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Review Article

Therapeutic Advancement in Cardiovascular Disorders: Molecular Mechanisms, Emerging Targets and Translational Perspectives

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Abstract

Cardiovascular disorders (CVD) have been addressed as the leading cause of global mortality and morbidity which majorly includes atherosclerosis, hypertension, heart failure, arrhythmias and cardiomyopathies. Its pathogenesis involves various interconnected molecular mechanisms such as endothelial dysfunction, oxidative stress, chronic inflammation, mitochondrial impairment, lipid dysregulation, fibrosis and genetic alterations. The conventional pharmacological strategy of CVD includes statins, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers and antiplatelet agents. Clinically, though these medications have provided substantial improved outcomes but its long-term usage has been frequently associated with drug resistance, hepatotoxicity, myopathy, renal dysfunction, bleeding risk and residual cardiovascular events. Moreover, these primarily target symptomatic and hemodynamic abnormalities rather than the underlying molecular pathology. Recent advances in molecular cardiology and translational medicine have facilitated the development of targeted therapeutic strategies that primarily aims to overcome these limitations. Specifically, targeting dysregulated lipid pathophysiology, stains utilization has evolved to PCSK9 inhibitors and small interfering RNA (siRNA)-based therapeutics, such as inclisiran. Precision medication strategy has made the use of RNA therapeutics and CRISPR-Cas9-mediated which enable precise regulation of disease-associated genes. Regenerative stem cell therapies, on the other hand promoted myocardial repair and angiogenesis, while nanotechnology-based drug delivery systems improved therapeutic specificity and bioavailability. In parallel to this, AI-assisted precision cardiology has enabled early diagnosis, risk stratification, and individualized treatment planning strategies. However, despite these advances, challenges related to safety, delivery efficacy, ethical concerns and expense remain the major barriers to widespread clinical translation of these therapeutic advancements in cardiac patients.

Keywords: Cardiovascular disorders, Conventional cardiac-therapeutics, PCSK9 inhibitors, RNA-based therapeutics, Gene editing, Stem cell therapy, Nanotechnology, Precision cardiology.

1. Introduction

Cardiac disorders are one of the widespread non-communicable diseases with increasing global mortality. According to World Health Organization (WHO) reports, cardiovascular diseases (CVD) account for approximately 17.9 million deaths globally every year[1]. Majorly, unhealthy dietary habits, lack of physical activities, smoking, diabetes mellitus, obesity and associated metabolic syndrome have been found to cause this global rise in cardiovascular diseases and continues to increase steadily over time. It not only affects the mortality, but also reduces the quality and duration of life along with increasing the burden at social-economic level, particularly in low as well as in middle income countries[2].

CVDs are generally seen to affect the heart as well as the blood vessels system but they involve a wide range of disorders such as atherosclerosis, heart failure, peripheral arterial and coronary artery disease, rheumatic heart disease, congenital heart disease, cerebrovascular diseases, heart failure and cardiomyopathies depending on the type of multi-factorial complication involved. However, globally the major causes of death, related to CVD are ischemic heart disease and stroke. Additionally, the increased incidence of hypertension and metabolic-associated diseases has significantly contributed to the rise of atrial fibrillation, heart failure and vascular complications which further worsen the clinical outcomes[3]. Current therapeutic strategy related to cardiovascular diagnosis and treatment have made significant improvement over the past decades. Statins, beta-blockers, antihypertensive agents, anticoagulants and antiplatelet drugs are the major examples of traditional pharmaceutical treatments, have reduced the mortality rate and improved the quality of life in patients. Besides pharmacological aspects, clinical management involves utilization of interventional techniques such as coronary angioplasty, stent implantation, cardiac ablation, and bypass grafting from serious and complicated patients. However, despite having all the clinical care and pharmacology developments, CVD continues to have higher morbidity, mortality rate and recurrent

hospitalizations. The limitation scenario of conventional strategies includes drug resistance, poor patient compliance, and associated long term medications complications. Additionally, their generalized approach further limits the efficacy across varied patient populations. Thus, the need for advanced and effective therapeutics shifted the focus from merely seeing symptoms towards development of mechanism-based and precision-targeted medications. This urge has led to the emergence of molecular cardiology, regenerative medicine, genomics and biomedical engineering for improving the understanding of CVDs progression and identifies potential treatment targets. Further advancements led the development of PCK9 inhibitors, RNA therapeutics, antisense oligonucleotides, CRISPR-Cas9 gene editing, stem cell therapy, tissue engineering and nanotechnology-based drug delivery system, which not only aimed to cure but to treat and restore the entire system[4,5]. Apart from these, artificial intelligence (AI), digital health and clinical health technologies are changing cardiovascular medicine through early detection, predictive analytics, remote monitoring, and individualized therapy planning[6]. Although these new solutions represent significant advancements in cardiovascular therapeutics, substantial translational obstacles remain, including safety issues, delivery restrictions, high treatment costs, ethical considerations, and insufficient long-term clinical validations. Therefore, rigorous clinical research is necessary for developing fully translated anti-CVD therapeutic which would be safer, more effective and patient-specific. This review addresses current breakthroughs in therapeutic techniques for cardiovascular illnesses, focusing on novel molecular targets, translational approaches, and future possibilities in precision cardiovascular medicine.

2. Methodology

A detailed literature search was carried out for evaluating the evolutionary landscape of CVD therapeutics in different peer-reviewed databases including PubMed, Google Scholar, NIH, WHO etc. using words related to CVDs types, pathophysiology, and clinical management strategy including both conventional and advanced prospective.

3. Results and Discussion

3.1. Types of cardiac disorders and their mechanistic pathophysiology

CVDs are a combination of conditions that affect the heart and circulatory system. Depending on the underlying cause and patients response parameters, each condition shows unique clinical manifestations, such as chest pain (angina), chest pressure, heaviness or discomfort, shortness of breath (dyspnea), excessive sweating, dizziness, fatigue/exhaustion etc. However, apart from these phenotypic symptoms, their progression has been seen to largely driven by interconnected molecular and cellular mechanism involving fibrosis, lipid dysregulation, endothelial dysfunction, chronic inflammation, neurohormonal activation, oxidative stress mitochondrial impairment, and genetic abnormalities as detailed in table 1. Collectively, these disorders share overlapping molecular pathways that contribute to cardiovascular dysfunction and disease progression[3]

Table 1. Major types of cardiovascular disorders and their molecular pathophysiology

Cardiovascular disorder	Major pathophysiological features	Important genes	Key proteins/ biomarkers	Major molecular pathways	Ref
Atherosclerosis	Endothelial dysfunction, LDL oxidation, foam cell formation, vascular inflammation, plaque instability	ABCA-1, ACE, ADAMTS7, ANRIL, APOA-1, APOB, APOE, CD36, CD40, CDKN2A, CDKN2B, CETP, CXCL12, ICAM-1, IL1B, IL6, LDLR, LPA, LPL, LOX1 (OLR1), MMP9, NLRP3, NOS3, NPC1L1, PCSK9, PHACTR-1, PLA2G7, SCARB1, SMAD3, SORT1, TCF21, TGFBR2, TLR4, TNF, VCAM-1, VEGFA	Ox-LDL, VCAM-1, ICAM-1, CD36, CRP, MCP-1, MMP-2, MMP-9	NF-κB signalling, oxidative stress pathway, inflammatory cytokine signalling, scavenger receptor pathway	7,8
Hypertension	Increased vascular resistance, endothelial dysfunction, vascular remodelling, sodium retention	ACE, AGT, AGTR-1, AGTR2, ADD1, ADRB1, ADRB2, ATP2B1, CACNA1C, CACNB2, CYP11B2, CYP17A1, EDN1, ENPEP, FGF5, GNB3, HSD11B2, KCNJ1, KLKB1, MTHFR, NOS3, NPPA, NPPB, NPR1, PHACTR1, PDE3A, REN, SCNN1A, SCNN1B, SCNN1G, SH2B3, SLC12A3, SLC4A7, STK39, TGFB1, UMOD, WNK1, WNK4	Angiotensin II, Aldosterone, eNOS, Endothelin-1, CRP	RAAS activation, NADPH oxidase pathway, ROS and NO signalling dysfunction	9–11

Heart failure	Ventricular remodelling, mitochondrial dysfunction, fibrosis, impaired calcium handling, apoptosis	ACE, ADRB1, ADRB2, AGT, AGTR1, ANP (NPPA), BAG3, CACNA1C, CAMK2D, DES, DMD, DSP, FLNC, GATA4, LMNA, MYBPC3, MYH6, MYH7, NPPB, NPPA, PLN, RBM20, RYR2, SCN5A, TBX5, TCAP, TGFB1, TNNT2, TPM1, TTN	BNP, ANP, SERCA2a, TGF-β, TNF-α, IL-1β	β-adrenergic signalling, TGF-β/SMAD pathway, NLRP3 inflammasome, mitochondrial dysfunction	12,13
Arrhythmias	Abnormal impulse generation, altered ion channel activity, electrical instability	ANK2, CACNA1C, CACNB2, CASQ2, DES, DSP, GJA5, GJA1, HCN4, KCNA5, KCND3, KCNH2, KCNJ2, KCNQ1, LMNA, NKX2-5, PKP2, PLN, RYR2, SCN1B, SCN5A, SNTA1, TBX5, TRDN KCNE1, RYR2	Sodium channels, Potassium channels, Ryanodine receptor, CA, SQ2	Ion channel signalling, calcium-handling pathway, autonomic signalling	14,15
Hypertrophic Cardiomyopathy (HCM)	Myocardial hypertrophy, sarcomeric dysfunction, diastolic dysfunction	ACTC1, ALPK3, CSRP3, DES, FLNC, GLA, LAMP2, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYBPC3, PLN, PRKAG2, RAF1, TNNI3, TNNC1, TNNT2, TPM1, TTN	β-myosin heavy chain, Troponin T, Myosin-binding protein C	Sarcomeric signalling pathway, calcium-sensitivity pathway	16,17
Dilated Cardiomyopathy (DCM)	Ventricular dilation, systolic dysfunction, impaired cytoskeletal integrity	ACTCI, BAG3, DES, DSP, DMD, FLNC, ILK, JPH2, LMNA, MYH7, NEXN, PLN, RBM20, SCN5A, TMEM43, TNNC1, TNNI3K, TPM1, TNNT2, TTN, VCL	Titin, Lamin A/C, Desmin, Dystrophin	Cytoskeletal remodelling, mitochondrial dysfunction, apoptotic signalling	18
Arrhythmogenic cardiomyopathy	Fibro-fatty myocardial replacement, ventricular arrhythmias	CDH2, CTNNA3, DSP, JUP, KCNQ1, LEMD2, RYR2, TGFB3, TJP1, TMEM43, TP63, PKP2,	Plakophilin-2, Desmoplakin, Plakoglobin	Desmosomal signalling pathway, fibrosis signalling	19,20
Coronary Artery Disease (CAD)	Coronary artery narrowing, myocardial ischemia, thrombosis	ABCA1, ACE, ACTA2, ADAMTS7, AGTR1, ANGPTL3, ANRIL, APOA5, APOB, APOC3, APOE, CD40, CDKN2A, CDKN2B, CETP, COL4A1, COL4A2, CXCL12, EDN1, F2, F5, GUCY1A3, HMGCR, ICAM1, IL1B, IL6, ITGA2B, ITGB3, JCAD, LDLR, LPA, LPL, MMP9, MRAS, NOS3, NPC1L1, P2RY12, PCSK9, PDGFD, PECAM-1, PHACTR-1, PLA2G7, PPARG, SCARB-1, SERPINE-1, SH2B3, SMAD3, SORT1, SVEP-1, TCF21, TGFBR2, THBD, TLR4, TNF, TRIB-1, VCAM-1, VEGFA, VWF	HIF-1α, VEGF, Troponins, P2Y12 receptor	Hypoxia signalling, platelet activation pathway, inflammatory signalling	21
Stroke / cerebrovascular disease	Cerebral ischemia, excitotoxicity, neuroinflammation, neuronal apoptosis	ACE, AGT, APOE, ATRNL-1, CADASIL (NOTCH3), COL4A1, COL4A2, CYP11B2, EDN1, F2, F5, FOXF2, GLA, HDAC9, HTRA-1, HBB, ICAM-1, IL6, MTHFR, NOS3, NOTCH3, PDE4D, PITX2, SERPINE1, SH2B3, TGFBR2, TNF, VCAM-1, VWF, ZFHX3	IL-6, TNF-α, MMPs, Glutamate	Oxidative stress pathway, inflammatory signalling, apoptosis pathway	22,23
Peripheral Arterial Disease (PAD)	Peripheral ischemia, endothelial dysfunction, impaired perfusion	ANRIL (CDKN2B-AS1), CD40, CHRNA3, DAB2IP, EDNRA, F5, HDAC9, HLA-B, ICAM-1, IL6, IPO5/RAP2A, LDLR, LPA, LPL, NOS3, OSBPL, PTPN-11, PAX2, SH2B3, SORT1/CELSR	Endothelin-1, VEGF, CRP, ICAM-1	NO signalling dysfunction, hypoxia signalling, inflammatory pathways	24,25

3.2. Conventional standardized treatment strategy

For decades, the key components of cardiovascular disease management have been possible because of the adopted traditional therapeutic approaches. These therapies aim to reduce cardiovascular mortality, prevent complications, including myocardial infarction, arrhythmias, heart failure, and stroke, alleviate symptoms, and control the progression of the disease. Although, these methods have improved the survival of patients, most traditional therapies primarily target the symptomatic manifestations and hemodynamic abnormalities, rather than focusing on the underlying molecular pathology[26].

3.2.1. Lipid-lowering agents

Lipid-lowering medications constitute the primary backbone of conventional CVD therapeutics. They are commonly used in the prevention and treatment of CAD and atherosclerosis. Statins are the first-line agents used in the therapeutic approach by blocking hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. The intracellular cholesterol synthesis and the upregulation of hepatic low-density lipoprotein receptors (LDLR) can be lowered by inhibiting HMG-CoA reductase. It can improve the LDL-C clearance from circulation. Statins have pleiotropic effects, which include better endothelial function, decreased oxidative stress, inhibition of inflammatory signalling, and atherosclerotic plaque stabilization[27]. Another major medication includes fibrates, work by promoting fatty acid oxidation and stimulating PPAR-α expression thereby ultimately lowering triglyceride production. Ezetimibe on the other hand, decreases intestinal cholesterol absorption by blocking Niemann-Pick C1-like protein 1 (NPC1L1), whereas bile acids lower cholesterol levels by increasing the production of bile acid excretion[28]. Despite this therapeutic usefulness, traditional lipid-lowering medicines are often limited by several disadvantages such as statin intolerance, hepatotoxicity, myopathy, residual inflammatory risk, and varying patient response[29].

3.2.2. Antihypertensive therapies

Anti-hypertensive treatment mainly targets vascular resistance, fluid imbalance, and neurohormonal activation. The Angiotensin receptors blocker (ARBs) reduce the signalling of angiotensin type-1 receptor, and are widely used in heart failure, nephropathy, and hypertension. Therefore, the conversion of angiotensin I to angiotensin II by inhibiting angiotensin-converting enzyme (ACE) results in decreasing oxidative stress, aldosterone secretion, vasoconstriction, and vascular remodelling. Beta-blockers block the β-adrenergic receptor signalling by lowering heart rate, sympathetic overactivation, myocardial oxygen demand, and arrhythmogenic risk. Calcium channel blockers on the other hand disrupt the L-type calcium channels in vascular smooth muscle and cardiomyocytes, increases vasodilation while lowering cardiac contractility. Diuretics reduce blood volume through enhanced sodium and water excretion, whereas renin inhibitors directly suppress renin-angiotensin-aldosterone-system (RAAS) activation. These therapies although effectively decreases the blood pressure and cardiovascular events but its prolonged utilization has been reported to lead electrolyte imbalance, drug resistance, renal dysfunction, hypotension, and fatigue[30].

3.2.3. Antithrombotic and antiplatelet therapies

Thrombosis and platelet aggregation play a significant role in myocardial infarction and ischemic stroke. Conventional medication such as aspirin inhibits cyclooxygenase-1 (COX-1) by reducing thromboxane A2-mediated platelet activation. P2Y12 receptor inhibitors such as clopidogrel and ticagrelor suppress ADP-mediated platelet aggregation and are commonly used in coronary interventions. Anticoagulants such as heparin, warfarin, and direct oral anticoagulants (DOACs) prevent thrombus formation by inhibiting the activation of the coagulation cascade. These drugs are widely used in atrial fibrillation, venous thromboembolism, and acute coronary syndromes. However, significant drawbacks include increased bleeding risk, limited therapeutic windows, medication interactions, and interindividual heterogeneity in therapeutic response[31,32].

3.2.4. Conventional heart failure therapies

Heart failure management primarily focuses on suppressing neurohormonal activation and reducing ventricular activity. In these cases, ACE inhibitors, beta-blockers, ARBs, mineralocorticoid receptor antagonists, and diuretics have been used conventionally to enhance hemodynamic stability and lower hospitalization rates[33]. Specifically in case of increasing myocardial contractility digoxin works by inhibiting Na+/K+-ATPase action and raising intracellular calcium levels[34]. Recently, sodium-glucose cotransporter-2 (SGLT2) inhibitors such as dapagliflozin and empagliflozin have shown substantial cardioprotective effects by improving myocardial energy, reducing inflammation, and promoting osmotic diuresis. Given recent therapeutic improvements, standard heart failure medicines cannot completely repair myocardial fibrosis, mitochondrial dysfunction, or cardiomyocyte loss[35].

3.2.5. Conventional surgical and interventional approaches

Surgical and interventional procedures, in addition to pharmacological therapy, are crucial in the management of cardiovascular diseases. Percutaneous coronary intervention (PCI) with angioplasty and stent insertion is a standard procedure for restoring coronary blood flow after acute coronary syndrome. Drug-eluting stents prevent restenosis by reducing vascular smooth muscle growth. Coronary artery bypass grafting (CABG) is a common surgical treatment for severe multivessel coronary artery disease. Pacemakers, implanted cardioverter defibrillators (ICDs), and catheter ablation treatments are used to treat cardiac rhythm abnormalities. Advanced heart failure patients may need ventricular assist devices (VADs) or a heart transplant. Although, these

treatments considerably increase mortality and heart function, procedural complications, restenosis, thrombosis, graft failure, infection, and donor limits are still serious issues[36–38].

3.2.6. Limitations of conventional therapies

Although conventional therapies have substantially reduced cardiovascular mortality, several limitations continue to hinder complete disease management. Most conventional drugs primarily alleviate symptoms and hemodynamic abnormalities rather than targeting molecular disease mechanisms. Long-term treatment dependency, drug intolerance, systemic toxicity, residual inflammatory risk, poor tissue regeneration, and patient non-compliance frequently reduce therapeutic efficacy. Furthermore, conventional therapies often fail to provide personalized treatment responses due to genetic and metabolic variability among patients[39].

4. Advancement in cardiac disorder therapeutic strategy

Recent developments in molecular cardiology, translational medicine, regenerative biology, nanotechnology and computational sciences have altered cardiovascular treatments from being a generalized symptom-based care to precision-targeted. Although traditional cardiovascular therapy has significantly decreased morbidity and mortality, persistent residual cardiovascular risk, increasing, chronic inflammation, myocardial remodelling, endothelial dysfunction and irreversible tissue injury continue to limit long-term clinical results[40]. As a result, advanced therapeutic research is increasingly focused on finding disease-specific molecular pathways involved in mitochondrial dysfunction, lipid dysregulation, fibrosis, thrombosis, oxidative stress and genetic anomalies. This have permitted the development of methods based on innovative treatment which are capable of selectively modifying cardiovascular pathophysiology along with improving therapeutic specificity and minimizing systemic side effects[41].

4.1. Targeted lipid-lowering molecular therapeutics

Despite the widespread statin usage, dyslipidemia and residual atherosclerotic cardiovascular risk continues to persist, and contribute to global surge of CVD morbidity and mortality cases. Although, statins efficiently lower low-density lipoprotein cholesterol (LDL-C) by inhibiting hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, certain patients continue to display progressive atherosclerosis, recurrent ischemic episodes, and statin intolerance. Recent advancements have developed selective lipid-lowering therapies targeting specific pathways involved in cholesterol metabolism and transport of lipoprotein[42].

One of the most significant achievements in cardiovascular therapy is the proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibitors. PCSK9 is a serine protease produced primarily in hepatocytes that interacts to hepatic low-density lipoprotein receptors (LDLRs) and facilitates lysosomal breakdown. Increase in the activity of PCSK9 lowers LDLR recycling and increases circulating LDL-C levels, hastening lipid accumulation, endothelial dysfunction, oxidative stress, foam cell production, and atherosclerotic plaque progression. The therapeutic relevance of PCSK9 inhibition was clearly established in the FOURIER and ODYSSEY OUTCOMES trials, which showed significant decreases in LDL-C levels and severe adverse cardiovascular events in high-risk cardiovascular patients. In addition to decreasing lipids, PCSK9 inhibitors have been shown to reduce vascular oxidative stress and inflammatory cytokine signalling, resulting in plaque stabilization. Despite their exceptional performance, widespread clinical utilization is limited by high treatment costs, injectable delivery, and accessibility limits[43,44]. Another major advancement in RNA therapies has enabled more precise lipid management via post-transcriptional gene silencing techniques. Inclisiran, a small interfering RNA (siRNA)-based therapy, preferentially targets hepatic PCSK9 mRNA via RNA interference mechanisms, reducing PCSK9 synthesis and resulting in persistent LDL-C reduction with infrequent dose schedules. The ORION clinical trials showed that inclisiran treatment has long-term lipid-lowering effectiveness and good tolerability profiles[45,46]. Compared to monoclonal antibodies, siRNA treatments provide longer pharmacological efficacy and enhanced patient adherence; however, delivery efficiency, long-term safety, and large-scale accessibility all require additional assessment. Besides, various new molecular targets implicated in triglyceride metabolism and lipoprotein control are now being studied. Angiopoietin-like protein-3 (ANGPTL3), apolipoprotein C-III (APOC3), and lipoprotein(a) [Lp(a)] have received significant interest because of their strong connections with residual cardiovascular risk and atherogenesis. Elevated Lp(a) levels have also been identified as independent genetic risk factors for atherosclerotic cardiovascular disease and calcific aortic valve disease. Lp(a) causes endothelial dysfunction, vascular inflammation, thrombosis, and plaque instability due to its proatherogenic and pro-inflammatory effects. As a result, other RNA-based therapies, such as pelacarsen and olpasiran, are now being studied for selective suppression of apolipoprotein(a) synthesis and decrease of circulating Lp(a) levels[47,48]. Simultaneously, breakthroughs in gene-editing technologies such as CRISPR-Cas9 have opened up the possibility of long-term repair of dyslipidemia-related genetic defects. These findings suggest that future curative cardiovascular medicines could overcome the limits of lifetime pharmaceutical treatment. Nonetheless, off-target mutations, immunological activation, ethical concerns, and long-term genomic safety remain significant translational challenges to clinical application[49].

4.2. Anti-inflammatory and immunomodulatory strategies

Chronic inflammation is increasingly recognized as a major cause of CVD initiation and progression, especially in atherosclerosis, myocardial infarction, heart failure, and vascular remodelling. Persistent inflammatory activation causes endothelial dysfunction, oxidative stress, foam cell production, plaque instability, myocardial fibrosis, and cardiomyocyte death by disrupting numerous cytokines, chemokines, adhesion molecules, and immunological signalling pathways. IL-1β has been found to be an important regulator of vascular inflammation and atherosclerosis. When the NLRP3 inflammasome is activated in macrophages, it converts pro-caspase-1 to active caspase-1, converting pro-IL-1β and pro-IL-18 into active inflammatory variants. Elevated IL-1β signalling increases the expression of IL-6, TNF-α, vascular adhesion molecules, and reactive oxygen species, causing endothelial dysfunction, leukocyte recruitment, vascular smooth muscle proliferation, and plaque instability[50]. Clinical manifestation of targeting inflammation in cardiovascular therapy has also been demonstrated in CANTOS trial. Canakinumab, a monoclonal antibody targeting IL-1β has has reduced recurrent cardiovascular events without lowering cholesterol levels. These findings offered the first direct clinical evidence inhibiting inflammatory signalling, which reduce cardiovascular risk. Furthermore, reduction in circulating inflammatory indicators, such as high-sensitivity C-reactive protein (hs-CRP), has also been linked with improved cardiovascular outcomes which emphasizes the significance of inflammation as an independent therapeutic target[51]. It confirmed chronic low-grade inflammation significantly contributes to cardiovascular disease development, even after conventional therapy. Thus, in addition to inhibiting IL-1β, decreasing NLRP3 inflammasome signalling has also emerged as an important therapeutic approach. These aspects made the utilization of Colchicine, a microtubule polymerization inhibitor which was earlier known for treating gout and inflammatory illnesses by inhibiting neutrophil activation, inflammasome assembly, leukocyte adherence, and releasing cytokine. Its efficacy in case of CVD was demonstrated in COLCOT and LoDoCo2 studies where it was found that low-dose colchicine significantly reduced recurrent ischemic cardiovascular events and coronary sequelae in patients with established coronary artery disease[52].

With the advancement in molecular techniques, other signalling pathways such as TNF-α, IL-6, and NF-κB, have been found to play a significant role in vascular inflammation, myocardial remodeling, and heart failure progression. Persistent activation of NF-κB signalling leads to increased production of inflammatory cytokines, chemokines, adhesion molecules, and fibrotic mediators, worsening vascular damage and myocardial dysfunction. Several medicines targeting IL-6 receptors, TNF-α signalling, and NF-κB-associated pathways are being investigated[53]. Additionally, studies have also identified oxidative stress-mediated inflammation as a prominent therapeutic target in cardiovascular disease. Excessive ROS production by NADPH oxidases, defective mitochondria, xanthine oxidase, and uncoupled endothelial nitric oxide synthase (eNOS) contributes to lipid peroxidation, endothelial damage, inflammatory cytokine activation, and mitochondrial dysfunction. As a result, antioxidant-based therapies such as Nrf2 activators, mitochondrial-targeted antioxidants, and ROS-scavenging nanotherapeutics are increasingly being studied for the suppression of inflammatory cardiovascular injury. Research has also found significant linkages between metabolic dysfunction and inflammation in cardiovascular disease progression. Sodium-glucose cotransporter-2 (SGLT2) inhibitors, such as dapagliflozin and empagliflozin, enhance glucose homeostasis while also lowering inflammatory signaling, oxidative stress, mitochondrial dysfunction, and cardiac fibrosis. The DAPA-HF and EMPEROR-Reduced studies showed significant decreases in cardiovascular mortality and heart failure hospitalization after SGLT2 inhibition, underscoring the therapeutic significance of metabolic-inflammatory interaction in cardiovascular disease[54].

4.3. Nanotechnology-based therapeutics

The complexity and multidimensionality of cardiovascular diseases can limit the efficacy of traditional pharmacological therapy due to inadequate tissue selectivity, limited drug absorption, systemic toxicity, and incorrect intracellular transport. These restrictions have hastened the adoption of nanotechnology in cardiovascular medicine, particularly for targeted drug administration, molecular imaging, controlled therapeutic release, and precision cardiovascular intervention. Atherosclerotic plaques and inflamed vascular regions exhibit enhanced endothelial permeability, oxidative stress, inflammatory activation, and changed cellular microenvironments, allowing for selective nanoparticle accumulation within diseased tissues. Several nanocarrier systems, including liposomes, polymeric nanoparticles, dendrimers, micelles, metallic nanoparticles, and biomimetic nanovesicles, have been developed for cardiovascular applications by leveraging these pathological properties[55]. In experimental cardiovascular models, these formulations such as AZ7379, temoporfin (mTHPC) etc., have been found to enhance plaque targeting while reducing systemic toxicity[56]. Nanotechnology has also made substantial advancement in RNA-based cardiovascular therapies as quick disintegration and low cellular uptake, siRNAs, antisense oligonucleotides, and CRISPR-associated nucleic acids continue to face significant barriers to effective intracellular delivery[57]. Another significant innovation has been observed in biomimetic and cell-membrane-coated nanoparticles, which have improved immune evasion and tissue-specific targeting abilities. Platelet membrane-coated nanoparticles, macrophage-derived nanovesicles, and exosome-mimetic systems can selectively accumulate in inflamed vascular lesions and thrombotic areas by interacting with adhesion molecules and inflammatory mediators[58].

Nanotechnology has also altered cardiovascular imaging and diagnostics by enabling the development of nano-theranostic systems that can detect and treat diseases simultaneously. The effectiveness of these combinatorial advancements has been evidenced in clinical researches, where using superparamagnetic iron oxide nanoparticles, quantum dots, and contrast-enhanced nanoprobes in magnetic resonance imaging (MRI), computed tomography (CT), and fluorescence imaging has improved visualization of vascular inflammation, plaque instability, myocardial fibrosis, and ischemic injury. Thus, integrating therapeutic and diagnostic activities inside a single nanosystem allows real-time monitoring of disease development and therapeutic response but its design-precision and implementing requires rigorous number of clinical trails[59].

4.4. Regenerative medicine and stem cell therapy

Regenerative medicine seeks to heal and restore injured myocardium through tissue repair, angiogenesis, and cardiomyocyte regeneration. Irreversible cardiomyocyte loss and poor intrinsic regenerative potential continue to be key difficulties in cardiovascular disease management, especially after myocardial infarction, ischemic injury, or chronic heart failure. As a result, regenerative medicine and stem cell-based therapies have developed as potential methods for myocardial repair, angiogenesis, tissue regeneration, and cardiac function restoration. Stem cells are the most well investigated of these techniques due to their immunomodulatory qualities, minimal immunogenicity, and ability to release growth factors, cytokines, and extracellular vesicles that aid in tissue repair. MSC-derived paracrine signalling enhances angiogenesis via the VEGF, FGF, and HGF pathways, while reducing inflammatory cytokines and oxidative stress. MSCs inhibit myocardial fibrosis and apoptosis by regulating TGF-β, PI3K/Akt, and ERK signalling pathways. Through the creation of cardiac scaffolds, hydrogels, bioengineered patches, and three-dimensional bio printed cardiac constructions, recent developments in tissue engineering and biomaterial sciences have further improved regenerative treatment approaches. These biomaterials aid in cellular integration into injured myocardium, enhance stem cell retention, and offer structural support. Exosome-based treatments have become a promising cell-free regeneration strategy at the same time. Without the dangers of direct stem cell transplantation, microRNAs, proteins, lipids, and signalling molecules found in stem-cell-derived exosomes can promote angiogenesis, reduce oxidative stress, suppress inflammation, and improve cardiomyocyte lifespan. However, by addressing the underlying constraint of irreversible cardiac injury, stem cell treatment and regenerative medicine represent significant advances in cardiovascular therapies. Future myocardial repair and cardiac regeneration may be greatly enhanced by the integration of stem cell engineering, tissue biomaterials, gene editing, exosome therapies, and precision regenerative techniques[60,61].

4.5. Advanced surgical and interventional cardiovascular techniques

Continuous advancements in cardiovascular surgery and interventional cardiology have substantially improved the management of complex structural and ischemic heart diseases. Conventional surgical approaches, although highly effective, are frequently associated with extensive tissue injury, prolonged hospitalization, perioperative complications, and delayed recovery. As a result, recent technology advances have focused on minimally invasive, image-guided, and precision-based cardiovascular therapies that can reduce procedural trauma while enhancing clinical outcomes. These sophisticated procedures combine robots, catheter-based interventions, biomaterial engineering, and hybrid surgical platforms to improve procedural precision, cardiovascular repair, and long-term patient survival[62].

Among the most notable advancements, transcatheter aortic valve replacement (TAVR) has transformed the treatment of severe aortic stenosis, especially in elderly and high-risk surgical patients. Unlike traditional surgical valve replacement, which requires open-heart surgery and cardiopulmonary bypass, TAVR uses catheters to implant bioprosthetic valves via transfemoral or transapical access. This surgical method minimizes perioperative mortality, inpatient duration, inflammatory damage, and healing time. TAVR mechanically restores valvular hemodynamics by replacing calcified and stenotic aortic valves while avoiding cardiac tension and widespread inflammatory response caused by conventional surgical operations. The PARTNER and Core Valve trials strongly verified TAVR's clinical efficacy, demonstrating lower mortality and better functional results than traditional surgery in selected patient categories. Furthermore, technological advancements in valve design, imaging guidance, and delivery systems have increased procedural safety and made TAVR available to intermediate and low-risk patients. However, problems such as paravalvular leak, vascular damage, prosthesis deterioration, stroke risk, and conduction anomalies necessitate permanent pacemaker implantation which, limits its widespread therapeutic usage[63,64]. Further, advancements in invasive robotic techniques decreased systemic inflammatory reactions, oxidative stress, endothelial injury, and neurohormonal activation, which are often associated with significant surgical trauma. Although these techniques showed advanced and precision benefits, robotic cardiovascular surgery has been often constrained by high procedure costs, steep learning curves, extended operating times, and a scarcity of specialist surgical infrastructure[65]. Consecutively, bioengineered vascular grafts and tissue-engineered cardiovascular substitutes have also emerged as promising replacements for synthetic graft materials and donor tissues. Conventional vascular grafts are prone to thrombosis, calcification, restricted biocompatibility, and graft failure due to persistent inflammatory activation and reduced endothelialization. To address these constraints, bioengineered grafts made of biodegradable polymers,

extracellular matrix scaffolds, stem-cell-seeded biomaterials, and de-cellularized tissues has been being created which would imitate natural vascular architecture along with facilitating tissue regeneration. These grafts promote endothelial cell adhesion, vascular smooth muscle architecture, extracellular matrix remodelling, and angiogenesis by modulating integrin signalling, growth factor release, and mechano-transduction pathways[66]. Furthermore, incorporating stem cells, growth hormones, and nanomaterials into bioengineered scaffolds promotes vascular regeneration while reducing inflammatory reactions. Experimental and early clinical studies have also demonstrated and validated the promising outcomes in small-diameter vascular reconstruction, coronary bypass surgery, and valvular tissue engineering. However, its long-term durability, immunological compatibility, biomaterial degradation, and large-scale manufacturing make up the major translational obstacles[67]. Despite these challenges, advanced surgical and interventional techniques represent a major evolution in cardiovascular therapeutics by integrating minimally invasive technology, regenerative engineering, and precision cardiovascular repair[68].

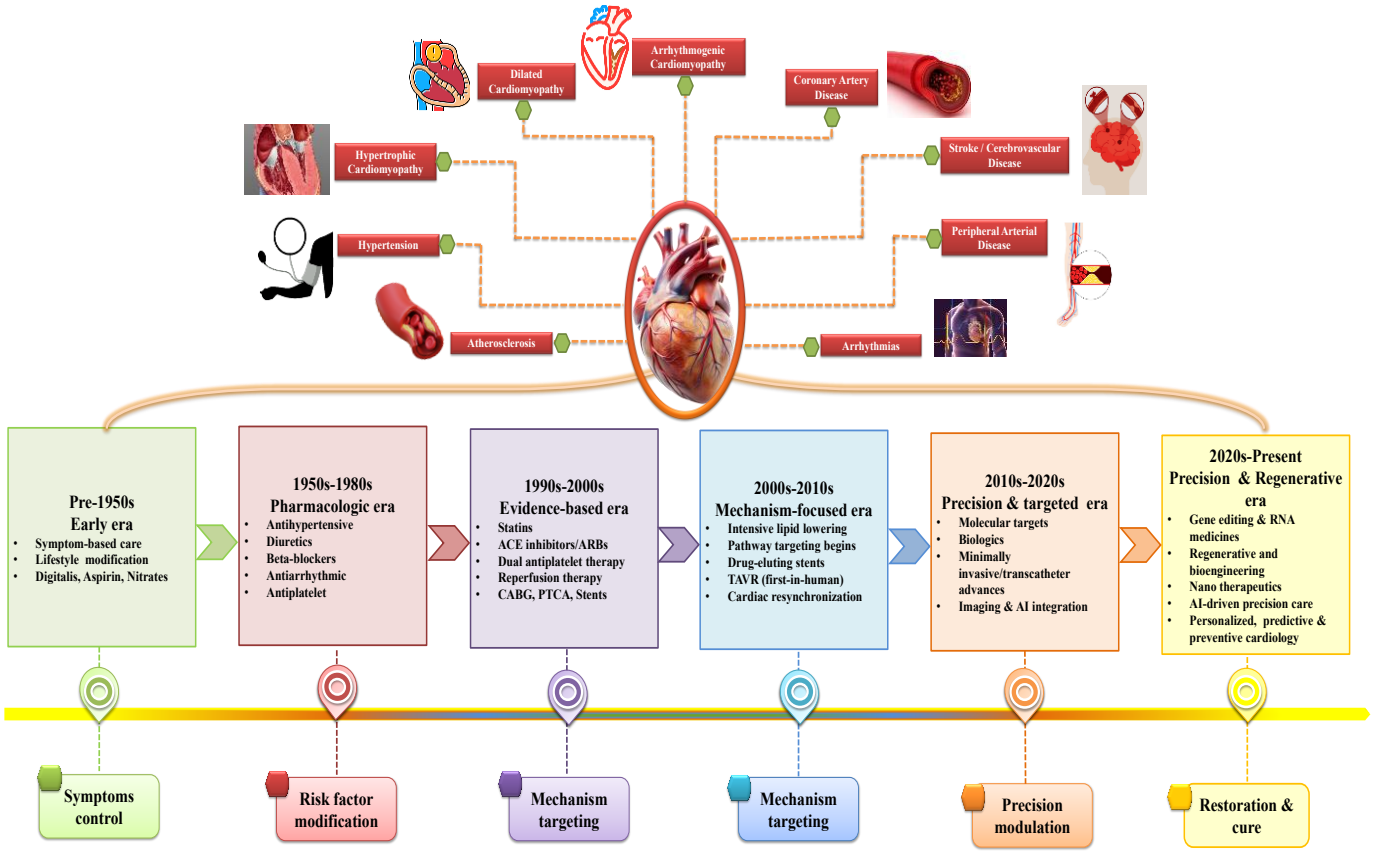

Figure 1. Evolutionary map of therapeutic strategy for treatment of cardiac disorders

5. Comparative analysis of conventional and advanced cardiovascular therapeutics

Despite significant development in pharmacological and therapeutic management, the global burden of cardiovascular diseases highlights the urgent need for more effective and mechanism-based therapeutic strategies. While conventional cardiovascular treatment improved survival and reduced disease-associated complications, persistent residual cardiovascular risk, recurrent adverse events, progressive myocardial remodelling, and incomplete tissue repair continue to limit long-term clinical outcomes. Moreover, the diverse nature of cardiovascular disorders involving oxidative stress, endothelial dysfunction, inflammation, mitochondrial impairment, and genetic disorders necessitates targeted therapeutic approaches which could both regulate disease both at genotypic and phenotypic level. Recent advances in molecular cardiology have therefore established novel therapeutic paradigms that mainly focused targeted pathway modulation and disease interception. Importantly, major clinical trials have validated several of these strategies, thereby confirming precise modulation of inflammatory, metabolic, and genetic pathways can substantially improve cardiovascular outcomes beyond conventional standards of care. However, these advancements also face critical challenges including delivery specificity, long-term genomic safety, immune compatibility, biomaterial toxicity, procedural scalability, and equitable accessibility which hinder the translational perspectives. Therefore, the quantitative evaluation (Table 2) of traditional and advanced cardiovascular treatments is essential for understanding their fundamental differences, clinical efficacy, translational potential, and their associated limitation which would suggest the sustainable and equitable utilization of advancements to the patients[69,70].

Table 2. Detailed comparative overview of conventional and advanced cardiovascular therapeutic strategies

Parameter	Conventional therapies	Advanced/Recent therapeutic approaches
Primary therapeutic Goal	Symptom control and hemodynamic stabilization	Disease-specific molecular targeting and precision intervention
Major targets	Blood pressure, cholesterol, thrombosis, cardiac workload	Genes, inflammatory mediators, RNA pathways, regenerative signalling
Mechanism of action	Broad pharmacological modulation	Precision-targeted molecular and cellular modulation
Representative therapies	Statins, ACE inhibitors, beta-blockers, diuretics, CABG	PCSK9 inhibitors, siRNA therapeutics, CRISPR-Cas9, stem cells, nanomedicine
Therapeutic specificity	Moderate	High
Regenerative capacity	Minimal	Potential myocardial regeneration and tissue repair
Duration of treatment	Lifelong chronic therapy	Long-acting or potentially curative interventions
Personalization	Limited	Genomics- and biomarker-guided personalized therapy
Advantages	Widely available, clinically established, cost-effective	Improved specificity, reduced residual risk, molecular precision
Limitations	Drug intolerance, adverse effects, residual cardiovascular risk	High cost, delivery barriers, immunogenicity, ethical concerns
Surgical approaches	CABG, valve replacement, angioplasty	TAVR, robotic surgery, bioengineered grafts, hybrid interventions
Future potential	Symptomatic management	Disease modification and precision cardiovascular medicine

6. Conclusion

The emerging treatment for cardiovascular disorders is experiencing a significant shift from being generalized hemodynamic management to molecularly stratified and precision targeted therapy. The increasing evidence studied showed that the cardiovascular pathogenesis involves complex interactions between inflammatory signalling, reprogramming, improper mitochondrial functioning, oxidative stress, endothelial injury, lack of proper regulation of genetics and fibrosis. As a result of this, the traditional medicines which are clinically transformed are insufficient to fully eliminate the residual cardiovascular risk or reverse ongoing myocardial and vascular remodelling. The recent breakthroughs made in the field of molecular cardiology have resulted in the development of novel treatment, based on pathway-specific regulation and prevention of disease. Further, RNA interference therapeutics, inflammasome-targeted immunomodulation, PSK9 inhibition, CRISPR-based genome editing, regenerative stem cell platforms, nanotechnology enabling the drug delivery, have shown the growing convergence of molecular medicine, bioengineering, and translational cardiovascular science. Most importantly, the improved clinical trials have proved that these techniques, which demonstrated the modulation of inflammatory, metabolic and genetic pathways can significantly improve the cardiovascular outcomes above and beyond the traditional methods of treatment. However, future successful clinical translation, necessitate higher resolution techniques possessing potential to face critical challenges such as the delivery specificity, long-term genomic safety, immunological compatibility, biomaterial toxicity, procedural scalability and fair access. Furthermore, the integration of multimodal techniques combined with the genetics, regenerative engineering, AI, and precision diagnostics has enabled personalised diagnostics to predict illness, target intervention and repair myocardial dysfunction etc. sustainable utilization of such convergence-driven solutions could eventually transform cardiovascular medicine from chronic disease management to biologically precise and potentially curative therapy.

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