© February 2026 | IJIRT | Volume 12 Issue 9 | ISSN: 2349-6002

Emerging Cardiovascular Medications: From SGLT2 Inhibitors to Gene-Based Therapies — A Comprehensive Review

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***Abstract*—Background During the last decade, the management of cardiovascular disease (CVD) has undergone substantial advancement. While earlier therapeutic strategies primarily focused on lipid lowering through statins and modulation of neurohormonal systems, recent developments have expanded treatment paradigms. Contemporary cardiovascular pharmacotherapy now incorporates agents that influence metabolic regulation, inflammatory pathways, and molecular targets that were previously not addressed in conventional care.**

Objective This review aims to critically analyze recently developed cardiovascular medications by consolidating current evidence related to their mechanisms of action, therapeutic outcomes, and safety profiles, thereby supporting informed and evidence-based clinical practice.

Methods An extensive review of major cardiovascular outcome trials (CVOTs) published between 2017 and 2025 was undertaken. The analysis focused on emerging therapeutic classes including sodium–glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, anti-inflammatory agents, novel lipid-lowering drugs, and gene-based therapeutic strategies.

Results Findings from pivotal clinical trials indicate that SGLT2 inhibitors, as demonstrated in studies such as DAPA-HF and EMPEROR-Reduced, reduce heart failure–related hospitalizations and cardiovascular mortality by nearly 25%, regardless of the presence of diabetes. GLP-1 receptor agonists, supported by outcomes from the SUSTAIN-6 and SELECT trials, significantly lower the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes and obesity. PCSK9 inhibitors, confirmed through the FOURIER and ODYSSEY trials, along with the small interfering RNA therapy inclisiran, achieve profound reductions in low-density lipoprotein cholesterol (LDL-C) with meaningful cardiovascular benefit. Evidence from anti-inflammatory studies such as CANTOS and COLCOT further reinforces the critical role of inflammation in atherosclerotic disease progression.

Additional agents including bempedoic acid and icosapent ethyl address residual cardiovascular risk beyond standard lipid management. Moreover, early-phase CRISPR-based gene-editing studies initiated between 2024 and 2025 suggest promising long-term modulation of cardiovascular risk factors.

Conclusions The advent of these innovative therapies signifies a paradigm shift in cardiovascular medicine — from broad risk-reduction strategies to precision-based, mechanism-oriented treatment approaches. Integrating these novel pharmacological options into clinical care may substantially enhance individualized cardiovascular disease prevention and management.

***Index Terms*—SGLT2 inhibitors, GLP-1 receptor agonists, PCSK9 inhibitors, anti-inflammatory therapy, gene editing, cardiovascular disease, precision medicine, inclisiran, bempedoic acid, icosapent ethyl**

I. INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of illness and death worldwide, accounting for an estimated 18 million fatalities annually. Despite widespread use of standard therapeutic strategies—including antiplatelet medications, statins, and β-adrenergic antagonists—a substantial proportion of patients continue to experience what is commonly described as "residual cardiovascular risk." This persistent risk has been further intensified by the rising global burden of cardiometabolic disorders, particularly obesity and type 2 diabetes mellitus (T2DM), conditions that are not fully addressed by conventional cardiovascular pharmacotherapy.[1,2] Consequently, the past decade has been marked by a growing scientific and clinical focus on identifying new biological pathways involved in the development of atherosclerosis and heart failure and translating these insights into therapeutic innovation.

Advances in molecular biology and genetic research have uncovered previously underappreciated contributors to cardiovascular disease, including chronic vascular inflammation, triglyceride-rich lipoprotein particles, and complex metabolic abnormalities within myocardial tissue. Improved understanding of these mechanisms has catalyzed the development of novel pharmacological agents targeting disease processes beyond traditional lipid lowering. As a result, cardiovascular therapeutics have moved beyond the historical "statin-dominated" model into a modern era characterized by alternative lipid-modifying approaches—such as PCSK9 inhibition and RNA-based therapies—alongside metabolic modulators including sodium–glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. In parallel, anti-inflammatory strategies have further expanded the therapeutic landscape. Most notably, the advent of gene-editing technologies has introduced the possibility of long-lasting or even permanent modification of cardiovascular risk following a single therapeutic intervention.

II. BACKGROUND AND CONTEXT OF CARDIOVASCULAR DISEASE TREATMENT

For many years, cardiovascular prevention and treatment strategies were largely centered on modulation of neurohormonal pathways through agents such as angiotensin-converting enzyme inhibitors and β-adrenergic blockers, combined with lipid lowering achieved primarily via statin therapy. The long-standing "lipid hypothesis," validated by pivotal statin trials, firmly established low-density lipoprotein cholesterol (LDL-C) as a major modifiable contributor to cardiovascular risk. However, despite intensive statin treatment, a significant proportion of patients continue to experience recurrent ischemic events. This ongoing vulnerability reflects the presence of residual cardiovascular risk, arising from a combination of persistent lipid-related abnormalities, chronic vascular inflammation, prothrombotic states, and associated metabolic disorders.

Acknowledgment of this multifactorial residual risk prompted the exploration of therapeutic strategies extending beyond conventional statin-based approaches. Early efforts to address this gap included the development of non-statin lipid-modifying agents; however, disappointing outcomes with cholesteryl ester transfer protein (CETP) inhibitors and the modest cardiovascular benefits observed with fibrates highlighted the limitations of nonspecific lipid manipulation and reinforced the need for more targeted molecular therapies.

At the same time, cardiovascular outcome trials mandated by regulatory agencies to assess the safety of newer antidiabetic drugs produced unexpected and clinically transformative findings. Medications such as sodium–glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists demonstrated significant reductions in cardiovascular events and heart failure outcomes that could not be explained solely by improvements in glycemic control. [5] These observations have reshaped contemporary cardiovascular management, redefining the role of metabolic therapies in the treatment of heart failure and atherosclerotic cardiovascular disease.

III. OVERVIEW OF EMERGING CARDIOVASCULAR PHARMACOTHERAPIES

A. Historical Evolution of Treatment Strategies

Cardiovascular drug therapy has advanced substantially over time, progressing from an initial focus on symptom relief to interventions capable of modifying disease progression. Early treatment strategies primarily aimed to alleviate clinical manifestations, such as the use of diuretics to manage fluid overload and nitrates to reduce anginal discomfort. Subsequent developments introduced therapies with proven structural and prognostic benefits, including angiotensin-converting enzyme (ACE) inhibitors, which demonstrated the ability to limit pathological ventricular remodeling and improve long-term outcomes.

In the current era, cardiovascular management has entered a further stage of evolution that extends beyond isolated hemodynamic control. Modern treatment strategies increasingly address the broader metabolic and inflammatory milieu contributing to disease progression. This shift reflects a growing emphasis on managing the interconnected "cardiometabolic" profile of patients, integrating metabolic regulation and inflammation control alongside traditional targets such as blood pressure and lipid levels.

B. Transition Toward Precision and Molecular Therapies

Cardiovascular medicine is undergoing a paradigm shift toward precision-oriented treatment models. Rather than relying on uniform therapeutic algorithms, contemporary practice increasingly tailors' interventions based on individual disease characteristics, biomarker patterns, and genetic profiles. This personalized approach allows for more accurate alignment between therapeutic mechanisms and underlying pathophysiology.

For example, anti-inflammatory therapies such as colchicine may offer the greatest benefit in individuals with elevated levels of high-sensitivity C-reactive protein (hsCRP), indicating active vascular inflammation. Likewise, emerging gene-directed therapies are designed to correct specific molecular abnormalities involved in lipid metabolism, including alterations in PCSK9 and angiopoietin-like protein 3 (ANGPTL3). By selectively targeting defined biological pathways, these therapies enable precise modulation of cardiovascular risk.

This evolving framework highlights the increasing role of biomarker assessment and genetic evaluation in guiding treatment selection. Such strategies not only enhance therapeutic effectiveness but also reduce unnecessary drug exposure and support more efficient use of healthcare resources.

IV. MECHANISMS OF ACTION OF KEY EMERGING DRUG CLASSES

A. SGLT2 Inhibitors (Empagliflozin, Dapagliflozin)

Sodium–glucose cotransporter-2 (SGLT2) inhibitors exert their primary pharmacological action by reducing glucose reabsorption in the proximal convoluted tubules of the kidney, leading to increased urinary glucose excretion. Importantly, extensive clinical evidence indicates that the cardiovascular benefits associated with this drug class extend well beyond their glucose-lowering effects.

Several complementary mechanisms have been proposed to explain their cardioprotective properties. One major contributor is the induction of mild natriuresis and osmotic diuresis, resulting in reductions in intravascular volume, cardiac preload, and systemic afterload. [6] These hemodynamic changes alleviate myocardial wall stress and contribute to improved heart failure outcomes.

At the myocardial level, SGLT2 inhibitors promote a favorable shift in cardiac energy metabolism. By increasing circulating ketone bodies—particularly β-hydroxybutyrate—these agents facilitate utilization of a more energy-efficient substrate, thereby enhancing myocardial energetic efficiency. Additional mechanistic pathways include suppression of the sodium–hydrogen exchanger-1 (NHE1) activity within cardiomyocytes, modulation of autonomic imbalance through reduced sympathetic activation, and attenuation of inflammatory signaling originating from adipose tissue. Collectively, these effects contribute to improved cardiac function and reduced progression of cardiovascular disease.

GLP-1 Receptor Agonists (Semaglutide, Liraglutide)

Glucagon-like peptide-1 (GLP-1) receptor agonists are synthetic compounds designed to mimic the physiological actions of the endogenous incretin hormone GLP-1. Their principal metabolic effect involves enhancement of glucose-dependent insulin secretion from pancreatic β-cells, accompanied by suppression of inappropriate glucagon release, thereby improving glycemic regulation with a low risk of hypoglycemia.

B. Beyond their metabolic actions

GLP-1 receptors are widely distributed within cardiovascular tissues, including vascular endothelial cells and cardiomyocytes. Activation of these receptors has been shown to improve endothelial function, reduce oxidative stress, and modulate inflammatory signaling within the vascular wall. [7] These effects contribute to improved vascular integrity and reduced progression of atherosclerotic disease.

Central nervous system–mediated mechanisms further augment cardiovascular benefit. GLP1 receptor agonists act on hypothalamic appetite centers to promote satiety and reduce caloric intake, resulting in clinically meaningful and sustained weight loss. This reduction in adiposity favorably influences blood pressure, lipid parameters, and insulin sensitivity, thereby improving the overall cardiometabolic risk profile. Emerging data also indicate potential direct anti-atherosclerotic properties, including stabilization of atherosclerotic plaques and attenuation of plaque inflammatory activity.

C. PCSK9 Inhibitors (Evolocumab, Alirocumab)

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a circulating protein primarily produced by the liver that plays a critical role in regulating plasma low-density lipoprotein cholesterol (LDL-C) levels. PCSK9 binds to LDL receptors on the surface of hepatocytes and directs them toward lysosomal degradation, thereby reducing receptor availability and limiting hepatic LDL-C uptake.

Monoclonal antibodies targeting PCSK9 interrupt this interaction, allowing LDL receptors to be recycled back to the hepatocyte membrane rather than degraded. This enhanced receptor recycling markedly increases hepatic clearance of circulating LDL-C. As a result, PCSK9 inhibitors achieve profound lipid-lowering effects, producing approximately 50–60% additional reductions in LDL-C when administered alongside maximally tolerated statin therapy.

Beyond cholesterol lowering, clinical and imaging studies have demonstrated that sustained PCSK9 inhibition contributes to favorable structural vascular changes, including regression of atherosclerotic plaque burden and improved plaque stability. [8] These properties position PCSK9 inhibitors as highly effective therapeutic options for patients with persistent hypercholesterolemia and elevated cardiovascular risk despite conventional lipid-lowering strategies.

D. Anti-Inflammatory Cardiovascular Drugs
Canakinumab:

Canakinumab is a fully human monoclonal antibody designed to selectively neutralize interleukin-1β (IL-1β), a key upstream mediator of vascular inflammation. By blocking IL-1β activity, the drug suppresses downstream inflammatory signaling pathways, including reductions in interleukin-6 (IL-6) and C-reactive protein (CRP) levels, without exerting any direct effect on lipid metabolism. This unique pharmacological profile enabled a direct clinical evaluation of the inflammatory hypothesis of atherosclerosis, demonstrating that cardiovascular risk reduction can be achieved independently of cholesterol lowering. [12] Colchicine:

Colchicine is an anti-inflammatory agent that acts by disrupting microtubule formation through inhibition of tubulin polymerization. This mechanism impairs neutrophil migration, adhesion, and activation—processes central to vascular inflammatory injury. In addition, colchicine suppresses activation of the NOD-like receptor protein 3 (NLRP3) inflammasome, a pivotal driver of cytokine release and atherothrombotic inflammation. [13]

E. RNA- and Gene-Based Therapies

Recent advances in genetic medicine have introduced RNA- and gene-based strategies as promising approaches for long-term cardiovascular risk modification. Among these, clustered regularly interspaced short palindromic repeats (CRISPR) combined with CRISPR-associated protein 9 (Cas9) technology is currently under active clinical investigation for its potential to produce durable or permanent therapeutic effects.

These interventions primarily focus on hepatic genes that play central roles in lipid regulation, including proprotein convertase subtilisin/kexin type 9 (PCSK9) and angiopoietin-like protein 3 (ANGPTL3). By selectively disrupting these genes, gene-editing therapies aim to achieve sustained reductions in circulating atherogenic lipoproteins. In vivo delivery systems, most commonly lipid nanoparticle platforms, facilitate transport of the gene-editing components directly to hepatocytes. Once internalized, the CRISPR-Cas9 complex induces targeted gene modification, potentially enabling lifelong lipid control following a single therapeutic administration. [14] Although these technologies remain in early stages of clinical development, they represent a transformative shift toward one-time, precision-based interventions in cardiovascular medicine.

V. PHARMACOLOGY OF SEMAGLUTIDE

A. Mechanism of Action

Semaglutide is a long-acting synthetic analog of glucagon-like peptide-1 (GLP-1) that shares approximately 94% structural homology with endogenous human GLP-1. Its prolonged activity is achieved through specific molecular modifications designed to enhance stability and systemic persistence. These include targeted amino acid substitutions that confer resistance to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4), as well as the attachment of a C18 fatty diacid side chain.

The fatty acid moiety enables strong, reversible binding to circulating serum albumin, which serves a dual function: protecting the peptide from enzymatic breakdown and markedly reducing renal filtration. Together, these structural adaptations significantly extend the biological half-life of semaglutide, allowing sustained receptor activation over prolonged periods.

B. Pharmacokinetic and Pharmacodynamic Profile

After subcutaneous administration, semaglutide exhibits high systemic absorption, with an estimated bioavailability of approximately 89%. The drug displays a prolonged elimination half-life of nearly one week, supporting a convenient once-weekly dosing regimen. Steadystate plasma concentrations are typically achieved within four to five weeks of regular administration.

Pharmacodynamically, semaglutide lowers plasma glucose levels in a glucose-dependent manner, thereby minimizing the risk of hypoglycemia when used as monotherapy. In addition to glycemic control, it produces clinically significant weight reduction by decreasing caloric intake. This anorectic effect is mediated through direct activation of GLP-1 receptors within hypothalamic and brainstem centers responsible for appetite regulation, satiety signaling, and energy balance.

VI. EVIDENCE FROM PRECLINICAL AND CLINICAL STUDIES

The clinical effectiveness of emerging cardiovascular therapies has been robustly validated through multiple large-scale cardiovascular outcome trials (CVOTs) (Table 1). These investigations have provided definitive evidence supporting the role of novel pharmacological agents in reducing cardiovascular morbidity and mortality.

A. SGLT2 Inhibitor Trials

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, published in 2019, enrolled 4,744 patients with heart failure with reduced ejection fraction (HFrEF) and randomly assigned them to receive either dapagliflozin or placebo in addition to standard therapy. Treatment with dapagliflozin resulted in a 26% relative reduction in the composite endpoint of worsening heart failure or cardiovascular death (hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.65–0.85; p<0.001). Importantly, this therapeutic benefit was consistent across subgroups, including patients with and without type 2 diabetes mellitus. [15]

Comparable findings were observed in the EMPEROR-Reduced trial completed in 2020, which evaluated empagliflozin in 3,730 individuals with HFrEF. Empagliflozin significantly lowered the risk of the primary composite outcome of cardiovascular death or hospitalization for heart failure (HR 0.75; 95% CI 0.65–0.86), further reinforcing the class effect of SGLT2 inhibitors in heart failure management. [16]

B. GLP-1 Receptor Agonist Trials

The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), reported in 2016, established both cardiovascular safety and efficacy of semaglutide in patients with type 2 diabetes mellitus and established cardiovascular disease. The study demonstrated a 26% reduction in major adverse cardiovascular events (MACE) compared with placebo (HR 0.74; 95% CI 0.58–0.95), confirming a significant cardioprotective effect beyond glycemic control. [17] More recently, the Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT) trial marked a pivotal advancement in cardiovascular prevention. This large-scale study enrolled 17,604 individuals with overweight or obesity and established cardiovascular disease but without diabetes. Administration of semaglutide 2.4 mg once weekly led to a 20% reduction in MACE (HR 0.80; 95% CI 0.72–0.90; p<0.001). These findings conclusively demonstrated that pharmacological weight reduction can function as a direct cardiovascular risk–modifying strategy. [18]

C. PCSK9 Inhibitor Trials

The Further Cardiovascular Outcomes Research with PCSK9Inhibition in Subjects with Elevated Risk (FOURIER) trial completed in 2017 enrolled 27,564 patients with stable atherosclerotic cardiovascular disease (ASCVD). Evolocumab reduced LDL-C by 59% from baseline and decreased the primary MACE endpoint by 15% (HR 0.85; 95% CI 0.79–0.92; p<0.001). [8] The ODYSSEY OUTCOMES trial published in 2018 demonstrated comparable benefits with alirocumab in patients with recent acute coronary syndrome (ACS) (HR 0.85; 95% CI 0.78–0.93). [19]

D. Anti-Inflammatory Trials

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), published in 2017, provided pivotal clinical evidence supporting inflammation as an independent therapeutic target in atherosclerotic cardiovascular disease. In this trial, post–myocardial infarction patients with persistently elevated high-sensitivity C-reactive protein (hsCRP) despite intensive statin therapy received canakinumab at a dose of 150 mg every three months. Treatment resulted in a 15% reduction in major adverse cardiovascular events (MACE) compared with placebo (hazard ratio [HR] 0.85; 95% confidence interval [CI] 0.74– 0.98; p=0.021), without significant changes in lipid levels. [12] These findings confirmed that suppression of vascular inflammation alone can yield meaningful cardiovascular benefit. Subsequently, the Colchicine Cardiovascular Outcomes Trial (COLCOT), reported in 2019, evaluated low-dose colchicine (0.5 mg daily) in patients following recent myocardial infarction. Colchicine therapy produced a 23% reduction in composite cardiovascular outcomes (HR 0.77; 95% CI 0.61–0.96; p=0.02), further supporting the role of inflammation modulation as an effective strategy for secondary cardiovascular prevention. [20]

E. Novel Lipid-Lowering Therapy Trials

The Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCEIT), published in 2018, demonstrated substantial cardiovascular risk reduction with targeted triglyceride lowering. In statin-treated patients presenting with elevated triglyceride concentrations and either established cardiovascular disease or diabetes with additional risk factors, high-dose icosapent ethyl (4 g/day) achieved a 25% relative reduction in MACE (HR 0.75; 95% CI 0.68–0.83; p<0.001). [21] This trial established triglyceride-rich lipoproteins as clinically relevant therapeutic targets beyond LDL-C.

The Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) Outcomes trial, completed in 2023, evaluated bempedoic acid in individuals unable to tolerate statin therapy. The study demonstrated a 13% reduction in major cardiovascular events (HR 0.87; 95% CI 0.79–0.96; p=0.004), confirming the drug’s utility as an alternative lipid-lowering option for high-risk, statin-intolerant populations. [22]

F. Mineralocorticoid Receptor Antagonist Trials

The cardiovascular and renal benefits of selective mineralocorticoid receptor antagonism were evaluated in two complementary clinical trials: FIDELIO-DKD (2020) and FIGARO-DKD (2021). These studies investigated finer none, a non-steroidal mineralocorticoid receptor antagonist, in patients with type 2 diabetes mellitus and chronic kidney disease. FIDELIO-DKD demonstrated a significant reduction in kidney disease progression, while FIGARO-DKD showed a meaningful decrease in cardiovascular morbidity and mortality.

Across both trials, finer none therapy was associated with reductions in renal outcomes (HR 0.82) and cardiovascular events (HR 0.87), highlighting its dual organ-protective role in this high-risk population. [23,24]

G. Gene Therapy Clinical Development

Early-phase clinical evaluation of gene-editing–based cardiovascular therapies has marked a significant milestone in translational medicine. Phase 1 studies initiated between 2024 and 2025 have investigated CRISPR–Cas9–based interventions, including agents such as VERVE101 and CTX310, designed to modify hepatic genes involved in lipid regulation, notably proprotein convertase subtilisin/kexin type 9 (PCSK9) and angiopoietin-like protein 3 (ANGPTL3).

Preliminary findings from these trials have demonstrated favorable safety and tolerability profiles, along with durable reductions in circulating atherogenic lipoproteins following a single administration. Although long-term efficacy and safety data remain under investigation, these early results represent an important step toward the feasibility of in vivo gene editing as a therapeutic strategy for cardiovascular disease prevention. [25]

H. Cardiovascular diseases (CVDs

are the leading cause of death globally and represent a major public health challenge. They include conditions such as coronary artery disease, stroke, heart failure, and peripheral vascular disease. According to global health estimates, millions of deaths each year are attributed to CVDs, with a significant proportion occurring prematurely. The increasing prevalence of risk factors such as unhealthy diets, physical inactivity, obesity, diabetes mellitus, and smoking has further intensified the global burden of cardiovascular diseases.

One of the most important modifiable risk factors for CVD is dyslipidemia, a condition characterized by abnormal levels of lipids in the blood. Elevated low-density lipoprotein cholesterol (LDL-C), increased triglycerides, and reduced high-density lipoprotein cholesterol (HDL-C) contribute directly to the development of atherosclerosis. In this process, excess LDL particles penetrate the arterial wall, undergo oxidation, and trigger inflammatory responses that lead to plaque formation. Over time, these plaques narrow blood vessels, reduce blood flow, and may rupture, resulting in myocardial infarction or stroke.

1: Role of Dyslipidemia in Atherosclerosis

Lipid-lowering therapies are therefore essential in reducing cardiovascular risk. Statins are the first-line treatment and act by inhibiting HMG-CoA reductase, a key enzyme in cholesterol synthesis. Statins effectively reduce LDL-C levels and have been shown to significantly lower cardiovascular events. However, some patients experience side effects such as muscle pain or liver enzyme abnormalities, while others fail to achieve target lipid levels even with high-dose therapy.

Ezetimibe, which inhibits intestinal cholesterol absorption, is often used in combination with statins to enhance LDL-C reduction. Although well tolerated, its lipid-lowering effect is modest when used alone. More recently, PCSK9 monoclonal antibodies have demonstrated powerful LDL-C lowering by increasing hepatic LDL receptor recycling. Despite their effectiveness, these agents require lifelong injections and are associated with high costs, which limit widespread use.

2: Limitations of Conventional Lipid-Lowering Therapies

Due to these limitations, there is a growing need for long-term and durable therapies that can provide sustained lipid control with minimal treatment burden. This need has driven interest in therapies that target the genetic regulation of lipid metabolism rather than downstream pathways.

Advances in genetic medicine have led to the development of RNA-based and gene-based therapies that directly modify the expression of genes involved in lipid regulation. RNAbased therapies, such as small interfering RNA (siRNA) and antisense oligonucleotides, reduce the production of specific proteins by interfering with messenger RNA. These therapies have already shown promising results in lowering LDL-C and triglyceride levels with infrequent dosing schedules.

Gene-based therapies represent an even more transformative approach. Among these, CRISPR-Cas9 technology has emerged as a groundbreaking tool that enables precise editing of disease-associated genes. By targeting genes such as PCSK9 and ANGPTL3, which play critical roles in lipid metabolism, CRISPR-based therapies aim to achieve long-lasting or potentially permanent reductions in atherogenic lipoproteins following a single treatment.

3. Evolution of Lipid-Lowering Therapies

While conventional lipid-lowering therapies have significantly improved cardiovascular outcomes, their limitations highlight the need for innovative treatment strategies. The emergence of RNA- and gene-based therapies marks a paradigm shift toward precision medicine, offering the potential for sustained lipid control and improved patient adherence.

Recent advances in molecular biology have enabled targeted genetic interventions for lipid control.

OVERVIEW OF RNA-BASED THERAPIES

RNA-based therapies are modern treatments that use RNA molecules to control gene expression and reduce the production of disease-causing proteins. Instead of acting on enzymes or receptors like traditional drugs, RNA therapies act before proteins are formed, at the messenger RNA (mRNA) level.

Difference Between Traditional Drugs and RNA Therapeutics

Traditional drugs

- Act on proteins or enzymes
- Effect is temporary
- Require frequent dosing
- Do not affect gene expression

RNA-based therapeutics

- Act on mRNA
- Prevent protein formation
- Longer duration of action

Types of RNA-Based Therapies

a) Small Interfering RNA (siRNA)

Small interfering RNA (siRNA) are short double-stranded RNA molecules that bind to specific mRNA and cause its degradation. This prevents the formation of harmful proteins. siRNA therapies are widely studied in lipid disorders, particularly targeting PCSK9, leading to reduced LDL cholesterol levels.

b) Antisense Oligonucleotides (ASOs)

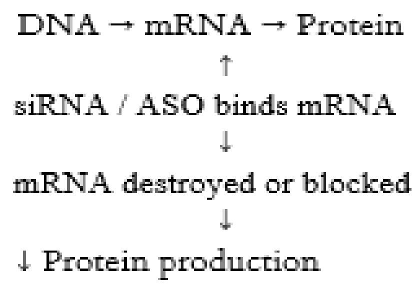
Antisense oligonucleotides (ASOs) are short single-stranded DNA or RNA molecules that bind directly to target mRNA. This binding block translation or leads to mRNA degradation. ASOs are used to reduce the production of proteins involved in lipid metabolism and inflammation.

c) mRNA-Based Therapies (Brief)

mRNA-based therapies work by introducing synthetic mRNA into cells to produce beneficial proteins. While widely used in vaccines, their role in cardiovascular disease is still under investigation and remains limited compared to siRNA and ASOs.

Mechanism of Action

RNA-based therapies act through gene silencing, meaning they stop harmful genes from producing proteins. This occurs at the mRNA level, before protein synthesis begins. The process is mainly mediated by the RNA interference (RNAi) pathway.



As a result, reduced protein synthesis leads to improved disease control, such as lower LDL cholesterol level.

Advantages of RNA-Based Therapies

RNA-based therapies offer several important advantages:

- High specificity

Target only the disease-causing gene

- Long duration of action Effects may last for months
- RNA interference (RNAi) pathway

Natural and efficient gene-silencing mechanism

- Reduced dosing frequency

Often given once or twice per year

These features improve patient compliance and treatment effectiveness.

Limitations of RNA-Based Therapies

Despite their benefits, RNA-based therapies have some limitations:

- Delivery challenges

RNA molecules require special carriers (e.g., lipid nanoparticles)

- Off-target effects

May unintentionally affect other genes

- High cost

Production and delivery are expensive

- Long-term safety concerns

GENE-BASED THERAPIES: CONCEPT AND PRINCIPLES

Gene-based therapies are advanced treatment approaches that act directly on DNA to treat or prevent disease. Instead of controlling symptoms, these therapies aim to correct or modify the genetic cause of disease, leading to long-term or permanent therapeutic effects.

Gene-based therapies can be classified into three main types:

a) Gene Addition

Gene addition involves introducing a healthy copy of a gene into a patient's cells to replace a defective or missing gene. The added gene produces the required functional protein.

b) Gene Silencing

Gene silencing aims to turn off or reduce the activity of a harmful gene. This prevents the production of disease-causing proteins. RNA-based therapies and some gene-based approaches use this strategy.

c) Gene Editing

Gene editing involves direct modification of the DNA sequence. Using special molecular tools, disease-causing genes can be cut, corrected, or permanently inactivated.

Diagram: Types of Gene-Based Therapies

Defective Gene

↓

Gene Addition → New healthy gene added

Gene Silencing → Harmful gene switched off

Gene Editing → Gene cut or corrected

Historical Background

The concept of gene therapy was introduced in the late 20th century as a potential cure for inherited and acquired diseases. Early gene therapy attempts focused on adding functional genes to compensate for defective ones.

Viral Vectors

In early studies, viral vectors were commonly used to deliver genes into cells. Modified viruses such as adenoviruses and retroviruses were designed to carry therapeutic genes without causing disease.

Safety Issues in Early Trials

Although early trials showed promise, several safety concerns limited progress:

- Immune reactions to viral vectors
- Uncontrolled gene expression
- Insertion of genes at unintended sites
- Rare but serious adverse events

These challenges highlighted the need for safer and more precise gene-editing technologies.

Modern Gene Editing Tools

Recent advances in molecular biology have led to the development of precise gene-editing tools, allowing accurate DNA modification.

a) Zinc Finger Nucleases (ZFNs)

ZFNs are engineered proteins that bind to specific DNA sequences and cut DNA at targeted sites. While effective, they are complex to design and expensive.

b) Transcription Activator-Like Effector Nucleases (TALENs)

TALENs work in a similar way to ZFNs but offer improved targeting accuracy. However, they are still difficult to manufacture and deliver.

c) CRISPR-Cas9 (Focus)

CRISPR-Cas9 is the most advanced and widely used gene-editing technology. It uses a guide RNA to locate the target gene and the Cas9 enzyme to cut the DNA precisely.

Diagram: CRISPR-Cas9 Gene Editing

Guide RNA

↓

Finds target DNA

↓

Cas9 cuts DNA

↓

Gene modified or inactivated

CRISPR-Cas9 is simpler, more efficient, and more cost-effective than earlier tools, making it highly suitable for clinical applications, including cardiovascular diseases.

Table 1: Major Cardiovascular Outcome Trials with Emerging Therapies (2017-2025)

Trial Name	Investigational Agent	Year	Sample Size	Population	Hazard Ratio (95% CI)
DAPA-HF	Dapagliflozin (SGLT2i)	2019	4,744	HFrEF (± T2DM)	0.74 (0.65–0.85)
EMPEROR-Reduced	Empagliflozin (SGLT2i)	2020	3,730	HFrEF (± T2DM)	0.75 (0.65–0.86)
SUSTAIN-6	Semaglutide (GLP-1 RA)	2016	3,297	T2DM + High CV Risk	0.74 (0.58–0.95)
SELECT	Semaglutide (GLP-1 RA)	2023	17,604	Obesity + CVD (No DM)	0.80 (0.72–0.90)
FOURIER	Evolocumab (PCSK9i)	2017	27,564	Stable ASCVD	0.85 (0.79–0.92)
ODYSSEY OUTCOMES	Alirocumab (PCSK9i)	2018	18,924	Post-ACS	0.85 (0.78–0.93)
CANTOS	Canakinumab (IL-1β mAb)	2017	10,061	Post-MI + High CRP	0.85 (0.74–0.98)
COLCOT	Colchicine	2019	4,745	Post-MI	0.77 (0.61–0.96)
REDUCE-IT	Icosapent Ethyl	2018	8,179	High TG + Statin	0.75 (0.68–0.83)
CLEAR Outcomes	Bempedoic Acid	2023	13,970	Statin Intolerant	0.87 (0.79–0.96)

VII. COMPARATIVE ANALYSIS OF EMERGING CARDIOVASCULAR DRUGS

A. Comparative Efficacy

Comparative evaluations and network meta-analyses have demonstrated that emerging cardiovascular therapies exhibit distinct patterns of clinical benefit depending on the underlying disease process. Sodium–glucose cotransporter-2 (SGLT2) inhibitors show particularly strong efficacy in reducing heart failure–related hospitalizations, with relative risk reductions ranging from approximately 25% to 35%. Notably, these benefits tend to appear early after treatment initiation, often within the first few weeks.

In contrast, glucagon-like peptide-1 (GLP-1) receptor agonists produce more gradual cardiovascular benefits. Reported reductions in major adverse cardiovascular events (MACE) range from 12% to 26%, with effects primarily driven by lower rates of myocardial infarction and ischemic stroke. These outcomes typically accumulate over longer treatment durations and parallel sustained weight reduction and metabolic improvement.

Lipid-lowering therapies, particularly PCSK9 inhibitors, demonstrate consistent reductions in ischemic cardiovascular events that correlate directly with the extent of low-density lipoprotein cholesterol (LDL-C) lowering achieved. This dose–response relationship reinforces the central role of LDL-C as a causal factor in atherosclerotic disease progression.

B. Mechanistic Distinctions

The therapeutic actions of these drug classes are largely complementary rather than overlapping. SGLT2 inhibitors exert favorable hemodynamic effects through natriuresis and volume modulation while simultaneously promoting beneficial myocardial metabolic adaptations. These mechanisms directly support cardiac function, particularly in heart failure populations.

GLP-1 receptor agonists primarily influence atherosclerotic disease through metabolic regulation, weight reduction, and vascular protective effects. Lipid-modifying therapies— including PCSK9 monoclonal antibodies, small interfering RNA agents, and adenosine triphosphate–citrate lyase inhibitors such as bempedoic acid—target the structural burden of atherosclerotic plaque. In parallel, anti-inflammatory agents act on plaque biology by reducing inflammatory activation, thereby lowering the risk of plaque rupture and thrombotic events.

Table 2: Comparative Overview of Emerging Cardiovascular Drug Classes

Drug Class	Representative Agent	Primary Mechanism	Key Indications	Dosing Frequency
SGLT2 Inhibitors	Empagliflozin	Glucosuria, Natriuresis	HFrEF, HFpEF, CKD, T2DM	Oral daily
GLP-1 RAs	Semaglutide	Incretin mimetic	T2DM, Obesity, ASCVD	SC weekly
PCSK9 Inhibitors	Evolocumab	LDLR recycling	High LDL-C, ASCVD	SC biweekly
Novel Lipids	Inclisiran	siRNA PCSK9 synthesis	High LDL-C, ASCVD	SC 6-monthly
Anti-inflammatory	Colchicine	Microtubule inhibition	Chronic CAD, Post-MI	Oral daily

VIII. SAFETY, TOLERABILITY, AND ADVERSE EFFECTS

A. SGLT2 Inhibitors

This mechanistic diversity underpins the modern concept of "therapeutic pillars," in which medications targeting distinct pathophysiological pathways are combined to comprehensively reduce cardiovascular risk rather than relying notice a single intervention strategy.

B. Clinical Implications

In contemporary practice, therapeutic selection should be guided by patient phenotype and dominant risk factors. SGLT2 inhibitors are preferentially indicated in individuals with heart failure and chronic kidney disease due to their robust cardiorenal protective effects. GLP-1 receptor agonists are particularly beneficial for patients with obesity, insulin resistance, and established atherosclerotic cardiovascular disease. SGLT2 inhibitors are generally well tolerated in clinical practice. The most commonly reported adverse events are genital mycotic infections, occurring in approximately 3–5% of treated patients, particularly among individuals with poor baseline glycemic control. Rare but clinically significant complications include euglycemic diabetic ketoacidosis, with an incidence of less than 1%, as well as volume depletion–related effects such as hypotension, especially in elderly patients or those receiving concurrent diuretic therapy. Early concerns regarding an increased risk of lower limb amputations, initially identified in the CANVAS program, have not been consistently observed in later trials or real-world studies.

C. GLP-1 Receptor Agonists

Gastrointestinal symptoms represent the most frequent adverse effects associated with GLP1 receptor agonist therapy. Nausea, vomiting, and diarrhea occur in approximately 20–40% of patients, particularly during treatment initiation or dose escalation, but typically diminish with continued use. An increased incidence of gallbladder-related disorders has also been reported, likely related to rapid weight loss. Although rodent studies suggested a potential association with thyroid C-cell tumors, this finding has not been replicated in human clinical trials or epidemiological studies, and no causal relationship has been established in clinical populations.

D. PCSK9 Inhibitors

PCSK9 monoclonal antibodies exhibit an excellent overall safety profile. Mild injection-site reactions are the most commonly reported adverse events and are generally self-limiting. Extensive long-term follow-up data have alleviated earlier concerns regarding possible neurocognitive impairment or increased incidence of diabetes associated with achieving very low LDL-C concentrations, confirming the long-term tolerability of intensive LDL-C lowering.

E. Anti-Inflammatory Agents

Canakinumab therapy has been associated with a small but statistically significant increase in fatal infections, which has limited its widespread clinical use despite demonstrated cardiovascular benefit. In contrast, low-dose colchicine is generally well tolerated; however, gastrointestinal disturbances such as diarrhea may occur. Clinicians must remain vigilant regarding important drug–drug interactions, particularly with strong cytochrome P450 3A4 inhibitors such as clarithromycin, which can significantly increase colchicine toxicity risk. [20]

F. Novel Lipid-Modifying Therapies

Bempedoic acid has been linked to elevations in serum uric acid levels, potentially triggering gout in predisposed individuals, and carries a small but notable risk of tendon rupture. Icosapent ethyl therapy has been associated with a higher incidence of atrial fibrillation compared with placebo (5.3% versus 3.9%), as well as a modest increase in bleeding events, particularly among patients receiving concomitant antithrombotic therapy.

IX. THERAPEUTIC IMPLICATIONS & CLINICAL PRACTICE IMPACT

The integration of these novel therapeutic modalities has necessitated substantial revisions to clinical practice guidelines. SGLT2 inhibitors and GLP-1 receptor agonists now carry Class I recommendations (highest level of evidence) for patients with T2DM and established cardiovascular disease, frequently prioritized before or in conjunction with metformin initiation. SGLT2 inhibitors have been established as a foundational therapeutic pillar in heart failure management regardless of diabetes status (Class I recommendation). The increasingly stringent LDL-C treatment targets (below 55 mg/dL for very high-risk patients according to European Society of Cardiology guidelines) mandate utilization of PCSK9 inhibitors or inclisiran for many high-risk patients. Clinical practice paradigms are progressively shifting toward earlier, more aggressive combination therapy strategies rather than sequential stepwise therapeutic escalation.

X. LIMITATIONS OF CURRENT EVIDENCE

A. Methodological Considerations

Although cardiovascular outcome trials offer high-quality evidence regarding therapeutic efficacy, their findings may not always be fully applicable to routine clinical practice. Many trials exclude patients with advanced multimorbidity, including individuals with severe chronic kidney disease, advanced age, or frailty syndromes, thereby limiting external validity. Furthermore, long-term safety outcomes for emerging gene-based therapies remain uncertain, as follow-up durations extending beyond 5–10 years are not yet available.

B. Translational and Implementation Barriers

A notable disparity persists between evidence generated in controlled clinical trials and its application in real-world settings. High acquisition costs and restrictive reimbursement policies, including prior authorization requirements, substantially limit access to therapies such as PCSK9 inhibitors and GLP-1 receptor agonists. In addition, real-world adherence challenges—particularly with injectable medications —along with the growing complexity of polypharmacy in high-risk cardiovascular patients, continue to complicate optimal therapeutic implementation.

XI. FUTURE RESEARCH DIRECTIONS

Current and ongoing research efforts are focused on improving accessibility, durability, and patient adherence to emerging cardiovascular therapies. Development of oral formulations targeting traditionally injectable biological pathways—such as oral PCSK9 inhibitors and oral semaglutide evaluated in the SOUL trial—represents a promising advancement.

Simultaneously, gene-editing strategies are progressing into Phase II and Phase III clinical development, raising the possibility of long-term or permanent cardiovascular risk modification following a single therapeutic intervention. Future investigations must also define optimal treatment sequencing, combination regimens, and patient selection strategies to maximize clinical benefit.

Equally important, forthcoming research should rigorously evaluate cost-effectiveness, health system sustainability, and equity of access across diverse populations and healthcare infrastructures to ensure that therapeutic innovation translates into meaningful population-level cardiovascular risk reduction.

XII. CONCLUSION

Over the past decade, cardiovascular pharmacotherapy has expanded at an unprecedented pace, fundamentally reshaping the prevention and management of cardiovascular disease. Modern clinical practice now encompasses a broad spectrum of therapeutic strategies that target multiple disease pathways, including glucose– sodium regulation, incretin signaling, lipid metabolism, thrombotic activity, and vascular inflammation. Evidence from pivotal trials such as DAPA-HF, SELECT, and FOURIER has conclusively demonstrated that these innovative agents significantly reduce cardiovascular morbidity and mortality across a wide range of patient populations.

The future direction of cardiovascular medicine increasingly lies in precision-oriented treatment models. By aligning specific molecular therapies with individual patient phenotypes—guided by biomarkers, metabolic characteristics, and genetic profiles—

clinicians can move beyond uniform treatment algorithms toward truly personalized care. As gene-based and RNA-directed therapies continue to advance through clinical development, the possibility of long-term or permanent modification of cardiovascular risk factors becomes increasingly attainable, signaling a potential paradigm shift away from lifelong pharmacotherapy.

The combined application of metabolic, lipid-lowering, anti-inflammatory, and gene targeted interventions offers an unparalleled opportunity to address the complex and interconnected nature of cardiovascular disease more comprehensively than ever before. To fully realize this potential, clinicians and healthcare systems must remain actively engaged with emerging evidence, continuously adapting therapeutic strategies to integrate innovation with patient-centered care. Through thoughtful implementation of these evolving therapies, the future of cardiovascular medicine holds promise for substantially improved outcomes and durable risk reduction.

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