Cardiovascular Disease Prevention and Control
https://cdpc.cultechpub.com/cdpc
Cultech Publishing

Review

The Immunometabolic Architecture of Cardiovascular Disease: From Molecular Mechanisms to Precision Therapeutic Strategies

Uzma Manzoor[1], Omneya Abdelkarem[2,*], Azraida Hajar[3]

[1]Department of Clinical Biochemistry, COMSATS University Islamabad, Sahiwal Campus, Sahiwal, Pakistan

[2]Department of Chemical Pathology, Medical Research Institute, Alexandria University, Alexandria, Egypt

[3]Department of Biology, Laboratory of Pharmacology, Neurobiology, Anthropobiology and Environment, Faculty of Sciences Semlalia, Cadi Ayyad University, Marrakesh-Safi, Morocco

Correspondence author: Omneya Abdelkarem, omneyaahmed@alexu.edu.eg

Abstract

Cardiovascular diseases (CVDs) remain the leading cause of global mortality, yet traditional hemodynamic and lipid-centric models prove insufficient to capture the biological complexity driving residual cardiovascular risk. Converging evidence increasingly reframes CVD pathophysiology as a systemic immunometabolic disorder driven by the interplay of mitochondrial dysfunction, chronic immune activation, clonal hematopoiesis of indeterminate potential, and metabolic stress. This review critically synthesizes emerging paradigms in precision cardiovascular medicine, spanning molecular bioenergetics, epigenetic reprogramming, and immune-metabolic crosstalk within a unified immunometabolic-precision medicine framework, and evaluates translational advances including Sodium-glucose cotransporter-2 inhibitors, senolytics, and AI-driven risk stratification that directly target these mechanisms. Looking beyond current limitations, it appraises the transformative potential of multi-omics integration and regenerative engineering as the next frontier of cardiovascular precision medicine. By translating immunometabolic mechanisms into actionable clinical frameworks, this review argues for a paradigm shift: from reactive disease management toward precision-guided, biologically informed, and equitably accessible cardiovascular care.

Keywords

Immunometabolic cardiovascular disease, Meta-inflammation mitochondrial dysfunction, SGLT2 inhibitors, Senolytics, Clonal hematopoiesis of indeterminate potential, Clonal genomic profiling

Article History

Received: 22 January 2026
Revised: 13 April 2026
Accepted: 16 April 2026
Available Online: 21 April 2026

Copyright

© 2026 by the authors. This article is published by the Cultech Publishing Sdn. Bhd. under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0): https://creativecommons.org/licenses/by/4.0

1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, responsible for an estimated 19.2 million deaths in 2023 rising steadily from 13.1 million in 1990 and affecting 626 million people globally [1,2]. This escalating burden, which now accounts for one in three global deaths and 437 million disability-adjusted life years (DALYs) annually [3,1].

CVDs comprise a heterogeneous group of disorders that include coronary artery disease (CAD), heart failure (HF), cerebrovascular disease, arrhythmias, peripheral vascular disease, and congenital heart anomalies. Despite substantial therapeutic advances, the persistent burden of cardiovascular disease (CVD) reflects its biological complexity and multi-layered pathophysiology rather than a failure of individual interventions alone [4].

The biological architecture of CVD can be understood across three interrelated domains: (1) systemic cardiometabolic stressors [5], (2) cellular-organellar dysfunction [6], and (3) molecular signalling networks driving vascular and myocardial remodeling [7,8].

At the systemic level, genetic predisposition interacts with environmental exposures and lifestyle-related factors including sedentary behavior, tobacco use, and pro-atherogenic dietary patterns to establish a state of meta-inflammation: a chronic, low-grade systemic inflammatory and metabolic stress response that serves as a critical upstream driver of cardiovascular pathology [9]. Unlike classical acute inflammation, meta-inflammation is chronic and self-perpetuating, sustained by nutrient excess, adipose tissue dysfunction, and innate immune activation, creating a systemic milieu that primes the vasculature for injury and remodeling. Comorbid conditions such as diabetes mellitus, obesity, chronic kidney disease (CKD), and hypertension amplify this meta-inflammatory burden, accelerating endothelial dysfunction and vascular remodeling [10]. Atherogenesis, the principal driver of ischemic cardiovascular events, emerges from sustained interactions between lipid accumulation, oxidative stress, and immune activation within this chronic inflammatory milieu [11]. The downstream inflammatory and immune pathways underpinning meta-inflammation are detailed in Sections 2.3 and 3.3.

At the cellular and organelle level, mitochondrial dysfunction has emerged as a central integrative mechanism linking metabolic stress to myocardial injury. Mitochondrial biogenesis, fission–fusion dynamics, and redox homeostasis regulate cardiomyocyte energetics and survival [12]. Perturbations in these processes promote excessive reactive oxygen species (ROS) generation, impaired substrate utilization, and activation of apoptotic pathways, thereby contributing to HF progression and ischemic injury [13]. Contemporary work further supports mitochondria as signalling hubs coordinating immunometabolic responses in cardiomyocytes and vascular cells [14,15].

At the molecular signalling level, maladaptive G-protein coupled receptor (GPCR) activation and age- associated clonal hematopoiesis of indeterminate potential (CHIP) have been implicated in sustaining vascular inflammation and immune dysregulation. GPCR-mediated maladaptive signalling drives pathological cardiac hypertrophy and fibrosis through sustained neurohormonal activation, while CHIP-associated somatic mutations in genes such as TET2 and DNMT3A amplify inflammatory cytokine production independently of conventional cardiovascular risk factors [16,17]. The molecular mechanisms underpinning both pathways are detailed in Section 2.3.

In recent years, cardiovascular medicine has progressively transitioned from generalized pharmacotherapy toward more individualized approaches informed by genomics, multi-omics integration, and digital health technologies. AI-assisted risk prediction models and biomarker-guided therapeutic strategies have shown potential to refine phenotyping and optimize treatment selection. However, the clinical integration of precision cardiovascular medicine remains heterogeneous, with variable external validation, limited cost-effectiveness data, and ongoing concerns regarding algorithmic bias and underrepresentation of diverse populations in training datasets [18,19]. Collectively, although molecular personalization represents an evolving frontier, its clinical utility in preventive cardiology remains under active investigation rather than established standard of care [20,21]. Systems- level tools that operationalize these precision concepts are described in Sections 4.4 and 5.

Parallel to these mechanistic insights, emerging therapeutic strategies have begun to target the pathological processes operating across all three domains. Emerging therapies including Sodium-glucose cotransporter-2 (SGLT2) inhibitors, PCSK9 inhibitors, and anti-inflammatory biologics have demonstrated substantial cardiometabolic and renal benefits in large randomized trials, signalling a shift toward integrated cardiometabolic therapeutics (see Section 4.1.1), yet treatment response variability and implementation challenges persist [22,23]. Beyond pharmacological advances, structured exercise rehabilitation and lifestyle interventions remain foundational components of cardiovascular prevention, with robust evidence supporting improvements in endothelial function, myocardial perfusion, and inflammatory modulation [24].

Interest in nutrigenomics and gene–diet interactions has expanded, particularly regarding folate metabolism and MTHFR polymorphisms. While certain variants influence homocysteine levels, large-scale randomized trials and contemporary cardiovascular guidelines have not consistently supported routine genetic screening or homocysteine-lowering strategies for primary cardiovascular prevention.

Taken together, these advances position CVD as a systemic and immunometabolic disorder amenable to molecular dissection, precision intervention, and systems-level integration. Yet despite this momentum, the field lacks a comprehensive synthesis integrating the molecular, immunometabolic, and systems-level dimensions of cardiovascular pathology within a unified translational framework. This review addresses that gap by critically synthesizing recent developments (2020-2026), emphasizing both emerging opportunities and the evidentiary limitations that shape their translational trajectory.

2. Molecular and Cellular Pathophysiology of CVDs

The following subsections examine the molecular and cellular mechanisms of CVD in sequence, culminating in an integrative systems perspective that frames their convergence as the pathophysiological foundation of contemporary CVD [25,26].

2.1 Endothelial Dysfunction and Oxidative Stress

The endothelium serves as a dynamic regulator of vascular tone, permeability, and thrombosis. In health, endothelial cells release nitric oxide (NO), prostacyclin, and other vasodilators that maintain vascular homeostasis. However, oxidative stress—arising from excessive production of ROS—impairs endothelial NO bioavailability, resulting in vasoconstriction, leukocyte adhesion, and platelet activation [27,28]. A recent meta-analysis in NO using stable isotope tracers reported significantly reduced in vivo NO production in patients with metabolic and CVDs compared with healthy individuals, highlighting NO deficiency as a shared mechanistic hallmark of cardiometabolic pathology. These reductions align with the well-characterized mechanisms by which NO deficiency, endothelial nitric oxide synthase (eNOS) uncoupling, and mitochondrial oxidative stress in promoting arterial stiffness, microvascular inflammation, and hypertension [29].

2.2 Mitochondrial Dysfunction and Energetic Derangement

Mitochondria are central to cardiac energy metabolism, generating nearly 90% of myocardial ATP via oxidative phosphorylation. Dysfunction in mitochondrial respiration, dynamics, or quality control leads to energetic insufficiency, ROS overproduction, and apoptotic signalling, which collectively drive myocardial injury and HF [30]. The concept of semi-autonomous mitochondrial inheritance, highlights how disturbances in mtDNA dynamics and mito-nuclear communication drive mitochondrial dysfunction, cardiac remodeling, and CVD progression [31]. Converging evidence confirms that mitochondrial dysfunction is not merely a byproduct but a causative axis in cardiac pathology, influencing calcium handling, oxidative phosphorylation efficiency, and cell death pathways [26]. Given this central role, mitochondria have become attractive therapeutic targets; however, translating mitochondria-directed interventions into durable clinical benefit has proven challenging, and the opportunities and limitations of these strategies are discussed in Section 4.3.

2.3 Inflammation, Immune Crosstalk, and Clonal Hematopoiesis

The energetic and oxidative dysregulation detailed in Section 2.2 does not occur in immunological isolation. Mitochondrial ROS accumulation and cytosolic mtDNA release directly activate innate immune sensors (including the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway and NLRP3 inflammasome), establishing a mitochondrial—innate immune coupling that translates energetic stress into sustained vascular inflammation. This coupling creates the mechanistic foundation upon which chronic, low-grade inflammation not only initiates cardiovascular injury but actively sustains disease progression through a self-reinforcing cycle of immune activation and vascular remodeling, driven centrally by IL-6, TNF-α, and IL-1β. As introduced in Section 1, CHIP-associated somatic mutations (particularly in TET2 and DNMT3A) extend this inflammatory burden well beyond conventional risk factors, with recent evidence delineating the specific molecular cascades through which these mutations amplify vascular injury and establish CHIP as a mechanistic bridge between aging, immune dysregulation, and CVD [32,33].

Through NLRP3 inflammasome activation and IL-1β/IL-6 amplification, CHIP-mutant clones establish a self-sustaining pro-inflammatory milieu that accelerates atherosclerosis and elevates cardiovascular mortality independently of traditional risk factors [34,35]. TET2-deficient macrophages exhibit exaggerated NLRP3-driven IL-1β secretion, while DNMT3A mutations promote expansion of pro-atherogenic monocyte subsets that infiltrate and sustain vascular lesions. Emerging data further implicate CHIP in HFpEF, where these mutations associate with diastolic dysfunction, adverse remodeling, and increased hospitalization risk [32].

Parallel to CHIP-driven immune dysregulation, cellular senescence and inflammaging represent interconnected amplifiers of cardiovascular inflammation mechanisms developed in detail in Section 3.3. Crucially, CHIP and cellular senescence are not independent processes: senescent immune cells preferentially harbor CHIP mutations, creating a convergent inflammatory axis that compounds vascular injury beyond what either mechanism produces alone. Therapeutic strategies targeting this convergence are discussed in Sections 3.3 and 4.2.1.

Emerging clinical evidence is beginning to translate these mechanistic insights into therapeutic strategies, including

CHIP-targeted NLRP3 inhibition and bispecific cytokine blockade [36,37], discussed in detail in Section 4.2.1. While these trials are still maturing, their design reflects a fundamental shift in cardiovascular pharmacology from broad anti-inflammatory strategies toward mutation-specific immune targeting informed by clonal genomic profiling.

Building on this mechanistic framework of immune-driven vascular injury, the following section examines how lipid metabolism and atherogenesis amplify these inflammatory processes to drive ischemic CVD progression.

2.4 Lipid Dysregulation, Foam Cell Formation, and Structural Atherogenesis

Atherosclerosis the hallmark of CAD arises from lipid deposition, macrophage infiltration, and smooth muscle cell migration within arterial walls. Oxidized low-density lipoproteins (oxLDL) are engulfed by macrophages, forming foam cells that evolve into fibrotic plaques prone to rupture. GPCR signalling further modulates lipid uptake and endothelial permeability within the vascular wall; dysregulated GPCR pathways amplify monocyte chemotaxis and cytokine release [38,39], mechanisms explored therapeutically in Section 4.2.2. The immunometabolic dimensions of this lipid-driven injury including macrophage metabolic reprogramming and VSMC phenotypic plasticity within atherosclerotic lesions are examined in Section 3.4.

2.5 Cardiometabolic Integration: The Heart-Kidney Axis

The cardio-renal-metabolic axis represents a tightly interconnected system wherein dysfunction in one organ exacerbates pathology in the others [40]. A large multi-cohort study analyzing data from over 300,000 participants demonstrated that glycemic status significantly modifies the association between the cardiometabolic index (CMI) and cardio-renal outcomes, with the highest risk conferred in normoglycemic individuals underscoring the importance of early metabolic risk stratification beyond conventional glycemic thresholds [41,42].

Therapeutic strategies targeting this axis, particularly SGLT2 inhibitors, have demonstrated substantial cardiorenal benefit [43]. The detailed mechanisms and trial evidence are examined in Section 4.1.1. Beyond hemodynamic and metabolic coupling, individual susceptibility to cardiometabolic dysfunction is further shaped by genetic architecture and epigenetic programming adding a layer of biological complexity that informs precision risk stratification.

2.6 Genetic and Epigenetic Determinants of Cardiovascular Susceptibility

The interplay between genetics and environment in CVD risk has become increasingly evident. Mutations in *MTHFR*, *APOE*, *PCSK9*, and *LPA* genes modulate lipid metabolism and vascular integrity. In parallel, epigenetic modifications including DNA methylation and histone modifications (acetylation, methylation) respond dynamically to environmental stimuli such as diet, physical activity, and psychosocial stress [44,45].

Studies have consistently shown that carriers of the *MTHFR* C677T TT homozygous genotype exhibit elevated plasma homocysteine levels and increased cardiovascular risk, particularly in the context of low dietary folate intake highlighting the clinical importance of genotype-guided nutritional interventions [46,47].

Collectively, these epigenetic modifications represent actionable therapeutic targets including histone deacetylase (HDAC) inhibitors and miRNA modulators [48]. Further details on the context of molecular therapeutics are discussed in Section 4.3.

2.7 Pathophysiological Networks: A Systems-Level Synthesis

Collectively, these insights support a systems-biology view of CVD, where oxidative stress, mitochondrial dysfunction, inflammation, and metabolism form a self-reinforcing pathogenic network [49,50]. Disruption of one node propagates dysfunction throughout the system, leading to progressive structural remodeling, fibrosis, and loss of contractile capacity [51] (Figure 1).

Figure 1 illustrates the interconnected molecular mechanisms contributing to the onset and progression of CVDs. Central to the figure is the heart and vascular system, representing the primary targets of these processes. (1) Oxidative stress and endothelial dysfunction: excessive ROS generation reduces NO bioavailability, leading to vasoconstriction, leukocyte adhesion, and endothelial inflammatory activation. (2) Mitochondrial dysfunction: impaired oxidative phosphorylation and mitochondrial DNA (mtDNA) damage decrease ATP production while increasing ROS, promoting cardiomyocyte apoptosis and metabolic failure. (3) Pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β) drive chronic vascular inflammation and myocardial remodeling; CHIP amplifies this inflammatory burden by generating proinflammatory immune cell clones with enhanced inflammasome activation, further accelerating CVD progression. (4) Lipid metabolism and atherogenesis: oxidized low-density lipoprotein (oxLDL) accumulation initiates macrophage infiltration and foam cell formation, culminating in atherosclerotic plaque development. (5) Genetic and epigenetic factors: mutations in key genes (e.g., MTHFR, APOE, PCSK9, LPA) and epigenetic alterations, such as DNA methylation and histone modifications, modulate vascular integrity and inflammatory responses. Collectively, these pathways form an integrated network of molecular disturbances that precipitate structural remodeling, fibrosis, and functional decline characteristic of CVD progression.

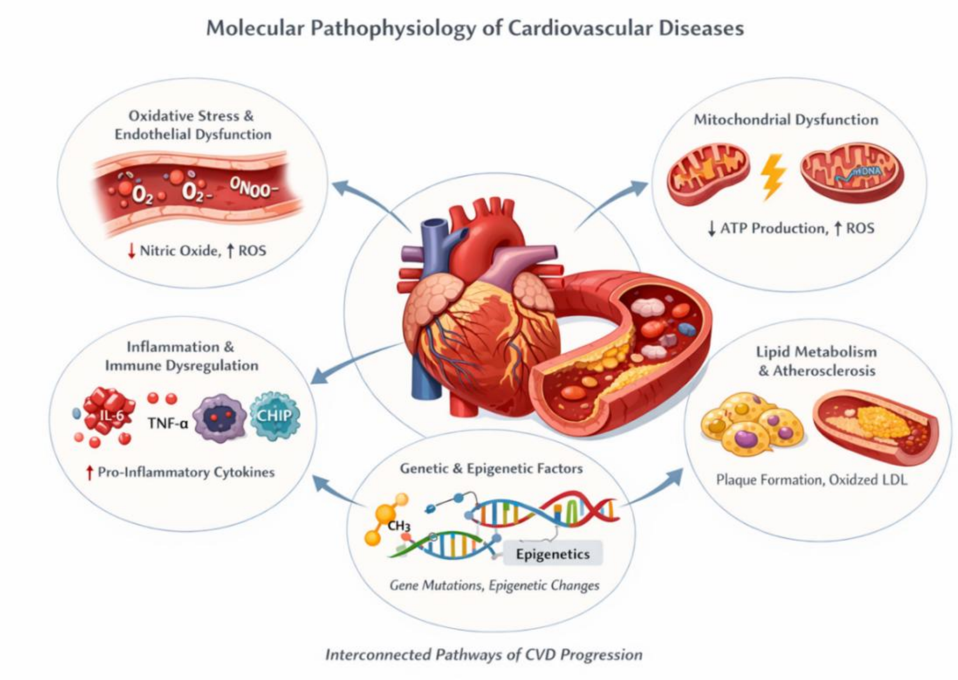

Figure 1. Molecular and cellular pathophysiology of CVDs.

Therefore, effective interventions must not only target single pathways but adopt multi-targeted, holistic strategies—encompassing pharmacological, lifestyle, and molecular approaches. The integration of omics data and computational modeling is increasingly revealing the systems-level architecture of this pathogenic complexity laying the biological foundation for the personalized therapeutic strategies developed in Sections 4 and 5 [52,53].Understanding how immune cell energetics and metabolic stress actively coordinate rather than merely respond to this pathogenic network forms the focus of Section 3, where the cardio-immune crosstalk underlying cardiovascular injury and repair is examined in depth.

3. Immunometabolism and Cardio-Immune Crosstalk

The concept of immunometabolism—the intersection of immune cell function and metabolic regulation—has significantly refined contemporary models of CVD. CVDs are no longer viewed solely as disorders of hemodynamics or lipid imbalance but as chronic inflammatory and metabolic syndromes driven by immune dysregulation, mitochondrial dysfunction, and maladaptive cellular energetics [54,55]. Experimental and clinical studies have demonstrated that immune cell subsets—including macrophages, T cells, and monocytes—undergo metabolic reprogramming that influences cytokine production, plaque stability, and myocardial remodeling [56,57].

A key advance has been the application of single-cell RNA sequencing and spatial transcriptomics to human atherosclerotic plaques and failing myocardium. These technologies have revealed diverse macrophage and T-cell subpopulations with distinct metabolic programs, challenging the oversimplified M1/M2 dichotomy and demonstrating context-dependent immune specialization. Rather than introducing entirely new inflammatory pathways, these approaches have deepened understanding of cellular plasticity and metabolic rewiring within established inflammatory frameworks [58,59]. Another emerging refinement involves metabolic checkpoint signalling in immune cells, including succinate-driven hypoxia-inducible factor-1 alpha (HIF-1α) activation, itaconate-mediated anti-inflammatory feedback, and trained immunity linked to epigenetic remodeling [60,61].

Another emerging refinement involves metabolic checkpoint signalling in immune cells, including succinate-driven HIF-1α activation, itaconate-mediated anti-inflammatory feedback, and trained immunity mediated by epigenetic rewiring of immune cells encompassing promoter demethylation and H3K4me3 histone marks that establish persistent pro- or anti-inflammatory transcriptional programs [62,63].

In contrast, other aspects of immunometabolism remain investigational. While mitochondrial dysfunction in immune cells and metabolic shifts toward glycolysis in activated macrophages are strongly supported by preclinical models, their direct modification as therapeutic strategies in human CVD remains under evaluation [55,64]. Similarly, the bidirectional metabolic signalling between cardiac tissue and circulating immune populations—although conceptually compelling—has yet to demonstrate consistent outcome-driven validation in large clinical trials [57,65].

Thus, while the cardio-immune paradigm provides a powerful framework for understanding CVD progression, the subsections that follow map its mechanistic foundations, immune-aging intersections, and emerging therapeutic implications charting the translational frontier from compelling biology to clinical application.

3.1 The Immune Landscape of the Cardiovascular System

The cardiovascular system is increasingly recognized as an immunologically dynamic environment populated by resident and recruited immune cells that coordinate tissue maintenance and injury responses. Cardiac macrophages comprising ontogenically distinct resident populations (embryo-derived, self-renewing TIMD4+ LYVE1+ cells) and recruited monocyte-derived subsets (CCR2+ bone marrow-derived cells) together with dendritic cells and T lymphocytes, contribute to homeostasis through efferocytosis of apoptotic cells, regulation of extracellular matrix turnover, and maintenance of electrophysiological integrity [66,67].

Earlier conceptual models categorized macrophages into pro-inflammatory (M1) and reparative (M2) subsets. This binary framework incompletely captures the spectrum of macrophage phenotypes identified by recent single-cell transcriptomic and spatial profiling studies. These analyses reveal heterogeneous macrophage populations with context-dependent metabolic and transcriptional programs that vary across disease stage, tissue niche, and systemic metabolic status. Rather than discrete M1/M2 states, macrophages exhibit dynamic plasticity along a multidimensional continuum [68,69].

Metabolic programming remains central to macrophage function. Glycolytic flux, mitochondrial respiration, and intermediary metabolites influence inflammatory signalling and reparative responses; however, metabolic phenotypes are not strictly segregated into binary states and may shift in response to microenvironmental cues. Accordingly, therapeutic strategies aimed at modulating immune metabolism must account for cellular heterogeneity and context-specific effects [55].

While preclinical studies suggest that dietary interventions and metabolic modulators can influence immune cell function, robust human cardiovascular outcome data supporting targeted “immunonutrition” remain limited. Thus, although immune–metabolic coupling represents a compelling mechanistic framework, its translation into clinically validated cardiovascular therapies requires further prospective investigation [70,71].

3.2 CHIP: From Inflammaging Mechanisms to Precision Cardiovascular Intervention

CHIP represents an age-associated expansion of mutated hematopoietic stem cells that links immune ageing with heightened inflammatory tone [72,73]. As established in Section 2.3, CHIP-related mutations amplify inflammatory signalling and accelerate cardiovascular risk functioning as a mechanistic bridge between immune aging and vascular injury. Within the cardio-immune context, CHIP can therefore be viewed as one component of a broader inflammaging landscape that shapes immune cell phenotypes and basal inflammatory set-points in older individuals, modulating their susceptibility to adverse remodelling and therapeutic response [74].

While population-level routine screening protocols are still being defined, emerging evidence including post-hoc analyses of the CANTOS trial demonstrating greater cardiovascular benefit from IL-1β inhibition in TET2-CHIP carriers supports CHIP as an actionable therapeutic target in high-risk individuals [75]. Mutation type, clone size, and cardiovascular risk profile are increasingly used to guide the intensity of cardioprotective and anti-inflammatory interventions, positioning CHIP at the frontier of precision cardiovascular medicine [76].

3.3 Inflammaging, Cellular Senescence, and the Senescence-Associated Secretory Phenotype (SASP)-Driven Cardiovascular Continuum

Aging-related immune dysregulation—termed inflammaging—is characterized by chronic, low-grade inflammation driven by senescent cells and dysfunctional mitochondria [77]. These senescence-driven circuits intersect with the CHIP-inflammatory axis established in Section 2.3, forming a compounding biological aging continuum.

Senescent endothelial and cardiac cells adopt a SASP, releasing pro-inflammatory cytokines, growth factors, and matrix metalloproteinases. While chronic SASP perpetuates endothelial dysfunction, vascular stiffness, and myocardial fibrosis, emerging evidence indicates that transient senescence and SASP components in the peri-infarct zone may exert context-dependent cardioprotective and anti-fibrotic effects, highlighting the complexity of targeting senescence therapeutically [78]. Senescence induction in cardiovascular cells is primarily mediated through the p53/p21 and p16INK4a/Rb tumour suppressor pathways, which enforce irreversible cell cycle arrest in response to oxidative stress, telomere shortening, and DNA damage accumulation [79].

Senolytic therapies that selectively eliminate senescent cells represent an emerging therapeutic strategy for attenuating SASP-driven cardiovascular inflammation their mechanisms, clinical evidence, and limitations are examined in Section 4.2.1.

3.4 Immunometabolic Reprogramming and Plaque Immune Dynamics

Atherosclerosis represents a quintessential immunometabolic disorder wherein lipid metabolism and inflammation are tightly intertwined. Macrophages, T cells, and smooth muscle cells within atherosclerotic plaques undergo metabolic reprogramming in response to local lipid accumulation and oxidative stress [41]. Notably, vascular smooth muscle cells (VSMCs) exhibit remarkable metabolic plasticity, undergoing reprogramming into osteogenic, foam cell-like, and macrophage-like phenotypes that actively drive plaque calcification and instability a paradigm shift in understanding VSMC contributions to atherogenesis [80].

Emerging evidence demonstrates that G protein-coupled receptor (GPCR) signalling plays a pivotal role in modulating immune cell recruitment and activation within atherosclerotic lesions, acting as a critical bridge between lipid sensing and vascular inflammation. GPCRs act as metabolic sensors that integrate signals from free fatty acids, sphingolipids, and oxidative metabolites, thus coordinating immune cell fate decisions [81].

Dysregulation of these receptors leads to exaggerated immune activation and plaque-destabilizing inflammation [82,83], with therapeutic implications addressed in Section 4.2.2. Reduced NO bioavailability as established in Section 2.1 further amplifies immune cell adhesion and nuclear factor kappa B (NF-κB)-driven inflammation within the atherosclerotic microenvironment, reinforcing the immunometabolic cycle of plaque progression [84].This self-perpetuating cardio-immune cycle of atherosclerosis forms the mechanistic foundation for the therapeutic strategies [85], as addressed in Sections 3.6 and 4.1.2.

3.5 Cardiac Remodeling and Immunometabolic Crosstalk

Following myocardial infarction (MI) or chronic pressure overload, the heart undergoes remodeling, involving cardiomyocyte hypertrophy, extracellular matrix deposition, and inflammatory infiltration. This remodeling process is both metabolically and immunologically driven. Activated macrophages and fibroblasts depend on glycolytic flux to sustain cytokine production and collagen synthesis, while cardiomyocytes shift from fatty acid oxidation toward glycolysis in response to hypoxia and pressure overload an initially adaptive but ultimately maladaptive metabolic transition that leads to energetic inefficiency and progressive contractile dysfunction [86,87].

mtDNA released into the cytoplasm under conditions of mitochondrial stress activates innate immune sensors via the cGAS-STING pathway, triggering IRF3/NF-κB-mediated transcription of pro-inflammatory cytokines and amplifying sterile inflammation [88,89].

This feedback loop between mitochondrial stress and immune signalling promotes fibrosis and left ventricular remodeling. Consequently, targeting mitochondrial-immune interactions has emerged as a promising therapeutic frontier [90,91]. The therapeutic strategies targeting this mitochondrial–immune axis are examined in Section 4.3.

3.6 Immunometabolic Therapeutic Targeting of the Cardio-Immune Axis

Therapeutic innovations increasingly aim to modulate immune metabolism and inflammatory tone, rather than merely suppressing downstream cytokine signalling. Several classes of drugs have demonstrated immunometabolic benefits [92]:

(1) SGLT2 inhibitors, originally developed as glucose- lowering agents, also reduce myocardial oxidative stress, macrophage infiltration, and inflammasome activation in experimental and clinical settings, providing an immunometabolic rationale that complements their established cardio- renal outcome benefits [93]; their emerging senotherapeutic properties, including attenuation of SASP-driven signalling and senescence biomarkers, further examined in Section 4.2.1.

(2) IL-1β antagonists, most notably canakinumab, target the NLRP3-driven inflammatory cascade central to plaque destabilization and myocardial injury [94,95], with clinical outcome evidence from the landmark CANTOS trial examined in Section 4.

(3) AMP-activated protein kinase (AMPK) activators such as metformin enhance mitochondrial quality control and autophagy via the AMPK/mechanistic target of rapamycin (mTOR) axis, restrain NLRP3 inflammasome activity, and suppress TLR4/NF-κB-driven pro-inflammatory signalling, thereby dampening pathological immune activation in the cardiovascular setting [96].

(4) Omega-3 fatty acids reduce vascular inflammation and improve endothelial function via specialized pro-resolving mediators and direct membrane effects, with cardiovascular outcome evidence from high-dose EPA trials; short-chain fatty acids (SCFAs), generated by gut microbiota fermentation, modulate endothelial function and immune tone via GPR41/GPR43 activation, though robust clinical cardiovascular outcome data for SCFAs remain limited [97,98].

Furthermore, lifestyle interventions particularly regular aerobic exercise and caloric restriction reprogram immune cell metabolism toward more oxidative, anti-inflammatory phenotypes via AMPK/PGC-1α activation and inflammasome suppression, suggesting that behavioral therapies can synergize with pharmacological immunomodulation in cardiovascular care [99]. The broader clinical evidence base for exercise-based cardiovascular therapeutics examined in Section 4.1.4.

Notably, while SGLT2 inhibitors, IL- 1β blockade, and omega- 3 fatty acids are supported by large cardiovascular outcome trials, NLRP3 inhibitors, SCFAs, and some AMPK- targeted strategies remain largely in the mechanistic and early translational stages.

3.7 Cardio-Immunometabolism: From Network Dysregulation to Precision Intervention

The cumulative evidence from the last decade underscores that metabolic dysfunction and immune activation are inseparable hallmarks of CVD [100]. The emerging field of cardio-immunometabolism redefines disease classification from an organ-based to a network-based framework, where immune cells, metabolic pathways, and cardiac tissue form a tightly coupled ecosystem [101]. Future directions in mapping these cardio-immune interactions at single-cell and multi-omics resolution are examined [102] (see Section 5.4).

Precision therapeutics targeting immunometabolic regulators including AMPK activators, mTOR inhibitors, and HIF-1α modulators represent a promising frontier for tailored interventions in HF, atherosclerosis, and cardiomyopathies [64].

Separately, co-inhibitory immune checkpoint pathways such as programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) are now recognized as endogenous regulators of vascular inflammation and plaque stability, functionally distinct from but mechanistically connected to immunometabolic reprogramming. The cardiovascular importance of these pathways is underscored by the accelerated atherosclerosis and immune-mediated myocarditis observed when checkpoint inhibitor therapies block PD-1/CTLA-4 in cancer patients, confirming that intact checkpoint signalling is essential for vascular homeostasis [103].

4. Novel Therapeutic Insights in CVD Management

Over the past decade, advances in cardiovascular therapeutics have increasingly aligned with a deeper mechanistic understanding of disease biology [104]. Rather than representing isolated pharmacologic innovations, contemporary interventions can be conceptualized along distinct yet interconnected biological axes: metabolic regulation, inflammatory and senescence modulation, mitochondrial and organelle reprogramming, epigenetic rewiring, immune aging modulation, systems-level precision integration, and regenerative reconstruction. This framework reflects the layered pathophysiology of CVD, spanning systemic cardiometabolic stress, immune dysregulation, immune aging and clonal hematopoiesis, mitochondrial dysfunction, epigenetic reprogramming, and tissue remodeling and provides a structured lens through which emerging therapies can be critically evaluated [105]. The following sections are therefore organized according to this hierarchical model, emphasizing both the mechanistic rationale and the translational maturity defined here as the progression from preclinical proof-of-concept through phase II/III clinical trial validation of each therapeutic domain.

4.1 Metabolic Modulation

CVD progression is closely linked to systemic metabolic imbalance, including dysregulated glucose utilization, lipid excess, and reduced capacity of the myocardium and vascular tissues to adapt to changing energy demands. Interventions targeting metabolic pathways therefore constitute a foundational therapeutic axis. The following approaches illustrate how pharmacologic, nutritional, and lifestyle strategies can modify metabolic drivers of cardiovascular risk and influence disease trajectory.

4.1.1 SGLT2 Inhibitors and Metabolic Modulation

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as cornerstone agents in cardio-renal-metabolic medicine, reducing HF hospitalizations and slowing CKD progression across diverse risk profiles. Originally introduced for type 2 diabetes, agents such as empagliflozin and dapagliflozin have redefined cardiovascular pharmacology by demonstrating robust benefits that extend beyond glycemic control [106,107].

These drugs exert pleiotropic cardioprotective effects, including reduced oxidative stress, modulation of inflammatory signalling, and improved myocardial energetics. A recent systematic review and multidomain synthesis confirmed that SGLT2 inhibitors consistently reduce HF-related hospitalizations and cardiovascular mortality, deliver early improvements in patient-centered outcomes, and enhance endothelial function, establishing their role as disease-modifying therapies regardless of ejection fraction or diabetes status [106].

Mechanistically, SGLT2 inhibition promotes a more efficient cardiac energetic profile through enhanced ketone body utilization as an oxygen-efficient alternative fuel for cardiomyocytes [108], restoration of mitochondrial function via reduced oxidative stress and improved calcium handling, and suppression of cardiac fibrosis through anti-inflammatory and anti-TGF-β-mediated pathways collectively exemplifying metabolic remodeling as a validated therapeutic target in HF management [109].

4.1.2 PCSK9 Inhibitors and Lipid Regulation

In parallel, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, notably *alirocumab* and *evolocumab*, have demonstrated potent low-density lipoprotein cholesterol (LDL-C) lowering effects by promoting LDL receptor recycling. Recent evidence suggests that PCSK9 inhibition not only decreases lipid burden but also exerts anti-inflammatory and plaque-stabilizing effects, thereby reducing recurrent cardiovascular events [110,111]. The combined

PCSK9 and statin therapy significantly reduced adverse cardiovascular outcomes in high-risk populations, validating dual-lipid-targeting approaches as a clinical standard for atherosclerotic disease management [112,113].

Nonetheless, a subset of patients demonstrates suboptimal LDL-C reduction or limited clinical event reduction despite profound lipid lowering. Factors contributing to reduced responsiveness include genetic variants affecting LDL receptor function (e.g., familial hypercholesterolemia with LDLR-null mutations). Additionally, lipoprotein(a) is only partially reduced by PCSK9 inhibition (~25%-30%), with residual Lp(a)-mediated cardiovascular risk persisting despite therapy.

Additionally, advanced calcified plaque phenotypes and long-standing atherosclerotic disease may derive less relative benefit despite profound LDL lowering. These findings highlight the need for genotype-informed therapy selection and integration of lipid-inflammatory profiling as foundational pillars of precision-guided cardiovascular risk reduction [111], which complementing the metabolic reprogramming strategies outlined in Section 4.1.1.

4.1.3 Nutrigenomics, Precision Nutrition, and Genotype-Guided Dietary Therapeutics

Translating the genetic and epigenetic mechanisms established in Section 2.6 into clinical practice, nutrigenomics enables molecularly targeted dietary strategies that move beyond population-level guidelines toward genotype-informed cardiovascular prevention [114]. The integration of AI-driven nutrigenomic profiling allows individualized dietary interventions tailored to genetic predispositions. AI-based nutritional models can now predict these responses, enabling personalized dietary plans rich in folate, omega-3 fatty acids, and polyphenols to mitigate vascular damage [115]. Broader AI clinical applications addressed in Section 4.4.

Functional foods containing bioactive peptides, plant sterols, and flavonoids are increasingly recognized for their ability to modulate lipid metabolism, endothelial health, and systemic inflammation [116]. The integration of nutrigenomics into cardiovascular care reframes dietary intervention as a molecularly targeted strategy complementing pharmacological approaches [117], outlined in Sections 4.1.1 and 4.1.2 and establishes genotype-informed nutrition as an essential pillar of precision cardiovascular prevention. Collectively, these approaches position precision immunonutrition as a complementary pillar of cardiovascular prevention alongside pharmacological strategies in Sections 4.1.1 and 4.1.2.

4.1.4 Exercise-Based and Lifestyle Therapeutics

Beyond pharmacology, lifestyle modification and structured exercise remain cornerstone therapies for cardiovascular prevention and rehabilitation. A meta-analysis demonstrated that combined aerobic and resistance training significantly reduces all-cause mortality and major adverse cardiovascular events in CAD patients, with evidence also supporting reductions in HF-related hospitalizations [118].

At the cellular level, exercise enhances eNOS activity, increases mitochondrial density, and reduces systemic inflammation via AMPK activation. Regular physical activity also modulates gut microbiome composition, promoting beneficial metabolites such as SCFAs that exert cardioprotective effects through immune-metabolic signalling [119].

Nevertheless, translational complexity persists. Dose–response relationships vary across age groups, comorbidity burden, sex, and baseline cardiorespiratory fitness. High-intensity interval training and moderate continuous training yield differential physiological adaptations, and adherence rates remain a significant determinant of real-world effectiveness. Furthermore, some trials report heterogeneous improvements in ventricular remodeling and inflammatory biomarkers, underscoring that exercise prescriptions require personalization rather than uniform recommendations [120,121].

Complementarily, interventions such as mindfulness-based stress reduction (MBSR) and sleep optimization demonstrate beneficial autonomic and inflammatory effects; however, outcome-driven cardiovascular endpoints remain limited, and long-term adherence remains variable [122].

4.2 Inflammatory & Senescence Targeting

Beyond metabolic dysregulation, persistent immune activation and age-associated cellular senescence contribute to vascular dysfunction and adverse cardiac remodeling. Therapeutic strategies within this domain aim to attenuate maladaptive inflammatory signalling and modify the cellular milieu that sustains chronic tissue injury. The following interventions target immune amplification pathways and senescence-related processes implicated in cardiovascular progression.

4.2.1 Senolytics, Senotherapeutics, and Inflammaging-Targeted Interventions

Senolytic agents, including dasatinib, quercetin, and fisetin, have emerged as novel interventions targeting cellular senescence and inflammaging, which are critical contributors to vascular stiffness and myocardial dysfunction [123,124]. In preclinical models and early clinical studies, dasatinib–quercetin combinations have demonstrated clearance of senescent cells with associated improvements in vascular elasticity, endothelial function, and attenuation of SASP- driven inflammation [125,126].

Anti-inflammatory biologics most notably canakinumab have validated IL-1β inhibition as a therapeutic target in post-MI patients, as established in Section 3.6; their mechanistic intersection with senolytic strategies represents an emerging combinatorial frontier in cardiovascular aging [127,128].

Emerging experimental evidence suggests that SGLT2 inhibitors may function as pragmatic senotherapeutics in CVD. Beyond their established cardiorenal benefits, SGLT2 inhibition attenuates senescence-associated markers (e.g., SA-β-gal, p16, p21) and suppresses SASP-driven inflammatory signalling in endothelial cells, cardiomyocytes, and vascular tissue. These effects are accompanied by improved NO bioavailability, reduced arterial stiffness, and attenuation of myocardial fibrosis [129]. Mechanistically, SGLT2 inhibitors activate AMPK/SIRT1 signalling, inhibit mTOR and NF-κB pathways, reduce oxidative stress, restore mitochondrial homeostasis, and enhance autophagic flux pathways central to the initiation and propagation of cellular senescence, mechanistically converging with the AMPK-mediated immunometabolic reprogramming described for metformin in Section 3.6. Notably, preclinical studies suggest that canagliflozin may reduce senescent cell burden via AMPK-dependent immune modulation, raising the possibility of context-dependent senolytic activity [129].

In parallel, dedicated senolytics—such as dasatinib–quercetin combinations and BCL-2 family inhibitors—have demonstrated proof-of-concept clearance of senescent cells and improvements in vascular and metabolic phenotypes in early-phase studies, although definitive cardiovascular outcome data remain lacking [130]. Conceptually, combining SGLT2 inhibitors with targeted senolytics may offer synergistic benefits by concurrently targeting inflammaging and metabolic stress, which represent a next-generation precision strategy for cardiometabolic aging, building on the metabolic remodeling effects detailed in Section 4.1.1; however, this strategy remains hypothetical and will require dedicated trials to establish safety and efficacy.

4.2.2 GPCR Modulators and Novel Drug Targets

GPCRs have emerged as master regulators of vascular tone and inflammation, with growing evidence supporting their modulation as a therapeutic strategy in CVD [17]. Novel GPCR modulators targeting angiotensin II type 2 receptors (AT2R) and adenosine A2A receptors show particular promise AT2R activation mediating NO-dependent vasodilation and NF-κB inhibition, and A2A receptor agonism suppressing neutrophil-endothelial adhesion and platelet activation via cAMP-PKA anti-inflammatory signalling collectively attenuating endothelial inflammation and ischemia-reperfusion injury [131,132]. Collectively, these findings position selective GPCR modulation particularly targeting AT2R and adenosine A2A receptors as a promising pharmacological avenue for precision vascular protection, complementing established renin-angiotensin-system therapies [131,132].

4.3 Mitochondrial & Epigenetic Reprogramming

This therapeutic domain targets intracellular regulatory mechanisms that govern cellular resilience and remodeling. By focusing on mitochondrial function and epigenetic control of gene expression, these strategies aim to modify pathological signalling at the organelle and transcriptional level rather than solely addressing upstream metabolic or inflammatory drivers complementing the pharmacological and anti-inflammatory strategies outlined in the preceding sections.

Mitochondrial biology has re-emerged as a focal point in cardiovascular drug discovery, driven by the recognition that dysfunctional mitochondria through excess ROS generation, impaired ATP synthesis, and dysregulated apoptotic signalling represent tractable therapeutic targets in both HF and ischemic heart disease. Emerging therapies include mitochondria-targeted antioxidants (e.g., MitoQ, SkQ1), PGC-1α activators, and cardiolipin stabilizers, which aim to restore myocardial bioenergetics and limit mitochondrial injury. MitoQ has demonstrated improvements in endothelial function and arterial stiffness in early-phase human trials, while SkQ1 shows cardioprotection in preclinical aging models; however, most agents remain in preclinical or early translational stages, and prior antioxidant strategies have yielded inconsistent clinical results [133] reflecting the persistent challenge of translating mitochondrial modulation into durable clinical benefit.

Translational failure in this domain stems from four interconnected barriers. First, mitochondrial dysfunction in HF and IHD is multifactorial encompassing excess ROS, impaired OXPHOS, disrupted Ca^{2+} handling, and defects in mitochondrial dynamics and mitophagy such that single-pathway interventions, particularly those targeting ROS scavenging exclusively, are mechanistically incomplete and may suppress adaptive redox signalling. This is exemplified by MitoTEMPO, which increased 28-day mortality in a murine sepsis model despite its antioxidant rationale [134,135]. Second, most mitochondrial agents rely on lipophilic cations such as TPP^{+} for matrix accumulation via membrane potential-dependent uptake; however, diseased myocardium commonly exhibits mitochondrial depolarization, reducing on-target delivery while promoting off-target accumulation in liver and kidney [136]. The clinical trajectory of elamipretide illustrates this dilemma: despite consistent improvements in mitochondrial ultrastructure and left ventricular function across preclinical models, Phase II/III trials failed to meet primary functional endpoints underscoring the preclinical-clinical translation gap [137]. Third, clinical populations with HF or IHD differ fundamentally from experimental models characterized by advanced age, multimorbidity, polypharmacy, and variable disease staging factors that attenuate pharmacodynamic responses and complicate dose optimization. Cariporide exemplifies this discrepancy: despite reducing ischemia-reperfusion injury experimentally and achieving its primary composite endpoint in EXPEDITION, it was associated with excess cerebrovascular mortality, precluding clinical adoption [138,139]. Fourth, the absence of validated mitochondrial biomarkers for patient stratification and target engagement hampers precision deployment, as most trials enroll heterogeneous cohorts without phenotyping bioenergetics, redox status, or mitophagic flux [140].

Successful mitochondrial therapeutics will therefore likely require multi-modal strategies addressing bioenergetics, redox balance, and quality control integratively; improved targeting systems independent of membrane potential; biomarker-guided patient selection; and trial designs reflecting the temporal complexity of human cardiac disease [141].

Similarly, epigenetic therapies including class I/II HDAC inhibitors and microRNA (miRNA) modulators such as miR-21 and miR-133 have shown promise in experimental models of cardiac hypertrophy and fibrosis through transcriptional reprogramming of pathological gene expression. However, off-target epigenome-wide effects, long-term safety concerns, and cardiac-specific delivery limitations remain unresolved barriers to clinical translation [142,143].

4.4 Systems-Level Precision Integration

In contrast to pathway-specific interventions, this domain focuses on integrating multidimensional clinical and molecular data to refine risk stratification and therapeutic selection. Systems-level approaches leverage computational modeling, multi-omics profiling, and digital monitoring to align treatment strategies with individual disease trajectories. The following sections examine tools designed to enhance precision in cardiovascular decision-making.

AI-assisted monitoring and digital therapeutic integration: Digital health technologies and AI-assisted monitoring are increasingly embedded within cardiovascular therapeutic workflows enabling real-time arrhythmia detection, HF decompensation prediction, and adaptive medication optimization at the point of care [144]. These approaches provide the infrastructure for precision stratification discussed conceptually in the Introduction and operationalized in Section 5.1.

Emerging digital twin technology represents a particularly promising frontier in therapeutic AI generating patient-specific computational cardiovascular models that simulate disease trajectories and predict individualized responses to pharmacological and device-based interventions, enabling prospective treatment optimization before clinical implementation [145]. AI-guided adaptive dosing algorithms are further transforming therapeutic management in HF, anticoagulation, and antihypertensive therapy dynamically adjusting drug titration in response to continuous physiological data streams from wearable biosensors, reducing adverse events and improving target attainment compared to standard protocol-driven approaches [146]. At the systems level, remote patient monitoring ecosystems integrating wearable sensors, implantable devices, and AI-powered clinical decision support platforms are enabling a shift from episodic hospital-based care toward continuous community-based cardiovascular management a transition with profound implications for both therapeutic efficacy and healthcare resource utilization [147].

Machine learning models integrating multi-omics datasets further enhance prediction of disease trajectories and drug responsiveness [148], capabilities explored in the context of systems biology in Section 5.4 (Figure 2). Despite these advances, substantial translational barriers including algorithmic bias, limited prospective validation, and inequitable deployment temper clinical adoption [149,150], as critically appraised in Section 5.1.

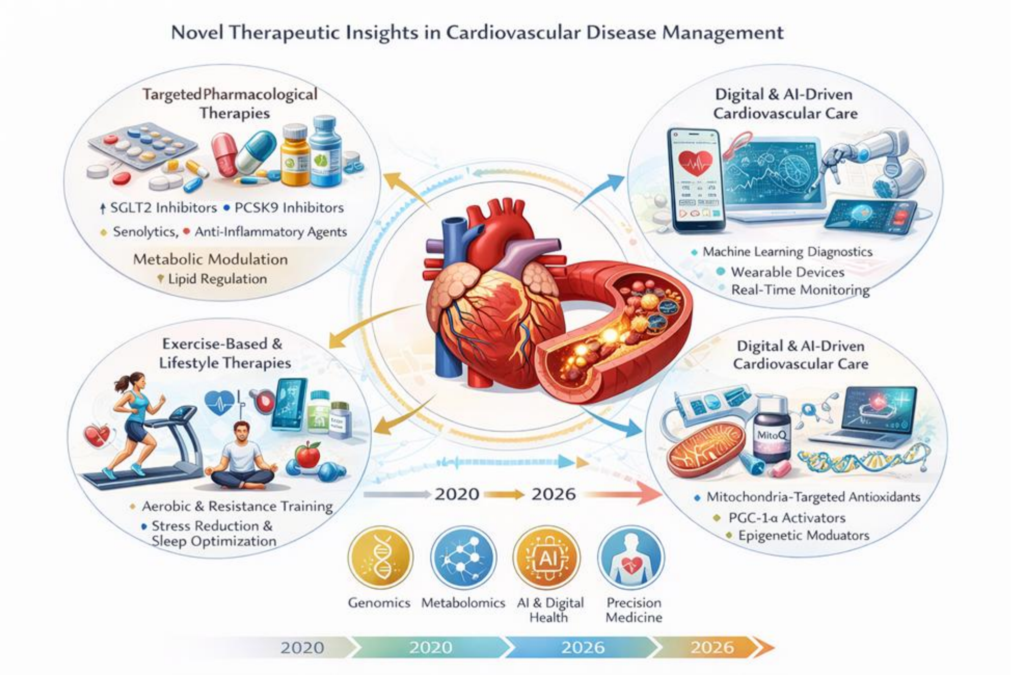

Figure 2. Novel therapeutic insights in CVD management (2020-2026).

This figure illustrates the integrated precision therapeutic strategies in CVD management, organized across five interconnected domains: metabolic and cardioprotective pharmacology, inflammatory and senescence targeting, mitochondrial and epigenetic reprogramming, systems-level precision integration, and regenerative reconstruction. Arrows and connectors denote mechanistic and clinical interdependencies between domains, reflecting the convergence of multi-omics profiling, digital health technologies, and precision phenotyping toward individualized, preventive, and regenerative cardiovascular care.

4.5 Regenerative Reconstruction

Beyond modifying disease pathways, regenerative strategies aim to restore structural and functional integrity of damaged cardiovascular tissue. This domain encompasses approaches designed to repair or replace injured myocardium and vasculature through bioengineering, cellular therapies, and tissue reconstruction. The following section considers emerging efforts to transition from disease control toward biological restoration.

From a systems-level perspective, the ultimate goal of cardiovascular therapeutics extends beyond disease management to regeneration and repair. Advances in 3D bioprinting and stem cell engineering explored in depth in Section 5.3 are paving the way for tissue-engineered vascular grafts and myocardial patches capable of reversing rather than merely managing structural cardiovascular damage [151,152].

The integration of multi-omics data, immunometabolic modulation, and regenerative medicine is poised to define the next era of cardiovascular therapy one rooted in systems-level precision medicine and oriented toward reversing, rather than merely controlling, the biological substrates of disease progression [153].

The translational barriers to clinical implementation including immune compatibility, construct vascularization, electromechanical integration, and regulatory complexity re critically examined in Section 5.3.

5. Emerging Technologies and Future Directions

The preceding sections examined therapeutic strategies targeting established CVD pathways. Section 5 shifts the perspective toward emerging technologies and future directions exploring how artificial intelligence (AI), nanomedicine, and regenerative engineering are converging to redefine the boundaries of cardiovascular diagnosis, treatment, and repair. Where current therapies modify disease, these emerging tools aspire to predict, intercept, and ultimately reverse it.

5.1 AI-Powered Cardiovascular Diagnostics, Prognostication, and Translational Challenges

AI and machine learning (ML) have demonstrated particular strength in cardiovascular diagnostics, with deep-learning echocardiography and cardiac magnetic resonance imaging (MRI) analytics achieving diagnostic precision that can surpass conventional visual interpretation for early diastolic dysfunction and subclinical myocardial fibrosis. Electrocardiogram (ECG)-integrated AI models have shown promising performance in predicting sudden cardiac death and atrial fibrillation recurrence, while AI-guided drug discovery platforms accelerate candidate identification through computational simulation of molecular docking, pharmacokinetics, and toxicity profiles [154,155].

However, critical translational barriers persist. Supervised learning models despite strong endpoint-specific performance remain vulnerable to dataset shift and algorithmic bias in underrepresented populations, while unsupervised approaches lack clinical interpretability and require extensive validation before guideline integration. Most algorithms have been developed in single-center or homogeneous cohorts, and evidence that AI-powered platforms improve hard cardiovascular outcomes and health equity beyond standard care remains preliminary [149].

AI should therefore presently be viewed as a decision-support adjunct rather than an autonomous driver of cardiovascular care, pending robust evidence from multicenter outcome trials [156]. Realizing its full potential will require multicenter prospective trials demonstrating not only enhanced prediction metrics but also improved patient outcomes and reduced health disparities—alongside robust regulatory frameworks and equity-focused deployment strategies.

5.2 Nanotechnology and Smart Drug Delivery Systems

Nanomedicine represents one of the most promising emerging platforms in precision cardiovascular therapeutics. Nanoparticles—engineered to deliver drugs, genes, or imaging agents enable site-specific targeting of atherosclerotic plaques, ischemic myocardium, or inflamed endothelium while potentially minimizing systemic toxicity [157].

Preclinical and early translational studies have demonstrated the potential of liposomal carriers, polymeric nanoparticles, and exosome-based nanocarriers in delivering antioxidants, small interfering RNAs (siRNAs), and anti-inflammatory molecules directly to diseased vascular tissues. These nanosystems exploit endothelial adhesion molecules (such as vascular cell adhesion molecule 1 (VCAM-1) and Intercellular adhesion molecule 1 (ICAM-1)) for vascular homing, thereby enhancing local bioavailability and therapeutic precision at the cost of increased formulation complexity and challenges in large-scale manufacturing and quality control [158]. Emerging “smart” nanocarriers combine biosensing and therapeutic capabilities, enabling responsive drug release in reaction to local stimuli such as pH, oxidative stress, or enzyme activity; for example, nitric-oxide-releasing nanoparticles are under preclinical evaluation for restoring endothelial function and reducing reperfusion injury in ischemic heart disease [159].

In comparative terms, inorganic and metallic nanoparticles often offer superior imaging contrast or payload stability but raise long-term safety concerns related to persistence and off-target accumulation, whereas biodegradable polymeric and lipid-based systems are more biocompatible yet may have less precise physicochemical control and batch-to-batch reproducibility. Regulatory pathways for complex nanomedicines remain less mature than for small molecules, and robust phase II/III cardiovascular outcome trials are largely lacking. Thus, while nanotechnology holds high promise for targeted delivery in CVD, its current role is best characterized as preclinical or early translational, with clinical deployment likely to begin in narrowly defined indications where conventional formulations have clearly failed, positioning nanomedicine as a complementary rather than competing platform within the broader precision cardiovascular therapeutics framework [158,160].

5.3 Regenerative Cardiovascular Medicine: Stem Cells, Bioprinting, and Gene-Edited Therapeutics

Among regenerative strategies, stem cell biology and 3D bioprinting represent some of the most clinically advanced experimental approaches, yet the field remains heterogeneous in evidence strength and readiness for routine practice [161].

Next-generation bioprinted cardiac constructs are advancing beyond structural vascularization toward electromechanically integrated myocardial substitutes incorporating conductive biomaterials such as carbon nanotubes and gold nanowires to synchronize contractile signalling, and innervation scaffolds seeded with neural progenitors to restore autonomic regulation of graft function [162].

Induced pluripotent stem cells (iPSCs) can be differentiated into cardiomyocytes, vascular cells, and fibroblasts, forming patient-specific myocardial patches capable of partially restoring contractile function after infarction in small and large animal studies. At the same time, early clinical trials of cell-based therapies in HF and ischemic cardiomyopathy have yielded modest and sometimes inconsistent benefits, often limited by poor cell engraftment, variable functional integration, and challenges in standardized manufacturing with arrhythmogenic risk most pronounced with earlier-generation cell therapies rather than iPSC-derived cardiomyocytes, which have demonstrated an acceptable safety profile in preclinical models [161].

Gene-editing strategies in cardiovascular regenerative medicine demand not only platform selection (most commonly CRISPR/Cas9) but equally critical vector choices, each carrying distinct translational trade-offs. Adeno-associated viral (AAV) vectors are small, non-integrating, replication-deficient viruses that package single-stranded DNA and have emerged as the most validated cardiac delivery systems; serotypes AAV9 and AAV6 in particular demonstrate high cardiomyocyte tropism and durable transgene expression suited to long-term gene correction. However, their limited packaging, pre-existing neutralizing antibodies in a significant patient proportion, and manufacturing scalability constraints collectively limit broader applicability. Non-viral systems, principally ionizable lipid nanoparticles (LNPs), are emerging as compelling alternatives, offering lower immunogenicity, flexible payload capacity, and industrial-scale manufacturability; recent preclinical work has demonstrated efficient cardiomyocyte transfection and negligible inflammatory perturbation in vivo. Non-viral platforms currently achieve lower transduction efficiency and less durable expression in post-mitotic cardiac tissue than AAV, and cardiac-specific targeting remains technically demanding. Consequently, a context-dependent framework is emerging: AAV serotypes are preferred for durable monogenic correction in low anti-AAV-titre subgroups, while LNPs are better suited for transient, repeat-dosable, or dose-titratable therapeutic applications, a complementarity likely to define the clinical architecture of cardiovascular gene therapy.

The next generation of regenerative therapies involves gene-edited and immunologically compatible cells, utilizing CRISPR/Cas9 to correct pathogenic mutations or enhance graft survival, as well as extracellular vesicle (EV)-based products—particularly exosomes derived from mesenchymal stem cells—that aim to capture paracrine benefits without the risks of live-cell transplantation [163,164]. Compared with cell therapies, EV-based approaches may offer improved safety, storage, and dosing control, but potency assays, long-term safety, and regulatory frameworks are still evolving. Overall, regenerative strategies remain largely within phase I/II translational domains, with their integration into standard care dependent on demonstrating durable functional improvement, acceptable arrhythmia risk, and scalable production milestones that will define whether regenerative medicine fulfills its promise as the final frontier of CVD reversal [165].

5.4 Multi-Omics Integration and Systems Biology

CVDs result from complex interactions among genomic, epigenomic, transcriptomic, proteomic, metabolomic, and microbiomic factors alongside environmental exposures that are incompletely captured by the single-dimension biomarkers underpinning conventional risk algorithms [166].

Network-based systems-biology models can map molecular interactions underlying myocardial remodeling, atherosclerosis, and arrhythmogenesis, and integrative omics studies have linked mitochondrial gene-expression signatures with immune activation and metabolic stress [167], reinforcing the concept of cardio-immunometabolic coupling discussed earlier.

However, multi-omics platforms differ substantially in their current clinical relevance: while individual polygenic risk scores have historically added only modest incremental discrimination over established clinical scores, newer combined approaches integrating polygenic, metabolomic, and clinical biomarker data demonstrate substantially improved risk stratification particularly in intermediate-risk populations. Transcriptomic and metabolomic signatures, though more dynamic and pathway-proximal, remain technically demanding and costly to implement at scale [168].

Despite the analytical power of AI-driven mining of multi-omics datasets, most resulting classifiers and biomarker panels remain exploratory and have not been prospectively tested to guide therapy in randomized cardiovascular trials [150].

In the near term, a pragmatic approach may involve layering selected omics markeparticularly metabolomic and polygenic scores onto established risk algorithms in intermediate-risk or genetically high-risk subgroups, rather than attempting wholesale replacement of current clinical decision frameworks [169].

5.5 Global Health Equity and the Digital Divide

While technological innovation has revolutionized cardiovascular care in high-income settings, persistent structural disparities spanning access, affordability, and health infrastructure have created a widening cardiovascular technology gap between regions with advanced infrastructure and those with constrained resources. Low- and middle-income countries (LMICs) continue to bear a disproportionate share of the cardiovascular burden, accounting for nearly 80% of global CVD deaths, and face significant barriers related to cost, infrastructure, workforce, and stable connectivity [170].

Implementation studies demonstrate that digital cardiovascular tools can be adapted to resource-limited settings: community-based screening programs in rural India have used smartphone-linked single-lead ECG devices operated by trained community health workers to identify atrial fibrillation and other arrhythmias, enabling earlier referral within primary-care systems [171]. Telecardiology networks in sub-Saharan Africa have expanded access to specialist consultation for HF and structural heart disease, improving diagnostic timeliness and reducing unnecessary transfers, although sustainability and coverage remain uneven [172]. These experiences highlight that digital tools may amplify existing inequities if deployed without representative LMIC training datasets, culturally adapted interfaces, and reimbursement frameworks that support decentralized care delivery [170]. Thus, narrowing the cardiovascular digital divide will require not only technological availability but also inclusive design, mitigation of algorithmic bias, and context-specific implementation strategies that align with local infrastructure and financing models [173-174].

5.6 The Future of Cardiovascular Medicine: Integration, Equity, and Translational Responsibility

The future of cardiovascular care lies in integration, personalization, and prevention rather than in any single technological breakthrough. The convergence of AI, multi-omics, immunometabolism, regenerative engineering, and targeted therapeutics is poised to shift the clinical paradigm from reactive treatment to proactive disease interception. Over the coming decade, clinicians may increasingly employ digital twins as introduced in Section 4.4 as pre-intervention simulation platforms, although their integration currently remains at proof-of-concept stage [153].

Advances in quantum computing, synthetic biology, and nanorobotic surgery will likely expand the theoretical frontier of cardiovascular intervention, yet their near-term impact remains contingent on overcoming substantial regulatory, safety, and cost hurdles. Across all emerging domains, a critical distinction must be maintained between technologies ready for guideline-level integration such as selected AI diagnostic tools and validated remote monitoring platforms and those still firmly in the investigational realm, including most regenerative therapies, nanorobotics, and multi-omics-guided decision systems [150].

Ultimately, the measure of this technological evolution will not be its molecular sophistication but its capacity to reduce cardiovascular morbidity and mortality equitably across diverse populations and healthcare systems. Achieving this requires rigorous evidence generation, ethical stewardship, and interdisciplinary collaboration ensuring that the promise of predictive, preventable, and potentially reversible CVD translates into tangible, globally inclusive health benefit [170].

6. Conclusion

Despite decades of therapeutic progress, CVDs remain the leading cause of preventable death worldwide a reality that demands not only scientific innovation but a fundamental reimagining of how cardiovascular care is delivered. The period spanning 2020-2026 has witnessed substantial and accelerating progress in understanding the molecular, metabolic, and immunological foundations of cardiovascular pathology. Modern cardiovascular research now recognizes CVDs not as isolated disorders of the heart and vasculature, but as systemic, multifactorial syndromes shaped by intricate interactions among genetics, metabolism, inflammation, environment, and lifestyle.

Emerging evidence underscores the pivotal role of mitochondrial dysfunction, oxidative stress, immune cell reprogramming, and immunometabolic dysregulation in disease progression. Simultaneously, transformative advances in pharmacological therapies including SGLT2 inhibitors, PCSK9 modulators, senolytics, and anti-inflammatory biologics are redefining the therapeutic paradigm. These interventions now extend beyond symptomatic relief to target the fundamental molecular architecture of disease, enabling meaningful modification of cardiovascular trajectories rather than mere event suppression.

Beyond pharmacotherapy, the integration of nutrigenomics, precision nutrition, and exercise physiology has broadened the scope of cardiovascular care toward personalized and preventive medicine. The application of AI, multi-omics analysis, and regenerative technologies including 3D bioprinting and stem cell-based therapies—offers transformative potential for early detection, tissue repair, and individualized treatment strategies.

The future of cardiovascular medicine will hinge on the purposeful convergence of three interdependent pillars: integration, personalization, and equity. Integration refers to the seamless convergence of genomics, digital health, and clinical data into unified systems capable of real-time disease modeling and predictive analysis. Through such integration, clinicians will be able to identify molecular abnormalities and physiological deviations long before the onset of clinical symptoms. Personalization, in turn, will enable the tailoring of interventions to each patient’s unique genetic, metabolic, and environmental profile, allowing for therapeutic strategies that are both precise and dynamically adaptable. Finally, equity must serve as the ethical foundation of these innovations, ensuring that technological progress and advanced cardiovascular care extend beyond high-income nations to benefit populations in low- and middle-income countries, where the burden of CVD remains most severe. Together, these principles do not merely describe a future aspiration they define the minimum standard to which the next generation of cardiovascular medicine must be held.

Ultimately, the convergence of molecular cardiology, AI, and regenerative science is transforming the field from a reactive discipline into one that is predictive, preventive, and regenerative. The next generation of cardiovascular medicine will be defined not by its technological sophistication alone, but by its capacity to extend healthy life, reduce suffering, and deliver equitable cardiovascular health to every population, fulfilling medicine's most fundamental promise: that scientific progress serves humanity not selectively, but universally.

Author Contributions

The authors contributed equally to the conception, literature review, writing, and editing of this mini-review. All authors have read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Abbreviations

AAV: Adeno-associated viral

AI: Artificial intelligence

AMPK: AMP-activated protein kinase

AT2R: Angiotensin II type 2 receptors

CAD: Coronary artery disease

cGAS-STING: Cyclic GMP-AMP synthase-stimulator of interferon genes

CHIP: Clonal hematopoiesis of indeterminate potential

CKD: Chronic kidney disease

CMI: Cardiometabolic index

CTLA-4: Cytotoxic T-lymphocyte associated protein 4

CVD: Cardiovascular disease

CVDs: Cardiovascular diseases

DALYs: Disability-adjusted life years

ECG: Electrocardiogram

eNOS: Endothelial nitric oxide synthase

EV: Extracellular vesicle

GPCR: G-protein coupled receptor

HDAC: Histone deacetylase

HF: Heart failure

HIF-1α: Hypoxia-inducible factor-1 alpha

ICAM-1: Intercellular adhesion molecule 1

iPSCs: Induced pluripotent stem cells

LDL-C: Low-density lipoprotein cholesterol

LNPs: Lipid nanoparticles

MBSR: Mindfulness-based stress reduction

MI: Myocardial infarction

miRNA: microRNA

ML: Machine learning

MRI: Magnetic resonance imaging

mtDNA: Mitochondrial DNA

mTOR: Mechanistic target of rapamycin

NF-κB: Nuclear factor kappa B

NO: Nitric oxide

PCSK9: Proprotein convertase subtilisin/kexin type 9

PD-1: Programmed cell death protein 1

PD-L1: Programmed death-ligand 1

ROS: Reactive oxygen species

SASP: Senescence-associated secretory phenotype

SCFAs: Short-chain fatty acids

SGLT2: Sodium-glucose cotransporter-2

siRNAs: Small interfering RNAs

VCAM-1: Vascular cell adhesion molecule 1

VSMCs: Vascular smooth muscle cells

References

[1] Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators. Global, regional, and national burden of cardiovascular diseases and risk factors in 204 countries and territories, 1990-2023. Journal of the American College of Cardiology, 2025, 86(22), 2167-2243. DOI: 10.1016/j.jacc.2025.08.015

[2] World Health Organization: WHO. Cardiovascular diseases (CVDs), 2025. Available at: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (accessed on 31 July 2025).

[3] Aikawa M, Sonawane AR, Chelvanambi S, Asano T, Halu A, Matamalas JT, et al. Precision cardiovascular medicine: Shifting the innovation paradigm. Frontiers in Science, 2025, 3, 1474469. DOI: 10.3389/fsci.2025.1474469

[4] Lopez EO, Ballard BD, Jan A. Cardiovascular disease statpearls NCBI bookshelf. National Library of Medicine, 2023.

[5] Pietrangelo D, Lopa C, Litterio M, Cotugno M, Rubattu S, Lombardi A. Metabolic disturbances involved in cardiovascular diseases: The role of mitochondrial dysfunction, altered bioenergetics and oxidative stress. International Journal of Molecular Sciences, 2025, 26(14), 6791. DOI: 10.3390/ijms26146791

[6] Pavlović N, Todorović P, Maglica M, Kumrić M, Vukojević K, Pogorelić Z, et al. Mitochondrial dysfunction in cardiomyopathy and heart failure: From energetic collapse to therapeutic opportunity. Biomolecules, 2025, 15(11), 1572. DOI: 10.3390/biom15111572

[7] Shah MS, Brownlee M. Molecular and cellular mechanisms of cardiovascular disorders in diabetes. Circulation Research, 2016, 118(11), 1808-1829. DOI: 10.1161/CIRCRESAHA.116.306923

[8] Zeng X, Yang Y. Molecular mechanisms underlying vascular remodeling in hypertension. Reviews in Cardiovascular Medicine, 2024, 25(2), 72. DOI: 10.31083/j.rcm2502072

[9] Blaustein JR, Quisel MJ, Hamburg NM, Wittkopp S. Environmental impacts on cardiovascular health and biology: An overview. Circulation Research, 2024, 134(9), 1048-1060. DOI: 10.1161/CIRCRESAHA.123.323613

[10] Młynarska E, Bojdo K, Frankenstein H, Krawiranda K, Kustosik N, Lisińska W, et al. Endothelial dysfunction as the common pathway linking obesity, hypertension and atherosclerosis. International Journal of Molecular Sciences, 2025, 26(20), 10096. DOI: 10.3390/ijms262010096

[11] Libby P, Soehnlein O. Inflammation in atherosclerosis: Lessons and therapeutic implications. Immunity, 2025, 58(10), 2383-2401. DOI: 10.1016/j.immuni.2025.09.012

[12] YYang HM. Mitochondrial dysfunction in cardiovascular diseases. International Journal of Molecular Sciences, 2025, 26(5), 1917. DOI: 10.3390/ijms26051917

[13] Liu H, Wang S, Wang J, Guo X, Song Y, Fu K, et al. Energy metabolism in health and diseases. Signal Transduction and Targeted Therapy, 2025, 10(1), 69. DOI: 10.1038/s41392-025-02141-x

[14] Salnikova D, Orekhova V, Grechko A, Starodubova A, Bezsonov E, Popkova T, et al. Mitochondrial dysfunction in vascular wall cells and its role in atherosclerosis. International Journal of Molecular Sciences, 2021, 22(16), 8990. DOI: 10.3390/ijms22168990

[15] Zong Y, Li H, Liao P, Chen L, Pan Y, Zheng Y, et al. Mitochondrial dysfunction: Mechanisms and advances in therapy. Signal Transduction and Targeted Therapy, 2024, 9(1), 124. DOI: 10.1038/s41392-024-01839-8

[16] Cobo I, Tanaka T, Glass CK, Yeang C. Clonal hematopoiesis driven by DNMT3A and TET2 mutations: Role in monocyte and macrophage biology and atherosclerotic cardiovascular disease. Current Opinion in Hematology, 2022, 29(1), 1-7. DOI: 10.1097/MOH.0000000000000688

[17] Liu S, Anderson PJ, Rajagopal S, Lefkowitz RJ, Rockman HA. G protein-coupled receptors: A century of research and discovery. Circulation Research, 2024, 135(1), 174-197. DOI: 10.1161/CIRCRESAHA.124.323067

[18] Nordestgaard LT, Wolford BN, de Gonzalo-Calvo D, Sopić M, Devaux Y, Matic L, et al. Multiomics in atherosclerotic cardiovascular disease. Atherosclerosis, 2025, 408, 120414. DOI: 10.1016/j.atherosclerosis.2025.120414

[19] Țapoș GF, Cîmpeanu IA, Predescu IA, Liga S, Păcurar AT, Vlad D, et al. An integrative review of the cardiovascular disease spectrum: Integrating multi-omics and artificial intelligence for precision cardiology. Diseases, 2026, 14(1), 31. DOI: 10.3390/diseases14010031

[20] Mullins VA, Bresette W, Johnstone L, Hallmark B, Chilton FH. Genomics in personalized nutrition: Can you "Eat for your genes"? Nutrients, 2020, 12(10), 3118. DOI: 10.3390/nu12103118

[21] Kiani AK, Bonetti G, Donato K, Kaftalli J, Herbst KL, Stuppia L, et al. Polymorphisms, diet and nutrigenomics. Journal of Preventive Medicine and Hygiene, 2022, 63(2S3), E125-E141. DOI: 10.15167/2421-4248/jpmh2022.63.2S3.2754

[22] Grigoriou K, Karakasis P, Nasoufidou A, Stachteas P, Klisic A, Karagiannidis E, et al. SGLT2 inhibitors in the management of cardio-renal-metabolic syndrome: A new therapeutic era. Medicina, 2025, 61(11), 1903. DOI: 10.3390/medicina61111903

[23] Bodapati AP, Hanif A, Okafor DK, Katyal G, Kaur G, Ashraf H, et al. PCSK-9 inhibitors and cardiovascular outcomes: A systematic review with meta-analysis. Cureus, 2023, 15(10), e46605. DOI: 10.7759/cureus.46605

[24] Papadakis Z. Exercise in CKM syndrome progression: A stage-specific approach to cardiovascular, metabolic, and renal health. Cardiovascular Diabetology, 2025, 24(1), 462. DOI: 10.1186/s12933-025-03029-4

[25] Frąk W, Wojtasińska A, Lisińska W, Młynarska E, Franczyk B, Rysz J. Pathophysiology of cardiovascular diseases: New insights into molecular mechanisms of atherosclerosis, arterial Hypertension, and coronary artery disease. Biomedicines, 2022, 10(8), 1938. DOI: 10.3390/biomedicines10081938

[26] Nevoit G, Potyazhenko M, Mintser O, Jarusevicius G, Vainoras A. Mitochondrial dysfunction in the cardiovascular disease continuum: Problems of studying the progression during the follow-up of the pathologies. International Journal of Molecular Sciences, 2025, 26(21), 10497. DOI: 10.3390/ijms262110497

[27] Józkowiak M, Niebora J, Domagała D, Data K, Partyńska A, Kulus M, et al. New insights into endothelial cell physiology and pathophysiology. Biomedicine & Pharmacotherapy, 2025, 190, 118415. DOI: 10.1016/j.biopha.2025.118415

[28] Pluta W, Lubkowska A, Dudzińska W. Vascular endothelium in health and disease: Structure, function, assessment and role in metabolic disorders. Vascular Health and Risk Management, 2025, 21, 729-747. DOI: 10.2147/VHRM.S519426

[29] Loftus T, Benjamim J, Vaccarezza M, Stephan BC, Nguyen VH, Ashor A, et al. Stable isotope measurement of *in vivo* nitric oxide production in health and disease: An updated systematic review and meta-analysis. Nitric Oxide, 2026, 161, 18-26. DOI: 10.1016/j.niox.2026.01.001

[30] Alia S, Pedriali G, Compagnucci P, Valeri Y, Membrino V, Di Crescenzo T, et al. Mitochondria at the crossroads of cardiovascular disease: Mechanistic drivers and emerging therapeutic strategies. Cells, 2026, 15(4), 372. DOI: 10.3390/cells15040372

[31] Xie X, Yu T, Deng W, Xie S. Mitochondrial semi-autonomous inheritance in cardiovascular pathology: Emerging mechanisms and therapeutic opportunities. Pharmacological Research, 2026, 224, 108106. DOI: 10.1016/j.phrs.2026.108106

[32] Cochran JD, Walsh K. Clonal Hematopoiesis: The emergent CVD risk factor. Arteriosclerosis, Thrombosis, and Vascular, 2024, 44(4), 768-771. DOI: 10.1161/ATVBAHA.123.319562

[33] Jaiswal S, Libby P. Clonal haematopoiesis: Connecting ageing and inflammation in cardiovascular disease. Nature Reviews Cardiology, 2020, 17(3), 137-144. DOI: 10.1038/s41569-019-0247-5

[34] Lin AE, Bapat AC, Xiao L, Niroula A, Ye J, Wong WJ, et al. Clonal hematopoiesis of indeterminate potential with loss of *Tet2* enhances risk for atrial fibrillation through *Nlrp3* inflammasome activation. Circulation, 2024, 149(18), 1419-1434. DOI: 10.1161/CIRCULATIONAHA.123.065597

[35] Chen P, Li X. NLRP3 inflammasome in atherosclerosis: Mechanisms and targeted therapies. Frontiers in Pharmacology, 2024, 15, 1430236. DOI: 10.3389/fphar.2024.1430236

[36] Anastasiou IA, Kounatidis D, Vallianou NG, Rebelos E, Karampela I, Dalamaga M. Clonal hematopoiesis of indeterminate potential and cardiometabolic disease: Challenges, controversies and future perspectives. International Journal of Molecular Sciences, 2025, 27(1), 233. DOI: 10.3390/ijms27010233

[37] Oren O, Small AM, Lin AE, Libby P. Managing cardiovascular risk in clonal hematopoiesis of indeterminate potential: JACC: CardioOncology short-form primer. JACC CardioOncology, 2025, 7(5), 496-500. DOI: 10.1016/j.jaccao.2025.05.013

[38] Li Y, Li B, Chen WD, Wang YD. Role of G-protein coupled receptors in cardiovascular diseases. Frontiers in Cardiovascular Medicine, 2023, 10, 1130312. DOI: 10.3389/fcvm.2023.1130312

[39] Sun L, Ye RD. Role of G protein-coupled receptors in inflammation. Acta Pharmacologica Sinica, 2012, 33(3), 342-350. DOI: 10.1038/aps.2011.200

[40] Tanasescu MD, Rosu AM, Minca A, Rosu AL, Grigorie MM, Timofte D, et al. Metabolic dysfunction at the core: Revisiting the overlap of cardiovascular, renal, hepatic, and endocrine disorders. Life, 2026, 16(1), 172. DOI: 10.3390/life16010172

[41] Wang YH, Chen YS, Wang SY, Jin BY, Han XY, Hua CJ. Dysregulated cellular metabolism drives atherosclerotic plaque progression: A multi-cellular perspective. Frontiers in Cardiovascular Medicine, 2025, 12, 1562707. DOI: 10.3389/fcvm.2025.1562707

[42] Xie Y, Song Y, Shi S, Guo Y, Song W, Dou K. Glycaemic status modifies the association between cardiometabolic index and cardio-kidney outcomes: A multi-cohort analysis. Diabetes/Metabolism Research and Reviews, 2026, 42(1), e70124. DOI: 10.1002/dmrr.70124

[43] Vallon V, Verma S. Effects of SGLT2 inhibitors on kidney and cardiovascular function. Annual Review of Physiology, 2021, 83, 503-528. DOI: 10.1146/annurev-physiol-031620-095920

[44] Grejtakova D, Boronova I, Bernasovska J, Bellosta S. PCSK9 and lipid metabolism: Genetic variants, current therapies, and cardiovascular outcomes. Cardiovascular Drugs and Therapy, 2025, 39(6), 1439-1451. DOI: 10.1007/s10557-024-07599-5

[45] Klerk M, Verhoef P, Clarke R, Blom HJ, Kok FJ, Schouten EG, et al. MTHFR 677C-->T polymorphism and risk of coronary heart disease: A meta-analysis. JAMA, 2002, 288(16), 2023-2031. DOI: 10.1001/jama.288.16.2023

[46] Gupta SK, Kotwal J, Kotwal A, Dhall A, Garg S. Role of homocysteine & MTHFR C677T gene polymorphism as risk factors for coronary artery disease in young Indians. Indian Journal of Medical Research, 2012, 135(4), 506-512.

[47] Huang X, Qin X, Yang W, Liu L, Jiang C, Zhang X, et al. MTHFR gene and serum folate interaction on serum homocysteine lowering: Prospect for precision folic acid treatment. Arteriosclerosis Thrombosis and Vascular Biology, 2018, 38(3), 679-685. DOI: 10.1161/ATVBAHA.117.310211

[48] Qiu Y, Xu Q, Xie P, He C, Li Q, Yao X, et al. Epigenetic modifications and emerging therapeutic targets in cardiovascular aging and diseases. Pharmacological Research, 2025, 211, 107546. DOI: 10.1016/j.phrs.2024.107546

[49] Krekora J, Derwich M, Drożdż J, Pawlowska E, Blasiak J. Oxidative stress, mitochondrial quality control, autophagy, and sirtuins in heart failure. International Journal of Molecular Sciences, 2025, 26(19), 9826. DOI: 10.3390/ijms26199826

[50] Liu S, Liu J, Wang Y, Deng F, Deng Z. Oxidative stress: Signaling pathways, biological functions, and disease. MedComm, 2025, 6(7), e70268. DOI: 10.1002/mco2.70268

[51] Elbatarny M, Lu YT, Hu M, Coles J, Mital S, Ross-White A, et al. Systems biology approaches investigating mitochondrial dysfunction in cyanotic heart disease: A systematic review. EBioMedicine, 2025, 118, 105839. DOI: 10.1016/j.ebiom.2025.105839

[52] Luo Y, Zhang N, Yang J, Cui M, Tsoi KKF, Lip GYH, et al. AI-based multiomics profiling reveals complementary omics contributions to personalized prediction of cardiovascular disease. Nature Communications, 2026, 17(1), 2269. DOI: 10.1038/s41467-026-68956-6

[53] Reitz CJ, Kuzmanov U, Gramolini AO. Multi-omic analyses and network biology in cardiovascular disease. Proteomics, 2023, 23(21-22), e2200289. DOI: 10.1002/pmic.202200289

[54] Thorp EB, Karlstaedt A. Intersection of immunology and metabolism in myocardial disease. Circulation Research, 2024, 134(12), 1824-1840. DOI: 10.1161/CIRCRESAHA.124.323660

[55] Xiang A, Chang A, Zhou J, Jin J, Zhang X, Wang Q. Macrophage metabolism in inflammatory heart disease: New insights and therapeutic implications. Frontiers in Medicine, 2025, 12, 1664538. DOI: 10.3389/fmed.2025.1664538

[56] Chen R, Zhang H, Tang B, Luo Y, Yang Y, Zhong X, et al. Macrophages in cardiovascular diseases: Molecular mechanisms and therapeutic targets. Signal Transduction and Targeted Therapy, 2024, 9(1), 130. DOI: 10.1038/s41392-024-01840-1

[57] Li M, Sun X, Zeng L, Sun A, Ge J. Metabolic homeostasis of immune cells modulates cardiovascular diseases. Research, 2025, 8, 0679. DOI: 10.34133/research.0679

[58] Adachi Y, Grogan A, Kawakami R, Shiraki T, Sekimoto T, Tanaka T, et al. Recent advances in single-cell analysis of atherosclerotic plaque biology. JMA Journal, 2026, 9(1), 24-37. DOI: 10.31662/jmaj.2025-0397

[59] Single-cell RNA sequencing (scRNA-seq) and its insights into cellular heterogeneity in atherosclerosis. Vascular Pharmacology, 2025, 159, 107499. DOI: 10.1016/j.vph.2025.107499

[60] Boden KA, Chai J, Kufazvinei TTJ, Choudhury RP. Trained immunity and cardiovascular risk: An immunological perspective. Immunological Reviews, 2026, 337(1), e70095. DOI: 10.1111/imr.70095

[61] Liu Y, Zhang P, Kong W, Li J, Yang H, Bai H, et al. IRG1-itaconate axis in immunometabolism: Mechanistic roles and therapeutic potential in inflammatory diseases. Frontiers in Immunology, 2026, 17, 1767601. DOI: 10.3389/fimmu.2026.1767601

[62] Atallah R, Gindlhuber J, Heinemann A. Succinate in innate immunity: Linking metabolic reprogramming to immune modulation. Frontiers in Immunology, 2025, 16, 1661948. DOI: 10.3389/fimmu.2025.1661948

[63] Fanucchi S, Domínguez-Andrés J, Joosten LAB, Netea MG, Mhlanga MM. The intersection of epigenetics and metabolism in trained immunity. Immunity, 2021, 54(1), 32-43. DOI: 10.1016/j.immuni.2020.10.011

[64] Xu R, He X, Xu J, Yu G, Wu Y. Immunometabolism: Signaling pathways, homeostasis, and therapeutic targets. MedComm, 2024, 5(11), e789. DOI: 10.1002/mco2.789

[65] Potere N, Bonaventura A, Abbate A. Novel therapeutics and upcoming clinical trials targeting inflammation in cardiovascular diseases. Arteriosclerosis Thrombosis and Vascular Biology, 2024, 44(12), 2371-2395. DOI: 10.1161/ATVBAHA.124.319980

[66] Wong NR, Mohan J, Kopecky BJ, Guo S, Du L, Leid J, et al. Resident cardiac macrophages mediate adaptive myocardial remodeling. Immunity, 2021, 54(9), 2072-2088.e7. DOI: 10.1016/j.immuni.2021.07.003

[67] Kang M, Jia H, Feng M, Ren H, Gao J, Liu Y, et al. Cardiac macrophages in maintaining heart homeostasis and regulating ventricular remodeling of heart diseases. Frontiers in Immunology, 2024, 15, 1467089. DOI: 10.3389/fimmu.2024.1467089

[68] Guan F, Wang R, Yi Z, Luo P, Liu W, Xie Y, et al. Tissue macrophages: Origin, heterogenity, biological functions, diseases and therapeutic targets. Signal Transduction and Targeted Therapy, 2025, 10(1), 93. DOI: 10.1038/s41392-025-02124-y

[69] Shrestha S, Dick SA. Cardiac macrophages across space and time: Roles in homeostasis, disease, and remodeling. Canadian Journal of Cardiology, 2026, S0828-282X(26)00142-X. DOI: 10.1016/j.cjca.2026.02.025

[70] López-Méndez I, Uribe M, Juárez-Hernández E. Immunonutrition: Another player on the MASLD field. International Journal of Molecular Sciences, 2025, 26(18), 8928. DOI: 10.3390/ijms26188928

[71] Nessel I, Tsang VSK, Schroth J, Janssen H. Immunometabolism, an emerging field in perioperative and critical care medicine: A narrative review. British Journal of Anaesthesia, 2026, 136(4), 1202-1216. DOI: 10.1016/j.bja.2026.01.003

[72] Hajishengallis G, Chavakis T. Inflammageing and clonal haematopoiesis interplay and their impact on human disease. Nature Reviews Molecular Cell Biology, 2026, 10.1038/s41580-025-00936-y. DOI: 10.1038/s41580-025-00936-y

[73] Nadar S, Dohadwala TK, Kumaresan N, Ahamed SI, Fatima S. Clonal hematopoiesis at the crossroads of inflammaging and cardiovascular disease: Mechanistic insights and translational horizons. Clinical Hematology International, 2025, 7(4), 54-63. DOI: 10.46989/001c.146275

[74] Wong CK, McDonald A, Buttigieg MM, Rauh MJ. CHIP ahoy: Charting a decade of discovery in clonal hematopoiesis. Haematologica, 2026, 111(2), 457-469. DOI: 10.3324/haematol.2023.283896

[75] Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: Analyses from the canakinumab anti-inflammatory thrombosis outcomes study (CANTOS). European Heart Journal, 2018, 39(38), 3499-3507. DOI: 10.1093/eurheartj/ehy310

[76] Oren O, Libby P. Incorporating management of clonal hematopoiesis of indeterminate potential into cardiovascular practice. Circulation, 2025, 152(14), 975-977. DOI: 10.1161/CIRCULATIONAHA.125.075769

[77] Zanders L, Arifaj D, Wagner JUG, Dimmeler S. Cellular senescence, inflammaging and cardiovascular disease. Immunological Reviews, 2026, 337(1), e70084. DOI: 10.1111/imr.70084

[78] Xue S, Su Z, Liu D. Immunometabolism and immune response regulate macrophage function in atherosclerosis. Ageing Research Reviews, 2023, 90, 101993. DOI: 10.1016/j.arr.2023.101993

[79] Picos A, Seoane N, Campos-Toimil M, Viña D. Vascular senescence and aging: Mechanisms, clinical implications, and therapeutic prospects. Biogerontology, 2025, 26(3), 118. DOI: 10.1007/s10522-025-10256-5

[80] Fu Z, Yang S, Chang X, Liu P, Wang Y. Vascular smooth muscle cell metabolic reprogramming and phenotypic remodeling in atherosclerosis. Cell Death Discovery, 2025, 12(1), 64. DOI: 10.1038/s41420-025-02932-9

[81] Shi F, Dou J, Zhang X. Advancements in research to mitigate residual risk of atherosclerotic cardiovascular disease. European Journal of Medical Research, 2025, 30(1), 735. DOI: 10.1186/s40001-025-03006-3

[82] Li N, Pi C, Zhu S, Li X, Wang L, Shi P, et al. Opportunities for the treatment of atherosclerosis: Selectins. Pharmacological Research, 2025, 217, 107807. DOI: 10.1016/j.phrs.2025.107807

[83] Xiao Q, Hou R, Xie L, Niu M, Pan X, Zhu X. Macrophage metabolic reprogramming and atherosclerotic plaque microenvironment: Fostering each other? Clinical and Translational Medicine, 2023, 13(5), e1257. DOI: 10.1002/ctm2.1257

[84] Kim ME, Lee JS. Advances in the regulation of inflammatory mediators in nitric oxide synthase: Implications for disease modulation and therapeutic approaches. International Journal of Molecular Sciences, 2025, 26(3), 1204. DOI: 10.3390/ijms26031204

[85] Zhili G, Zhimin G, Nenghua Z. Role of vascular endothelial dysfunction and metabolic eprogramming of immune cells in the development and ogression of atherosclerosis. Frontiers in Physiology, 2025, 16, 1624225. DOI: 10.3389/fphys.2025.1624225

[86] Gao C, Wang Y. YAP: The nexus between metabolism and cardiac remodeling. Journal of Clinical Investigation, 2022, 132(6), e157664. DOI: 10.1172/JCI157664

[87] Kopecky BJ, Lavine KJ. Cardiac macrophage metabolism in health and disease. Trends in Endocrinology and Metabolism, 2024, 35(3), 249-262. DOI: 10.1016/j.tem.2023.10.011

[88] Cai G, Zhang X, Jiao J, Du W, Yan M. Targeting the cGAS-STING pathway to modulate immune inflammation in diabetes and cardiovascular complications: Mechanisms and therapeutic insights. Current Issues in Molecular Biology, 2025, 47(9), 750. DOI: 10.3390/cimb47090750

[89] Szabo M, Lagos D, Cross E, Collier J, Horvath R. Mitochondrial DNA release and inflammation in mitochondrial disease pathogenesis. Brain, 2026, awag037. DOI: 10.1093/brain/awag037

[90] Mou J, Chen Y, Zhu X, Xu B, Wang M, Xie J, et al. Emerging role of the cGAS-STING pathway in cardiovascular diseases: Biologic function, mechanisms and targeted therapy. Molecular Medicine, 2025, 31(1), 218. DOI: 10.1186/s10020-025-01273-8

[91] Yue T, Zheng D, He J, Xiong S, Xu J, Hou J. Mitochondrial dysfunction as a therapeutic nexus in HFpEF: Therapeutic target and pharmacological advances. Frontiers in Pharmacology, 2025, 16, 1676988. DOI: 10.3389/fphar.2025.1676988

[92] Kumar V, Yepuri G, Kumar G, Schmidt AM. Editorial: Cardiovascular immunometabolism-a complex interplay between the immune system and metabolism in the heart. Frontiers in Endocrinology, 2025, 16, 1613774. DOI: 10.3389/fendo.2025.1613774

[93] Shu B, Chen X, Liu Z, Tang H, Yang B, Fu C. Pleiotropic effects of SGLT2 inhibitors: A focus on macrophage-mediated action. Pharmacological Research, 2025, 222, 108046. DOI: 10.1016/j.phrs.2025.108046

[94] Ma T, Wang L, Yan X, Li F. Targeted Anti-inflammatory therapy in cardiovascular events: Challenges and opportunities. Journal of Clinical Hypertension, 2025, 27(11), e70172. DOI: 10.1111/jch.70172

[95] Shah SR, Abbasi Z, Fatima M, Ochani RK, Shahnawaz W, Asim Khan M, et al. Canakinumab and cardiovascular outcomes: Results of the CANTOS trial. Journal of Community Hospital Internal Medicine Perspectives, 2018, 8(1), 21-22. DOI: 10.1080/20009666.2018.1428023

[96] Khinchin J, Rakoubian A, Romano V, Ryan T, Yarbro J, Kobayashi S, et al. Repurposing metformin for cardioprotection: Mechanisms and therapeutic potential across cardiovascular pathologies. Frontiers in Pharmacology, 2026, 17, 1681783. DOI: 10.3389/fphar.2026.1681783

[97] Kret Z, Akinola OM, Ahlidja W, Joe B. Food as medicine for hypertension: Microbiota as mediators. Hypertension, 2025, 82(10), 1569-1589. DOI: 10.1161/HYPERTENSIONAHA.125.17950

[98] Pisaniello AD, Psaltis PJ, King PM, Liu G, Gibson RA, Tan JT, et al. Omega-3 fatty acids ameliorate vascular inflammation: A rationale for their atheroprotective effects. Atherosclerosis, 2021, 324, 27-37. DOI: 10.1016/j.atherosclerosis.2021.03.003

[99] Sheng Z, Luo Q, Liu X, Yang X. Bioactives and exercise synergize to modulate AMPK and inflammation. Frontiers in Immunology, 2026, 16, 1670379. DOI: 10.3389/fimmu.2025.1670379

[100] Wang X, Chen L, Wei J, Zheng H, Zhou N, Xu X, et al. The immune system in cardiovascular diseases: From basic mechanisms to therapeutic implications. Signal Transduction and Targeted Therapy, 2025, 10(1), 166. DOI: 10.1038/s41392-025-02220-z

[101] Rong W, Zhou Y. Decoding cardiac metabolic reprogramming through single-cell multi-omics: From mechanisms to therapeutic applications. Frontiers in Cell and Developmental Biology, 2025, 13, 1710474. DOI: 10.3389/fcell.2025.1710474

[102] Li K, Samiei S, Pikulska D, Foecking S, Kuppe C. Advancing cardiovascular research with single-cell and spatial transcriptomics. Circulation Research, 2026, 138(1), e325795. DOI: 10.1161/CIRCRESAHA.125.325795

[103] Barcia Durán JG, Das D, Gildea M, Amadori L, Gourvest M, Kaur R, et al. Immune checkpoint landscape of human atherosclerosis and influence of cardiometabolic factors. Nature Cardiovascular Research, 2024, 3(12), 1482-1502. DOI: 10.1038/s44161-024-00563-4

[104] Lancellotti P, Oury C. Recent advances in cardiovascular medicine: From molecular mechanisms to precision care. Acta Cardiologica, 2025, 80(9), 949-953. DOI: 10.1080/00015385.2025.2579430

[105] Spray L, Richardson G, Haendeler J, Altschmied J, Rumampouw V, Wallis SB, et al. Cardiovascular inflammaging: Mechanisms, consequences, and therapeutic perspectives. Cell Reports Medicine, 2025, 6(9), 102264. DOI: 10.1016/j.xcrm.2025.102264

[106] Lopaschuk GD, Karwi QG, Tian R, Wende AR, Abel ED. Cardiac energy metabolism in heart failure. Circulation Research, 2021, 128(10), 1487-1513. DOI: 10.1161/CIRCRESAHA.121.318241

[107] Chen B, Guo J, Ye H, Wang X, Feng Y. Role and molecular mechanisms of SGLT2 inhibitors in pathological cardiac remodeling (Review). Molecular Medicine Reports, 2024, 29(5), 73. DOI: 10.3892/mmr.2024.13197

[108] Bodea OM, Serban S, Craciun ML, Mateescu DM, Florescu E, Muresan CO, et al. Effects of SGLT2 inhibitors on clinical outcomes, symptoms, functional capacity, and cardiac remodeling in heart failure: A comprehensive systematic review and multidomain meta-analysis of randomized trials. Journal of Clinical Medicine, 2026, 15(1), 378. DOI: 10.3390/jcm15010378

[109] Svanström H, Mkoma GF, Hviid A, Pasternak B. SGLT-2 inhibitors and mortality among patients with heart failure with reduced ejection fraction: Linked database study. BMJ, 2024, 387, e080925. DOI: 10.1136/bmj-2024-080925

[110] Barbieri L, Tumminello G, Fichtner I, Corsini A, Santos RD, Carugo S, et al. PCSK9 and coronary artery plaque-new opportunity or red herring? Current Atherosclerosis Reports, 2024, 26(10), 589-602. DOI: 10.1007/s11883-024-01230-6

[111] Tavori H, Giunzioni I, Fazio S. PCSK9 inhibition to reduce cardiovascular disease risk: Recent findings from the biology of PCSK9. Current Opinion in Endocrinology Diabetes and Obesity, 2015, 22(2), 126-132. DOI: 10.1097/MED.0000000000000137

[112] Jiang Y, Wang Y, Ma S, Qian L, Jing Y, Chen X, et al. Efficacy and safety of PCSK9 inhibitors, potent statins, and their combinations for reducing low-density lipoprotein cholesterol in hyperlipidemia patients: A systematic network meta-analysis. Frontiers in Cardiovascular Medicine, 2025, 11, 1415668. DOI: 10.3389/fcvm.2024.1415668

[113] Priyanka F, Durga F, Affan M, Venjhraj F. The PCSK9 inhibitors: A lipid-lowering therapy to treat atherosclerotic cardiovascular diseases. Nature Cell and Science, 2025, 3(2), 92-99. DOI: 10.61474/ncs.2024.00056

[114] Chaudhary D, Guleria D, Aggarwal H, Mishra V, Chauhan A, Dufossé L, et al. Nutrigenomics and personalized diets-Tailoring nutrition for optimal health. Applied Food Research, 2025, 5(1), 100980. DOI: 10.1016/j.afres.2025.100980

[115] Mundt C, Yusufoğlu B, Kudenko D, Mertoğlu K, Esatbeyoglu T. AI-driven personalized nutrition: Integrating omics, ethics, and digital health. Molecular Nutrition & Food Research, 2025, 69(24), e70293. DOI: 10.1002/mnfr.70293

[116] Debri RP, De Lorenzo A, Conte R, Peluso G. Functional foods as vehicles for bioactive compounds: Chemical and nutritional perspectives on health and disease prevention. International Journal of Molecular Sciences, 2026, 27(5), 2293. DOI: 10.3390/ijms27052293

[117] Balamurugan J, Adeyeye SAO. Artificial intelligence in nutrigenomics: A critical review on functional food insights and personalized nutrition pathways. Journal of Human Nutrition and Dietetics, 2026, 39(1), e70200. DOI: 10.1111/jhn.70200

[118] Saeidifard F, Medina-Inojosa JR, West CP, Olson TP, Somers VK, Bonikowske AR, et al. The association of resistance training with mortality: A systematic review and meta-analysis. European Journal of Preventive Cardiology, 2019, 26(15), 1647-1665. DOI: 10.1177/2047487319850718

[119] Clark A, Mach N. The crosstalk between the gut microbiota and mitochondria during exercise. Frontiers in Physiology, 2017, 8, 319. DOI: 10.3389/fphys.2017.00319

[120] Paluch AE, Boyer WR, Franklin BA, Laddu D, Lobelo F, Lee DC, et al. Resistance exercise training in individuals with and without cardiovascular disease: 2023 update: A scientific statement from the American Heart Association. Circulation, 2024, 149(3), e217-e231. DOI: 10.1161/CIR.0000000000001189

[121] Shero JA, Lindholm ME, Sandri M, Stanford KI. Skeletal muscle as a mediator of interorgan crosstalk during exercise: Implications for aging and obesity. Circulation Research, 2025, 136(11), 1407-1432. DOI: 10.1161/CIRCRESAHA.124.325614

[122] Conversano C, Orrù G, Pozza A, Miccoli M, Ciacchini R, Marchi L, et al. Is mindfulness-based stress reduction effective for people with hypertension? A systematic review and meta-analysis of 30 years of evidence. International Journal of Environmental Research and Public Health, 2021, 18(6), 2882. DOI: 10.3390/ijerph18062882

[123] Kumar M, Yan P, Kuchel GA, Xu M. Cellular senescence as a targetable risk factor for cardiovascular diseases: Therapeutic implications: JACC family series. JACC Basic to Translational Science, 2024, 9(4), 522-534. DOI: 10.1016/j.jacbts.2023.12.003

[124] Fang YP, Zhao Y, Huang JY, Yang X, Liu Y, Zhang XL. The functional role of cellular senescence during vascular calcification in chronic kidney disease. Frontiers in Endocrinology, 2024, 15, 1330942. DOI: 10.3389/fendo.2024.1330942

[125] Atlante S, Gottardi Zamperla M, Cis L, Farsetti A, Gaetano C. Senolytic therapies for cardiovascular aging: Tackling fibrosis and metabolic dysfunction. European Journal of Internal Medicine, 2025, 140, 106413. DOI: 10.1016/j.ejim.2025.07.009

[126] Bian X, Snow ZK, Zinn CJ, Bratulin AL, Elhusseiny KM, Tchkonia T, et al. Senolytics, dasatanib plus quercetin, reduce kidney inflammation, senescent cell abundance, and injury while restoring geroprotective factors in murine diabetic kidney disease. EBioMedicine, 2026, 124, 106124. DOI: 10.1016/j.ebiom.2026.106124

[127] Thompson PL, Nidorf SM. Anti-inflammatory therapy with canakinumab for atherosclerotic disease: Lessons from the CANTOS trial. Journal of Thoracic Disease, 2018, 10(2), 695-698. DOI: 10.21037/jtd.2018.01.119

[128] Viana-Huete V, Fuster JJ. Potential therapeutic value of interleukin 1b-targeted strategies in atherosclerotic cardiovascular disease. Revista Española De Cardiología (English Edition), 2019, 72(9), 760-766. DOI: 10.1016/j.rec.2019.03.006

[129] Yesilyurt-Dirican ZE, Qi C, Wang YC, Simm A, Deelen L, Hafiz Abbas Gasim A, et al. SGLT2 inhibitors as a novel senotherapeutic approach. NPJ Aging, 2025, 11(1), 35. DOI: 10.1038/s41514-025-00227-y

[130] Mansfield L, Ramponi V, Gupta K, Stevenson T, Mathew AB, Barinda AJ, et al. Emerging insights in senescence: Pathways from preclinical models to therapeutic innovations. NPJ Aging, 2024, 10(1), 53. DOI: 10.1038/s41514-024-00181-1

[131] Antonioli L, Fornai M, Pellegrini C, Pacher P, Haskó G. Adenosine signaling as target in cardiovascular pharmacology. Current Opinion in Pharmacology, 2023, 71, 102393. DOI: 10.1016/j.coph.2023.102393

[132] Qian Y, Dong S, Nie M, Tian Y, Liu M, Liu X, et al. Delayed administration of an angiotensin II type 2 receptor agonist promotes functional recovery of the brain and heart after traumatic brain injury. Journal of Neurotrauma, 2024, 41(5-6), 660-670. DOI: 10.1089/neu.2023.0375

[133] Singh DD, Yadav DK, Shin D. Next-generation antioxidants in cardiovascular disease: Mechanistic insights and emerging therapeutic strategies. Antioxidants, 2026, 15(2), 164. DOI: 10.3390/antiox15020164

[134] Liu B, Chen L, Gao M, Dai M, Zheng Y, Qu L, et al. A comparative study of the efficiency of mitochondria-targeted antioxidants MitoTEMPO and SKQ1 under oxidative stress. Free Radical Biology and Medicine, 2024, 224, 117-129. DOI: 10.1016/j.freeradbiomed.2024.08.022

[135] Fonseka O, Gare SR, Chen X, Zhang J, Alatawi NH, Ross C, et al. Molecular mechanisms underlying heart failure and their therapeutic potential. Cells, 2025, 14(5), 324. DOI: 10.3390/cells14050324

[136] Zielonka J, Joseph J, Sikora A, Hardy M, Ouari O, Vasquez-Vivar J, et al. Mitochondria-targeted triphenylphosphonium-based compounds: Syntheses, mechanisms of action, and therapeutic and diagnostic applications. Chemical Reviews, 2017, 117(15), 10043-10120. DOI: 10.1021/acs.chemrev.7b00042

[137] Tung C, Varzideh F, Farroni E, Mone P, Kansakar U, Jankauskas SS, et al. Elamipretide: A review of its structure, mechanism of action, and therapeutic potential. International Journal of Molecular Sciences, 2025, 26(3), 944. DOI: 10.3390/ijms26030944

[138] Mentzer RM Jr, Bartels C, Bolli R, Boyce S, Buckberg GD, Chaitman B, et al. Sodium-hydrogen exchange inhibition by cariporide to reduce the risk of ischemic cardiac events in patients undergoing coronary artery bypass grafting: Results of the EXPEDITION study. The Annals of Thoracic Surgery, 2008, 85(4), 1261-1270. DOI: 10.1016/j.athoracsur.2007.10.054

[139] Mitchell W, Pharaoh G, Tyshkovskiy A, Campbell M, Marcinek DJ, Gladyshev VN. The mitochondria-targeted peptide therapeutic elamipretide improves cardiac and skeletal muscle function during aging without detectable changes in tissue epigenetic or transcriptomic age. Aging Cell, 2025, 24(6), e70026. DOI: 10.1111/acel.70026

[140] Ball M, van Bergen NJ, Compton AG, Thorburn DR, Rahman S, Christodoulou J. Therapies for mitochondrial disease: Past, present, and future. Journal of Inherited Metabolic Disease, 2025, 48(4), e70065. DOI: 10.1002/jimd.70065

[141] Nahar N, Sohag MSU. Advancements in mitochondrial-targeted antioxidants: Organelle-specific drug delivery for disease management. Advances in Redox Research, 2025, 100142. DOI: 10.1016/j.arres.2025.100142

[142] Fatehi Hassanabad A, Zarzycki AN, Patel VB, Fedak PWM. Current concepts in the epigenetic regulation of cardiac fibrosis. Cardiovascular Pathology, 2024, 73, 107673. DOI: 10.1016/j.carpath.2024.107673

[143] Yan H, Yin Y, Zhou Y, Li Z, Li Y, Ren L, et al. Regulation of cardiovascular diseases by histone deacetylases and NADPH oxidases. Redox Biology, 2024, 77, 103379. DOI: 10.1016/j.redox.2024.103379

[144] Desroche LM, Trimaille A, Garban T, Bouleti C. Artificial intelligence in cardiovascular medicine: An exoskeleton for perception, reasoning and action. Archives of Cardiovascular Diseases, 2025, 118(11), 613-620. DOI: 10.1016/j.acvd.2025.07.012

[145] Khoshfekr Rudsari H, Tseng B, Zhu H, Song L, Gu C, Roy A, et al. Digital twins in healthcare: A comprehensive review and future directions. Frontiers in Digital Health, 2025, 7, 1633539. DOI: 10.3389/fdgth.2025.1633539

[146] Mirzoyev U, Mirzoyev K. Digital medicine in the management of heart failure: From reactive care to predictive, pathophysiology-driven strategies. Healthcare, 2026, 14(4), 455. DOI: 10.3390/healthcare14040455

[147] Gaoudam N, Sakhamudi SK, Kamal B, Addla N, Reddy EP, Ambala M, et al. Wearable devices and ai-driven remote monitoring in cardiovascular medicine: A narrative review. Cureus, 2025, 17(8), e90208. DOI: 10.7759/cureus.90208

[148] Lin M, Guo J, Gu Z, Tang W, Tao H, You S, et al. Machine learning and multi-omics integration: Advancing cardiovascular translational research and clinical practice. Journal of Translational Medicine, 2025, 23(1), 388. DOI: 10.1186/s12967-025-06425-2

[149] Cunningham JW, Abraham WT, Bhatt AS, Dunn J, Felker GM, Jain SS, et al. Artificial intelligence in cardiovascular clinical trials. Journal of the American College of Cardiology, 2024, 84(20), 2051-2062. DOI: 10.1016/j.jacc.2024.08.069

[150] Xu Q, Li Y, Zhu M, Cai Y, Cheng X, Wang W, et al. Precision cardiovascular medicine with big data and AI. npj Digital Medicine, 2026. DOI: 10.1038/s41746-026-02538-0

[151] Marei I, Abu Samaan T, Al-Quradaghi MA, Farah AA, Mahmud SH, Ding H, et al. 3D tissue-engineered vascular drug screening platforms: Promise and considerations. Frontiers in Cardiovascular Medicine, 2022, 9, 847554. DOI: 10.3389/fcvm.2022.847554

[152] Shen D, Wang Y, Zhou X, Xu Z, Zhou J, Balasubramanian V, et al. The application of 3d printing in cardiac patch manufacture. Advanced Healthcare Materials, 2026, e04250. DOI: 10.1002/adhm.202504250

[153] Osório TG, Pavesi E, El-Ardat KA, Qureshi N, Cassidy L, St John TL, et al. Single-cell multi-omics for precision cardiovascular and longevity medicine: From methods to clinical translation. Frontiers in Aging, 2025, 6, 1656727. DOI: 10.3389/fragi.2025.1656727

[154] Costa F, Gomez Doblas JJ, Díaz Expósito A, Adamo M, D'Ascenzo F, Kołtowski L, et al. Artificial intelligence in cardiovascular pharmacotherapy: Applications and perspectives. European Heart Journal, 2025, 46(37), 3616-3627. DOI: 10.1093/eurheartj/ehaf474

[155] Kolk MZH, Ruipérez-Campillo S, Wilde AAM, Knops RE, Narayan SM, Tjong FVY. Prediction of sudden cardiac death using artificial intelligence: Current status and future directions. Heart Rhythm, 2025, 22(3), 756-766. DOI: 10.1016/j.hrthm.2024.09.003

[156] Magouliotis DE, Sicouri N, Ramlawi L, Baudo M, Androutsopoulou V, Sicouri S. Artificial intelligence in adult cardiovascular medicine and surgery: Real-world deployments and outcomes. Journal of Personalized Medicine, 2026, 16(2), 69. DOI: 10.3390/jpm16020069

[157] Bartusik-Aebisher D, Podgórski R, Serafin I, Aebisher D. Targeted and biomimetic nanoparticles for atherosclerosis therapy: A review of emerging strategies. Biomedicines, 2025, 13(7), 1720. DOI: 10.3390/biomedicines13071720

[158] Jha G, Sharma RB, Sridhar S, Hayagreev D, Sinha T, Kaur H, et al. Nanoparticle-based therapies for cardiovascular diseases: A literature review of recent advances and clinical potential. Cureus, 2024, 16(10), e72808. DOI: 10.7759/cureus.72808

[159] Ćurčić M, Hadžić B, Gilić M, Lazarević Z, Ilić A. $BaTiO_3$ nanocarriers: Advancing targeted therapies with smart drug release. Pharmaceutics, 2025, 17(9), 1203. DOI: 10.3390/pharmaceutics17091203

[160] Desai N, Rana D, Patel M, Bajwa N, Prasad R, Vora LK. Nanoparticle therapeutics in clinical perspective: Classification, marketed products, and regulatory landscape. Small, 2025, 21(29), e2502315. DOI: 10.1002/smll.202502315

[161] Vo QD, Saito Y, Nakamura K, Iida T, Yuasa S. Induced pluripotent stem cell-derived cardiomyocytes therapy for ischemic heart disease in animal model: A meta-analysis. International Journal of Molecular Sciences, 2024, 25(2), 987. DOI: 10.3390/ijms25020987

[162] Kim WJ, Yoon JW, Sim WS, Kim YS, Chae S, Choi B, et al. Bioprinting of cardiac patches with gold-nanowires and tri-culture system for the treatment of myocardial infarction. Chemical Engineering Journal, 2025, 171562. DOI: 10.1016/j.cej.2025.171562

[163] Dashti M, Mohammaddust Sarab M, Shad F, Dehnavi S. CRISPR-mediated engineering of mesenchymal stromal/stem cells: A summary of recent progress in immunological applications for regenerative medicine and cancer therapy. Stem Cell Research & Therapy, 2025, 16(1), 592. DOI: 10.1186/s13287-025-04723-6

[164] Rayat Pisheh H, Sani M. Mesenchymal stem cells derived exosomes: A new era in cardiac regeneration. Stem Cell Research & Therapy, 2025, 16(1), 16. DOI: 10.1186/s13287-024-04123-2

[165] Jebran AF, Seidler T, Tiburcy M, Daskalaki M, Kutschka I, Fujita B, et al. Engineered heart muscle allografts for heart repair in primates and humans. Nature, 2025, 639(8054), 503-511. DOI: 10.1038/s41586-024-08463-0

[166] Leon-Mimila P, Wang J, Huertas-Vazquez A. Relevance of multi-omics studies in cardiovascular diseases. Frontiers in Cardiovascular Medicine, 2019, 6, 91. DOI: 10.3389/fcvm.2019.00091

[167] Joshi A, Rienks M, Theofilatos K, Mayr M. Systems biology in cardiovascular disease: A multiomics approach. Nature Reviews Cardiology, 2021, 18(5), 313-330. DOI: 10.1038/s41569-020-00477-1

[168] de Ruiter SC, van Vugt M, Finan C, Grobbee DE, de Kleijn DPV, Pasterkamp G, et al. Integrating multi-modal omics to identify therapeutic atherosclerosis pathways for coronary heart disease. EBioMedicine, 2025, 121, 105966. DOI: 10.1016/j.ebiom.2025.105966

[169] Ritchie SC, Jiang X, Pennells L, Xu Y, Coffey C, Liu Y, et al. Combined clinical, metabolomic, and polygenic scores for cardiovascular risk prediction. European Heart Journal, 2025, ehaf947. DOI: 10.1093/eurheartj/ehaf947

[170] Mocumbi AO. Cardiovascular health care in low- and middle-income countries. Circulation, 2024, 149(8), 557-559. DOI: 10.1161/CIRCULATIONAHA.123.065717

[171] Soni A, Karna S, Patel H, Fahey N, Raithatha S, Handorf A, et al. Study protocol for smartphone monitoring for atrial fibrillation in real-time in India (SMART-India): A community-based screening and referral programme. BMJ Open, 2017, 7(12), e017668. DOI: 10.1136/bmjopen-2017-017668

[172] Tolu-Akinnawo O, Ezekwueme F, Awoyemi T. Telemedicine in cardiology: Enhancing access to care and improving patient outcomes. Cureus, 2024, 16(6), e62852. DOI: 10.7759/cureus.62852

[173] Hon JJ, Carr-White G. The digital divide in cardiovascular care: Who gets left behind? European Heart Journal-Digital Health, 2026, 7(2), ztag011. DOI: 10.1093/ehjdh/ztag011

[174] Sharma PK, Chen CY. AI-integrated micro/nanorobots for biomedical applications: Recent advances in design, fabrication, and functions. Biosensors, 2025, 15(12), 793. DOI: 10.3390/bios15120793