol, also harm blood vessels.⁶¹⁻⁶⁵ Insulin resistance can worsen this condition, increasing the likelihood of acute cardiovascular events like heart attacks and strokes.^{65,66}

This calls for a tailored approach to be managed effectively. This approach should target cardiovascular risk factors and blood sugar regulation. Setting excessively stringent glucose targets can increase the risk of hypoglycaemia without improving cardiovascular outcomes, even though blood sugar control is essential.^{66,67} Most clinical guidelines recommend aiming for HbA1c targets of approximately 7%, with adjustments made for age, other medical conditions, and prior cardiovascular history.⁶⁶⁻⁶⁸

Another crucial element is controlling blood pressure. Most people should aim for a blood pressure reading of less than 140/90 mmHg, according to the American Diabetes Association. However, if it's safe, stricter control (<130/80 mmHg) may benefit those with a higher cardiovascular risk.⁶⁶ Because of their protective effects on the kidneys and heart, medications like ACE inhibitors and ARBs are frequently recommended.⁶³ Controlling lipid levels is also essential. High-intensity statins are typically recommended for diabetic patients over the age of 40, particularly if they have additional cardiovascular risk factors.^{61,63,69} If statins alone are not able to meet cholesterol targets, other medications, like ezetimibe or PCSK9 inhibitors, may be prescribed.⁶⁹ Recent advancements in treatment have altered the way we treat type 2 diabetes in patients who are at risk for cardiovascular disease.

Empagliflozin is one example of an SGLT2 inhibitor that has been shown to reduce cardiovascular mortality and hospitalizations for heart failure and severe cardiovascular events.⁷⁰⁻⁷² GLP-1 receptor agonists such as liraglutide and semaglutide help control blood sugar, promote weight loss, and enhance cardiovascular health.⁶⁷

Risk reduction can be achieved by lifestyle management. A heart-healthy diet, staying active, quitting smoking, and maintaining a healthy weight are important ways to reduce both microvascular and macrovascular risks.^{63,66,69} To provide patients with individualized and continuous care, a multidisciplinary team comprising physicians, dietitians, educators, and pharmacists should collaborate.^{63,73}

Additionally, there is growing evidence that non-traditional factors, such as environmental exposures, psychological stress, and sleep problems, may also have an impact on cardiovascular outcomes in diabetics. By resolving these problems, a better long-term health outcome could be achieved.^{74,75} Both T2DM and CVD require a thorough, patient-centred approach to treatment. By combining careful risk factor management, consistent lifestyle changes, and the right medications, healthcare professionals can help people with this double challenge to live longer and have a higher quality of life.

CKD and Cardiovascular Risk Interactions

Globally, CVD continues to be the leading cause of death for patients with CKD, and CKD is becoming more widely acknowledged as a substantial independent risk factor for CVD.⁷⁶ The relationship between CKD and CVD is complex. It includes both CKD-specific factors like oxidative stress, chronic inflammation, and abnormalities in mineral and bone metabolism as well as more conventional risk factors such as diabetes mellitus, hypertension, and dyslipidaemia.^{77,78}

Rapid atherosclerosis and growing vascular calcification are two important characteristics of vascular disease associated with chronic kidney disease. A higher risk of heart failure, left ventricular hypertrophy, and increased arterial stiffness are all consequences of medial arterial calcification. Secondary hyperparathyroidism, systemic inflammation, calcium and phosphate imbalances are the main causes of this process.^{79,80} The accumulation of uremic toxins and compromised endothelial function brought on by elevated Asymmetric Dimethylarginine (ADMA) can accelerate the risk of atherogenesis.⁸¹

Cardiovascular risk is greatly increased by the presence of albuminuria or even modest declines in estimated Glomerular Filtration Rate (eGFR). Studies reveal that cardiovascular related (Figure 1) and all-cause mortality are independently predicted by both increased albuminuria and decreased eGFR. These conclusions are supported by extensive meta-analyses, which include research from the Chronic Kidney Disease Prognosis Consortium. To lessen the burden of cardiovascular

disease, CKD must be detected and treated early.^{82,83} The concept of cardiorenal syndrome highlights the connection between heart and kidney disorders. Arrhythmias and hypertrophy can be caused by acid-base imbalances, anaemia, hyperphosphatemia, and chronic volume overload.⁸⁴ It was common for problems in one system to cause or worsen issues in another.^{85,86} Both general and CKD-specific risk factors must be addressed by management strategies meant to reduce cardiovascular risk in CKD patients. Medications such as ACE inhibitors and ARBs are essential to slow the progression of chronic kidney disease and lower cardiovascular risk, since they lower blood pressure and proteinuria. For CKD patients not receiving dialysis, statins help to reduce cholesterol. Alternative lipid-lowering therapies may be required for dialysis patients, as research like SHARP and AURORA shows limited benefit for this group.^{86,87} Also crucial in targeted treatments for side effects like anaemia and hyperkalaemia. With the use of erythropoiesis-stimulating agents, iron supplements, and new-generation potassium binders these conditions can be managed, which may lessen cardiovascular stress and enhance results.^{88,89} A comprehensive and multidisciplinary approach is essential because of the interdisciplinary relationship between CKD and CVD. Collaboration between nephrologists, cardiologists, and primary care teams, as well as early kidney assessment and thorough risk factor management, is necessary to reduce cardiovascular events in patients with chronic kidney disease.

Obesity-Related Hypertension: Pharmacologic Management Strategies

The global obesity epidemic has resulted in a significant increase in the number of people with obesity-related hypertension. Due to insulin resistance, elevated Renin-Angiotensin-Aldosterone System (RAAS) activation, elevated sympathetic nervous system activity, and adipokine-induced inflammation, the blood pressure is raised through excess body fat via a several interconnected pathways.^{90,91} The capacity of the kidneys to regulate sodium is also impacted by obesity, which results in poor natriuresis and sodium retention, both of which increase blood pressure.⁹²

Choosing the appropriate medication for hypertension in obese people is essential to reducing detrimental metabolic effects.⁹³

Table 1: CYP2C19 polymorphisms, their functional characteristics, and reliable sources.

Allele	Functional characteristics	Metabolizers
*1	Normal enzyme activity	Normal (extensive) metabolizer. ¹⁴³
*2, *3	Loss-of-function alleles	Poor metabolizer. ¹⁴⁴
*17	Gain-of-function allele	Rapid or ultrarapid metabolizer. ¹⁴⁵

Because they increase insulin sensitivity, lower blood pressure, and generally improve glucose and lipid metabolism, ACE inhibitors and ARBs are frequently used as first-line treatments.⁹⁴ These medications are associated with a lower incidence of sudden type 2 diabetes than beta-blockers and thiazide diuretics.⁹⁵ Another good alternative that causes less metabolic disruption is Calcium Channel Blockers (CCBs). They are best used in combination regimens and are particularly useful in treating salt-sensitive hypertension, which is frequently seen in obese individuals.⁹⁶ CCBs also maintain a neutral metabolic profile and offer additional cardiovascular benefits when used in conjunction with RAAS blockers.⁹⁷

It is still possible to reduce long-term blood pressure and cardiovascular risk with thiazide diuretics. To counteract their potential to worsen insulin resistance and change lipid profiles, they are best taken in small doses in combination with drugs like ACE inhibitors.^{98,99} According to clinical studies, chlorthalidone has performed better than hydrochlorothiazide in terms of blood pressure control and cardiovascular outcomes.¹⁰⁰ Because they tend to increase body weight that affect glucose and lipid metabolism, traditional beta-blockers are less popular.¹⁰¹ Better metabolic effects are offered by more recent vasodilating beta-blockers, like carvedilol and nebivolol. Some conditions, such as myocardial infarction or heart failure, respond well to them.^{102,103}

Spironolactone and eplerenone are two examples of Mineralocorticoid Receptor Antagonists (MRAs) that are especially useful in treating resistant hypertension, which is frequently observed in obese individuals. Since RAAS inhibitors reverse the sodium-retaining effects of aldosterone, these drugs complement them well.^{104,105} Metabolic medications that also reduce blood pressure have gained popularity recently. By improving natriuresis, promoting weight loss, and having direct

vasodilatory effects, GLP-1 receptor agonists which are commonly used to control blood sugar and reduce body weight can also lower blood pressure.¹⁰⁶ Initially developed to treat type 2 diabetes, SGLT2 inhibitors have demonstrated modest but significant decreases in blood pressure and cardiovascular risk.^{107,108} A key component of treatment is changing one's lifestyle. Medication should be used in conjunction with structured lifestyle plans that emphasize healthy eating, consistent exercise, and behavioural adjustments. These can significantly enhance blood pressure control and weight management.^{109,110} Dual GIP and GLP-1 receptor agonists, two novel treatments specifically targeted at obesity, have demonstrated promise in lowering body weight and enhancing blood pressure regulation. Future treatment regimens for hypertension are probably going to include these medications.¹¹¹ For obesity-related hypertension to be effectively managed, a customized, multifaceted strategy is needed. While selective beta-blockers, calcium channel blockers, and low-dose diuretics are additional medications that offer additional benefits, RAAS inhibitors are typically the first-line treatment. Metabolic outcomes are improved by incorporating more recent medications such as GLP-1 receptor agonists and SGLT2 inhibitors. Drug treatment must be paired with evidence-based lifestyle modifications for sustained success.¹¹²

Cardiovascular toxicity of Cancer Drugs (Cardio-Oncogenic Agents)

Concern over potential long-term effects on cardiovascular health is growing as cancer treatments advance and patient survival rates rise. This need has led to the development of cardio-oncology. It acknowledges that several cancer treatments can impact on heart health. Heart failure, irregular heartbeats, hypertension, vascular blockages, and ischemic injury are among the cardiovascular problems that can result from many commonly used cancer treatments.¹¹³ A well-known

Table 2: Comparison of Therapeutic Approaches Targeting PCSK9 to Lower LDL Cholesterol: Drug Types, Mechanisms of Action, and Clinical Effectiveness.

Approach	Type of Drug	Mechanism of Action	Effectiveness / Notes
Inhibition of PCSK9-LDL-R binding	Monoclonal antibodies and Adnectins (monobodies)	The EGF-A domain of LDLR is bound by PCSK9, which also improves binding in acidic pH, inhibits recycling and encourages receptor degradation.	PCSK9 inhibitors (Evolocumab, Alirocumab) lower LDL-C by 50-75%, outperforming statins or placebo across diverse patients. ^{146,147}
Inhibition of PCSK9 mRNA translation	Antisense oligonucleotides (ASOs)	PCSK9 binds to ApoB100 on LDL, preventing its receptor interaction, and binds LDLR for lysosomal destruction.	Baseline lipid-lowering medication, PCSK9 inhibitors effectively cut LDL-C levels by about 60%, leading to notable decreases in myocardial infarction. ^{148,149}
Disruption of PCSK9 protein structure	Small molecules	The process decreases plasma cholesterol and restores hepatic LDL absorption by preventing PCSK9 from binding to LDLR.	Ligand dissociation and binding affinity, dictate how successful protein-ligand interactions are. By altering these dynamics, ligand residence time can be engineered, impacting regulatory mechanisms and protein function. ^{150,151}

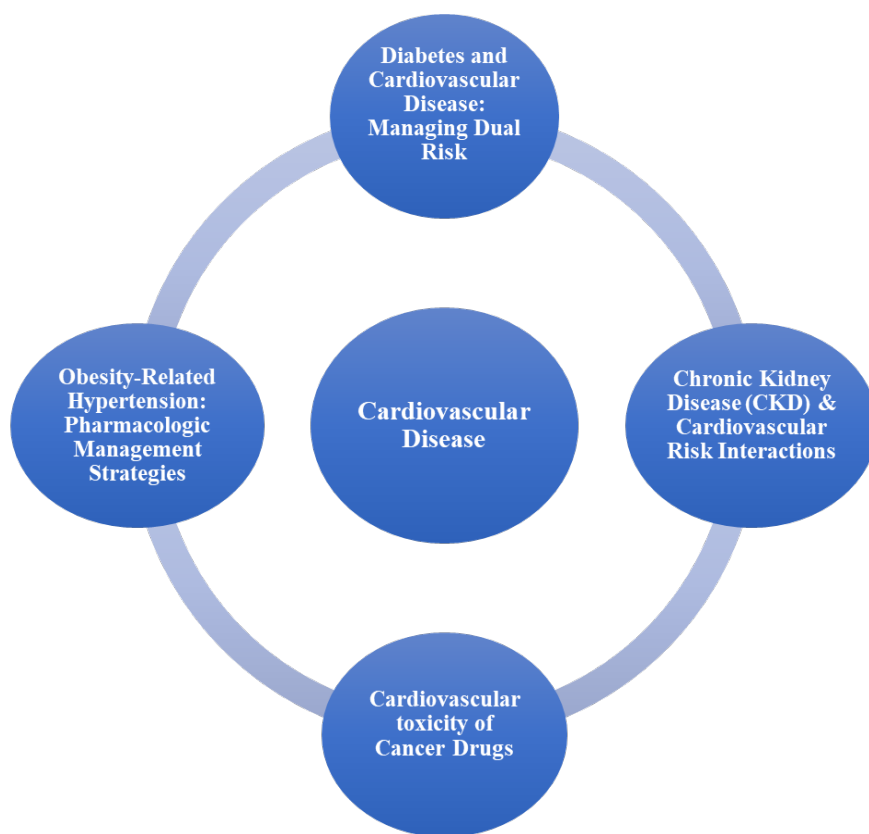


Figure 1: Various comorbidities driving CVD risk and management.

example is the anthracycline group, specifically doxorubicin. These medications have the potential to damage heart tissue in a dose-dependent and often irreversible manner because of their effects on mitochondria and oxidative pathways.¹¹⁴ The monoclonal antibody trastuzumab, commonly used in HER2-positive breast cancer, also impacts heart function, unlike anthracyclines. However, its negative effects are usually reversible when treatment is stopped.¹¹⁵

Some targeted therapies present cardiovascular risks as well. Inhibitors of Vascular Endothelial Growth Factor (VEGF), like bevacizumab, and tyrosine kinase inhibitors such as sunitinib and sorafenib, have been linked to high blood pressure, blood clots, and heart dysfunction. These issues are thought to arise from stress on the endothelium and difficulty in vascular repair.¹¹⁶ Proteasome inhibitors, including bortezomib, are also associated with heart rhythm problems and congestive heart failure. The likely cause involves disruptions in how cells manage proteins and maintain balance.¹¹⁷ The use of Immune Checkpoint Inhibitors (ICIs), which have changed treatment for various cancers, brings its own concerns. Although rare, cases of myocarditis, pericardial inflammation, and vasculitis have been documented. These conditions are believed to stem from excessive immune responses targeting cardiac tissue, driven by T-cells.^{118,119} Additionally, radiation therapy, especially when directed at the mediastinal area, raises the risk of coronary artery disease, valve injury, and conduction issues. When radiation is paired with

cardiotoxic drugs, the overall stress on the cardiovascular system can substantially increase.¹²⁰ Baseline cardiac evaluations must be performed before to beginning cancer treatments known to impact the heart. Echocardiograms and biomarker tests, such as those for troponin and BNP, are typically among them.¹²¹ To identify early indications of heart damage, treatment requires ongoing monitoring. Depending on the type of treatment and patient risk, beta-blockers, ACE inhibitors, or dexrazoxane may be used as preventive measures for patients with pre-existing risk factors.¹²²

Nowadays, long-term cancer patient care involves more than just limiting tumour growth. Additionally, it entails safeguarding cardiac health, particularly as survival rates rise. Collaboration between oncologists and cardiologists is crucial. As research develops, a better understanding of drug-related cardiac toxicity will help to improve treatment plans and enhance the quality of life for cancer survivors.¹²³

Biomarkers for Early Detection of CVD

Biomarkers are used to diagnose and manage CVD to reduce mortality. Cardiac biomarkers are biochemical substances derived through venous puncture and are released into the blood during an injured or compromised heart. Heart biomarkers are tests that may help to assess a person's risk of cardiovascular diseases and to manage and diagnose an individual with suspected Acute Coronary Syndrome (ACS) and cardiac ischemia.¹²⁴ Biomarkers

are a strong indicator of high-risk individuals, rapid and reliable diagnosis of illness conditions, and appropriately diagnosing and managing patients. Most other biomarkers appear to be either up-regulated or down-regulated with illnesses other than CVD. The trends for identifying the number of biomarkers that might consistently support prognosis in early disease states are far from robust.¹²⁵ This review is to present examples of commonly used CVD biomarkers based on the carbon scaffold from which they are constructed. Presenting some of their strengths and weaknesses, providing a strategy for innovation regarding biomarker research in the future.¹²⁶

Cardiovascular Diseases (CVDs) continue to be a leading cause of global mortality, highlighting an ongoing need for diagnostic and prognostic advances. Existing biomarkers such as C-reactive protein, troponin, and natriuretic peptides provide excellent value, but they are limited by a lack of sensitivity and specificity. In this review, we provide a summary of newly described biomarkers that provide insights into CVD pathophysiology such as oxidative stress, endothelial dysfunction, inflammation, and myocardial injury.¹²⁷ New biomarkers including gamma-glutamyl transferase, microRNAs, placental growth factor, and trimethylamine N-oxide indicated the potential for early diagnosis and risk prediction. This article promotes a strategic multiple-marker approach using traditional and new biomarkers to improve diagnostic accuracy and treatment plans for individual patients. This would enable a transition away from reactive cardiovascular care towards more proactive cardiovascular care based on early diagnosis and intervention before the development of clinical symptoms.¹²⁸ There is an increasing burden of CVD in low- and middle-income countries and with CVDs often being a result of lifestyle choices, cost-effective diagnostic approaches must be developed. In addition to this, the authors stress that new biomarkers should be validated through large multicentre multiethnic trials. The authors also contend that new markers alongside traditional markers could help bridge the current diagnostic gap to optimise patient outcomes. Overall, the study provided a timely overview of the fast-evolving biomarker space and the potential that it offers.¹²⁹

Primary Biomarkers for Early Detection of CVD

Cardiac Troponins (cTnT, cTnI): High-sensitivity assays for cardiac troponin T (hs-cTnT) identified cardiac troponin T as the gold standard biomarker of myocardial injury. Increased concentrations of cardiac troponin T and I can be noted early in the course of myocardial damage and will help to identify their future cardiac risk, such as chronic heart failure and coronary artery disease.¹³⁰

B-type Natriuretic Peptides (BNP, NT-proBNP): B-type natriuretic peptides and their N-terminal prohormone (NT-proBNP) are important diagnostic biomarkers for the diagnosis and risk determination in patients with heart failure.

B-type natriuretic peptides determine the degree of stress and dysfunction of the heart so that the clinician has an early diagnosis and prognosis.¹³¹ C-reactive Protein (CRP): A marker of systemic inflammation that is associated with cardiovascular risk factors and CVD progression. Higher levels of CRP correlate with a higher risk for adverse cardiac events.¹³² Heart-type Fatty Acid Binding Protein (H-FABP): H-FABP is released rapidly into the circulation following myocardial injury. H-FABP is a good early marker for myocardial injury due to its rapid kinetics and cardiac specificity.¹³³ Glycogen Phosphorylase BB (GPBB): GPBB is a glycosylated protein that is involved in glycogen metabolism. Studies have shown good sensitivity and specificity for early detection of myocardial ischemia and Acute Coronary Syndrome (ACS).¹³⁴

Herbs used in the cardiovascular

Astragalus membranaceus contains the active constituents, polysaccharides and astragaloside IV, which have antioxidant, anti-inflammatory and cardioprotective properties. *Astragalus* improves cardiac energy metabolism and inhibits oxidative stress. Experimental studies and clinical evidence suggest that *Astragalus* may improve cardiac function, improve symptoms of heart failure and ischemic heart disease, and improve angiogenesis in models of ischemic injury. It is often used as an adjunct therapy in heart failure and ischemic heart disease and for overall cardiac support.¹³⁵ *Crataegus*, or *Hawthorn*, has active constituents including oligomeric procyanidins and flavonoids. These constituents have antioxidant activity and vasodilator activity, as well as positive inotropic, anti-arrhythmic, ACE-inhibitory, and anti-atherosclerotic activity. Meta-analyses noted *Hawthorn* improved chronic heart failure symptoms, improved exercise tolerance, and possibly lowered blood pressure and lipid levels. Moreover, it may enhance digitalis effects. *Hawthorn* is used for chronic heart failure, angina, and hypertension. *Hawthorn* is available in the forms of extracts, tea and capsules.¹³⁶

Salvia miltiorrhiza, commonly referred to as *Danshen*, has active ingredients including tanshinones and salvianolic acids. These have antioxidant, vasodilatory, and anti-inflammatory properties, improving coronary circulation while protecting against ischemia-reperfusion injury. Clinical studies have shown that *Danshen's* significant effects on blood pressure and pulse rate. It is commonly used in Traditional Chinese Medicine for the management of hypertension, angina, and coronary artery disease.¹³⁷ *Allium sativum*, commonly known as Garlic, contains active compounds such as allicin and other sulfur compounds which have antihypertensive, lipid-lowering, antioxidant and anti-platelet action. Garlic has been widely studied and shown to lower cholesterol values and blood pressure; improve blood circulation and reduce platelet aggregation. Garlic is also a popular dietary supplement for the management of cholesterol levels, hypertension, and protection of the cardiovascular system.¹³⁸

Ginkgo biloba has active components, including flavonoids and terpenoids, that possess strong antioxidant properties and contribute to vascular, or cerebral, and peripheral circulation. Some studies that demonstrate *Ginkgo* can promote blood flow, and some evidence that suggests cardioprotective effects. Of note, there is a risk of bleeding (i.e. in combination with anticoagulants). *Ginkgo* is often used for vascular insufficiency and cerebral circulation. That said, when consumers use *Ginkgo biloba*, they often experience some degree of poor blood flow to the brain.¹³⁹ *Foeniculum vulgare* (referred to as *Fennel*) has active constituents of anethole and flavonoids exhibiting antihypertensive, lipid-lowering, and antioxidant activity. Traditionally, *Fennel* has been used for modest benefits for cardiovascular health, specifically in its efficacy for managing blood pressure and cholesterol. *Fennel* can frequently be found as a tea or added raw to the diet to improve cardiovascular health.¹⁴⁰ *Tinospora cordifolia* has active substances including alkaloids and glycosides that have antioxidant and cardioprotective effects. This herb has been shown to decrease oxidative stress and support heart health within the context of traditional medicine. *Tinospora cordifolia* is widely used in Ayurveda to promote cardiovascular health.¹⁴¹ *Curcuma longa* (*Turmeric*) is the source of the active ingredient curcumin, which is a strong anti-inflammatory, antioxidant, and hypolipidemic. Preclinical studies have assessed its antiatherosclerotic and antithrombotic properties, demonstrating cardiovascular protection. A common use in *Turmeric* as a supplement to reduce inflammation and for cardiovascular protection.¹⁴²

CONCLUSION

CVD remains a major contributor to global morbidity and mortality, but advances in pharmacogenetics, drug development, and disease management may improve the prognosis for our patients. This review article emphasizes the value of managing genetic variability and engaging in novel target development, as well as addressing common comorbidities that exacerbate cardiovascular risk when taking an integrated approach. Pharmacogenomics is already providing pharmacogenomic opportunities (CYP2C19 polymorphism) to optimize the pharmacological treatment of antiplatelet medications, potentially leading to enhanced drug efficacy and a decrease in adverse drug events. Though precise, personalized medicine is still developing, it is now easier to implement precision medicine, and the personalized approach to care can greatly enhance our treatment paradigms in cardiovascular care, including safety and overall treatment effect. The introduction of PCSK9 therapeutics has revolutionized the management of lipids, making LDL-C much more attainable in patients who are statin intolerant and those who do not reach their cholesterol goal with statins. Similarly, SGLT2 inhibitors were developed for glycemic control, but these medications highlight remarkably positive effects on managing heart failure,

regardless of diabetes, and have provided an important shift in the cardiopulmonary-renal-endocrine systems, if you will.

Equally as important is addressing common comorbidities such as diabetes, chronic kidney disease, and obesity-related hypertension. Notably, it is common that these comorbidities coexist, amplify cardiac risk, and may often feed back into the other comorbidities. An integrated pharmacological, lifestyle, and interdisciplinary approach to care when managing these conditions holistically will ultimately enhance the overall outcomes. Lastly, the emerging field of cardio-oncology highlights the importance of weighing effective cancer care against cardiovascular toxicity. As more patients survive cancer, significant cardiovascular complications associated with chemotherapy and targeted therapies mandate risk assessment and risk management. Ultimately, the future of cardiovascular therapy will focus on precision, prevention, and the individual needs of patients. By using genomic information, integrating new therapies, and managing co-morbidities effectively, clinicians will be able to provide more effective, targeted, and patient-centered care. More work and collaborative efforts throughout the breadth of specialties will be needed to move this evolving field forward and to lessen the global burden of cardiovascular disease.

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ABBREVIATIONS

CVD: Cardiovascular Diseases; **CYP:** Cytochrome; **PCSK9:** Proprotein Convertase Subtilisin/Kexin Type 9; **SGLT2:** Sodium-Glucose Transport Protein 2; **CKD:** Chronic Kidney Disease; **GLP-1:** Glucagon-like Peptide-1; **PGx:** Pharmacogenomics; **CYP2C19:** Cytochrome P450 2C19; **PPI:** Proton Pump Inhibitor; **AMI:** Acute Myocardial Infraction; **FH:** Familial Hypercholesterolemia; **HCM:** Hypertrophic Cardiomyopathy; **LDLR:** Low-Density Lipoprotein Receptor; **APOB:** Apolipoprotein B; **MYH7:** Myosin Heavy Chain 7 (beta-cardiac myosin heavy chain); **RNA:** Ribo-nucleic Acid; **SCD:** Sudden Cardiac Death; **EGF-A:** Epidermal Growth Factor-like Domain A; **T2DM:** Type 2 Diabetes Mellitus; **ADMA:** Asymmetric Dimethylarginine; **eGFR:** Estimated Glomerular Filtration Rate; **ACE:** Acetyl Choline Esterase Inhibitors; **CCB:** Calcium Channel Blockers; **RAAS:** Renin-Angiotensin-Aldosterone

System; **MRA**: Mineralocorticoid Receptor Antagonists; **HER2**: Human Epidermal Growth Factor Receptor 2; **VEGF**: Vascular Endothelial Growth Factor; **ICI**: Immune Checkpoint Inhibitors; **BNP**: Brain Natriuretic Peptide; **CTnT**: Cardiac Troponins; **CRP**: C-reactive Protein; **H-FABP**: Heart-type Fatty Acid Binding Protein; **GPBB**: Glycogen Phosphorylase BB; **ACS**: Acute Coronary Syndrome.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

Around the world, cardiovascular diseases remain the leading cause of death and the need for new and personalized therapies has never been greater. Pharmacogenomics specifically, genetic polymorphisms for CYP2C19 allow for personalized therapy with clopidogrel, and provide the opportunity for care to optimize safety and efficacy. New options have emerged with the development of PCSK9 inhibitors to provide patients with lipids lowering therapy with patient's intolerant or not adequately responsive to statin therapy. The use of SGLT2 inhibitors has increased the therapeutic armamentarium beyond glycemic control and offers patients substantial benefits in heart failure and renal protection. The burden of comorbidities such as diabetes, chronic kidney disease, and obesity-related hypertensive patients adds to cardiovascular risk. Comprehensive pharmacotherapeutics and lifestyle approaches will enhance long-term outcomes. Cardio-oncology is an emerging field that addresses the cardiovascular toxicities associated with cancer therapies. The future of managing CVD will involve precision medicine with an emphasis on prevention and person-centered care.

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