Aging and Disease
www.aginganddisease.org
Early access date: August 1, 2026
http://dx.doi.org/10.14336/AD.2025.1308

Review

Metformin: A Promising Candidate for Slowing the Progression of Cardiovascular Aging

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[Received December 21, 2025; Revised July 19, 2026; Accepted July 22, 2026]

ABSTRACT: Cardiovascular aging, characterized by endothelial dysfunction, arterial stiffening, and myocardial remodeling, is a major contributor to the development of age-related cardiovascular disease. Metformin, a first-line therapy for type 2 diabetes, has attracted interest as a promising geroprotective agent due to its ability to target several fundamental aging pathways. Mechanism: Beyond glucose-lowering effects, metformin may confer cardiovascular benefits through activation of AMP-activated protein kinase and inhibition of mitochondrial complex I. Preclinical work suggests these pathways enhance mitochondrial biogenesis, reduce oxidative stress, promote autophagy, and suppress chronic inflammation. Furthermore, metformin has been reported to modulate epigenetic clocks and support genomic stability, potentially mitigating several hallmarks of aging. Clinical Evidence: Although preclinical evidence is substantial, clinical findings remain heterogeneous. Observational studies and trials like UKPDS suggest cardiovascular benefits, whereas randomized controlled trials (RCTs) such as TAYSIDE, GIPS-III, REMOVAL and GOMET yielded inconsistent results for both clinical and surrogate cardiovascular endpoints. Result interpretations are often limited by relatively small sample sizes and short follow-up durations. Sex Differences and Limitations: Emerging evidence suggests sexual dimorphism in metformin responses, potentially influenced by hormonal status and pharmacokinetics. Additional challenges include the hormetic dose-response, the heterogeneity and frailty of older populations, and the absence of validated aging-specific cardiovascular endpoints. Metformin remains a promising candidate to mitigate cardiovascular aging. However, definitive conclusions regarding its efficacy in non-diabetic older adults will require large-scale, long-term RCTs incorporating aging-related biomarkers and stratification according to sex and metabolic status.

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Keywords: metformin, cardiovascular aging, molecular mechanisms, oxidative stress, autophagy

1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of mortality globally, accounting for nearly 18 million deaths annually [1]. Aging is a major risk factor for CVD development, with epidemiological studies indicating that adults over 65 years have a tenfold higher incidence of heart failure than younger individuals [2]. Age-associated cardiovascular changes—characterized by endothelial dysfunction, arterial stiffening, and mitochondrial impairment—contribute to pathogenesis of atherosclerosis, heart failure, and hypertension [3]. By 2050, more than one-fifth of the global population is projected to be over 60 years of age, underscoring the growing socioeconomic burden of age-related cardiovascular disorders. Despite this challenge, no approved therapy specifically targets the underlying processes of cardiovascular aging.

Metformin, a biguanide derivative first synthesized in 1922 and clinically introduced in the 1950s, remains the cornerstone therapy for type 2 diabetes mellitus (T2DM). Its primary pharmacological action involves suppressing hepatic gluconeogenesis and improvement of peripheral insulin sensitivity [4]. Beyond glycemic control, metformin influences multiple cellular pathways, including inhibition of mitochondrial complex I and subsequent AMP-activated protein kinase (AMPK) activation, resulting in broad metabolic adaptations. Importantly, the 10-year post-trial monitoring of the UK Prospective Diabetes Study (UKPDS 80) reported sustained cardiovascular benefits associated with early metformin use in overweight patients with T2DM, including a 33% reduction in myocardial infarction risk compared with conventional dietary therapy, despite the attenuation of glycemic differences over time [5]. Moreover, a Mendelian randomization study suggested that metformin-related pathways may exert cardioprotective effects in nondiabetic individuals, potentially through improving body weight and blood pressure maintenance [6]. However, these findings require further validation in adequately powered clinical trials. Collectively, these observations raise a critical question: can metformin attenuate cardiovascular aging independently of its glucose-lowering effects?

Accumulating preclinical and clinical evidence has identified metformin as a potential geroprotective agent. Its anti-inflammatory, antioxidant, and autophagy-enhancing properties have been shown to modulate pathways linked to several hallmarks of aging in experimental models [7, 8]. In animal and *ex vivo* human vascular studies, metformin improved vascular function and reduced arterial stiffness [9]. Proposed mechanisms involve reducing vascular reactive oxygen species (ROS) production, upregulating endothelial nitric oxide synthase (eNOS) to improve endothelium-dependent vasodilation, and enhancing antioxidant defenses through pathways involving AMPK activation [10]. Metformin has also been reported to decrease infarct size and promote contractile recovery in aging hearts [11]. In humans, the pilot randomized controlled Metformin in Longevity Study (MILES) provided evidence that metformin modulates aging-related molecular pathways [12]. A cross-sectional T2DM study further suggests that metformin use may improve endothelial function and reduce inflammatory markers [13]. Given its established safety profile, low-cost, and potential to target aging-related biological processes, metformin warrants further investigation as a candidate intervention for cardiovascular aging.

In this review, we summarize age-related cardiovascular alterations and examine the mechanisms through which metformin may mitigate these changes. We further evaluate the current clinical evidence and discuss key challenges and considerations for translating these findings into interventions targeting cardiovascular aging. Details on the literature retrieval strategy are provided in the Supplementary Materials. Additionally, reference lists of relevant publications were manually screened to identify potentially eligible studies.

2. Age-Related Cardiovascular Alterations

Cardiovascular aging encompasses a series of interconnected biological processes that progressively impair cardiac and vascular structure and function. Hallmarks include mitochondrial redox imbalance, dysregulated signaling pathways, defective autophagy, chronic low-grade inflammation, epigenetic modifications, and genomic instability. Collectively, these processes contribute to four major manifestations of cardiovascular aging: myocardial remodeling, atherosclerosis and arterial stiffening, neuroendocrine dysregulation, and degeneration of the cardiac conduction system (Fig. 1).

2.1 Myocardial Remodeling

Myocardial remodeling describes the structural, functional, and molecular adaptations in the heart in response to physiological or pathological stimuli. Key features include cardiomyocyte hypertrophy, interstitial fibrosis, and progressive cell loss, collectively reducing

myocardial compliance and cardiac reserve in older adults [14]. Cardiac hypertrophy initially serves as an adaptive response to pressure or volume overload by increasing myocardial mass and preserving contractile function [15]. Over time, however, sustained hypertrophy is associated with increased oxygen demand and impaired myocardial energy metabolism, contributing to diastolic dysfunction and eventual heart failure [16, 17]. Another hallmark of cardiac aging is interstitial fibrosis, characterized by excessive collagen deposition within the myocardium. Fibrosis disrupts both mechanical and electrical properties of cardiac tissue [18, 19], contributing to the development of heart failure with preserved ejection fraction (HFpEF) [17]. Fibrotic regions also create electrophysiological heterogeneity that can facilitate re-entrant circuits and increase susceptibility to arrhythmias [20].

Cardiomyocyte loss further accelerates age-related remodeling. Apoptosis increases with age, partly owing to increased vulnerability to cellular stressors, including mitochondrial ROS accumulation [21]. Concurrently, the regenerative capability of the myocardium declines substantially. Studies of human cardiomyocytes estimate that annual renewal rates decrease from 1% to 0.45% between the ages of 25 to 75 [22].

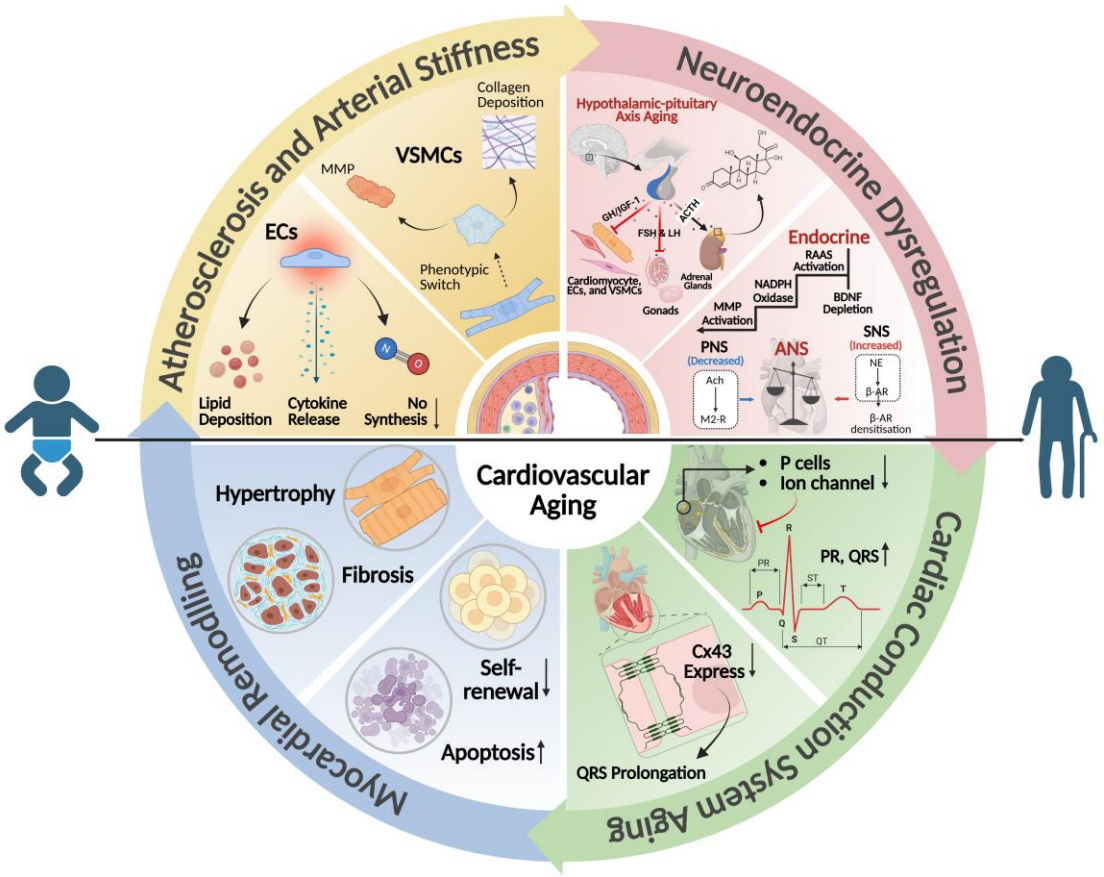

Figure 1. Age-related structural and functional alterations in the cardiovascular system. Key aging-associated changes (middle ring) include the following: **Atherosclerosis and Arterial Stiffness:** Dysfunctional endothelial cells (ECs) reduce nitric oxide (NO) synthesis, increase cytokine release, and promote lipid deposition. The phenotypic switch in vascular smooth muscle cells (VSMCs) from a contractile to a synthetic state, characterized by increased secretion of MMPs and collagen deposition, leads to arterial stiffening. **Neuroendocrine Dysregulation:** Aging of the hypothalamic-pituitary axis leads to progressive degeneration of the hypothalamic-pituitary-growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis, impairs the regenerative and endothelial repair capacity of cardiomyocytes, ECs and VSMCs. It also causes deterioration of the hypothalamic-pituitary-gonadal axis with reduced gonadal sensitivity to luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Meanwhile, hyperactivation of the hypothalamic-pituitary-adrenal axis elevates cortisol levels; this axis acts as the upstream master hub regulating systemic cardiovascular aging; The 'balance scale' icon depicts autonomic dysfunction: Sympathetic overactivity elevates norepinephrine (NE) and β-adrenergic receptor (β-AR) desensitization, whereas parasympathetic decline reduces acetylcholine (ACh)/M2 signaling. Endocrine shifts, including renin-angiotensin-aldosterone system (RAAS) activation and brain-derived neurotrophic factor (BDNF) depletion, exacerbate oxidative stress (NADPH oxidase) and fibrosis (MMP activation). **Cardiac Conduction System Aging:** Loss of sinoatrial nodal pacemaker cells (P cells) and downregulated ion channel expression exert detrimental cardiac effects; the electrocardiogram manifests as prolonged PR interval and QRS complex. The expression of Connexin

43 (Cx43), the core gap junction protein in ventricular myocardium, declines with aging, hindering intercellular electrical conduction and slowing depolarization wave (QRS complex) propagation, which predisposes the elderly to arrhythmias. **Myocardial Remodeling:** Cardiomyocyte hypertrophy, fibrosis, increased apoptosis, and reduced self-renewal potential collectively impair cardiac compliance and functional reserve. VSMCs = Vascular Smooth Muscle Cells, NO = Nitric Oxide, ECs = Endothelial Cells, MMP = Matrix Metalloproteinase, GH = Growth Hormone, IGF-1 = Insulin-like Growth Factor 1, LH = Luteinizing Hormone, FSH = Follicle-Stimulating Hormone, ANS = Autonomic Nervous System, SNS = Sympathetic Nervous System, PNS = Parasympathetic Nervous System, M2-R = M2 Receptor, BDNF = Brain-Derived Neurotrophic Factor, RAAS = Renin-Angiotensin-Aldosterone System, NADPH = Nicotinamide Adenine Dinucleotide Phosphate, P cells = Sinoatrial Nodal Pacemaker Cells, Cx43 = Connexin 43.

2.2 Atherosclerosis and Arterial Stiffening

Atherosclerosis and arterial stiffening are major structural manifestations of cardiovascular aging and contribute substantially to diseases such as coronary artery disease (CAD) and heart failure [23]. These processes develop through complex interactions among vascular cell populations, particularly endothelial cells (ECs) and vascular smooth muscle cells (VSMCs). Endothelial dysfunction is a central early event in both conditions. It promotes lipid accumulation and vascular inflammation, facilitating atherosclerotic plaque formation. Concurrently, endothelial dysfunction alters vascular wall composition through alterations in elastin and collagen content, thereby increasing arterial stiffness. Reduced nitric oxide (NO) bioavailability further impairs vasodilation and exacerbates vascular dysfunction [24].

VSMCs contribute to disease progression through age-related phenotypic switching driven by oxidative stress, inflammation, and metabolic disturbances [25]. In atherosclerosis, VSMCs transition from a contractile phenotype to multiple pathological states that influence plaque growth and stability. For example, selective deletion of *Klf4* in VSMCs attenuated diet-induced atherosclerosis and improved plaque stability in *ApoE*$^{-/-}$ mice by limiting phenotypic switching [26]. Similarly, single-cell sequencing studies revealed that VSMC-specific deletion of transcription factor 21 (*TCF21*) reduced phenotypic switching and fibromyocyte formation within lesions. Consistent with these findings, higher *TCF21* expression in human coronary vessels has been associated with lower CAD risk [27].

VSMCs also contribute to arterial stiffening through transition to a synthetic phenotype characterized by increased production of collagen and matrix metalloproteinases (MMPs). These changes remodel the extracellular matrix, reduce arterial compliance, and are particularly prominent following vascular injury contributing to cardiovascular aging [10, 28].

2.3 Neuroendocrine Dysregulation

Neuroendocrine regulation is essential for maintaining cardiovascular homeostasis through coordinated neural and hormonal signaling. Aging is accompanied by progressive neuroendocrine dysregulation, which contributes to cardiovascular decline [29].

A key hallmark of cardiovascular aging is autonomic nervous system (ANS) imbalance, characterized by increased sympathetic nervous system (SNS) activity and reduced parasympathetic tone. This shift is associated with elevated heart rate, hypertension, and cardiac rhythm disturbances. In a radiotracer study, older adults (64–74 years, mean 69 years) exhibited significantly higher arterialized plasma norepinephrine (NE) levels than younger individuals (19–26 years, mean 22.5 years) (217 ± 13 vs. 149 ± 12 pg/mL, $P < 0.005$), accompanied by reduced NE clearance (1.38 ± 0.06 vs. 1.64 ± 0.10 L/min·m²; $P < 0.05$) [30]. Chronic sympathetic hyperactivation is linked to age-related β-adrenergic system degeneration. A postmortem study of 26 human hearts (age ranging 1–71 years) revealed significant declines in cardiac β-adrenergic receptor function with age, together with reduced receptor affinity and impaired downstream G-protein signaling [31].

Parasympathetic function similarly declines during aging. Deep breathing, Valsalva maneuver, and standing tests revealed significantly reduced parasympathetic responses in individuals aged 60–74 years compared with younger controls (18–33 years), with little additional decline after 75 years (75–90) [32]. Supporting these findings, a recent mouse study found reduced Schwann cell numbers and parasympathetic nerve fibers in aged hearts, accompanied by lower muscarinic acetylcholine receptor M2 (M2R) expression and increased vulnerability to ventricular arrhythmias [33].

Age-related ANS dysfunction is also associated with dysregulation of the hypothalamic-pituitary axis, a central regulator of systemic homeostasis. Progressive hypothalamic dysfunction disrupts endocrine feedback mechanisms, promoting hormonal imbalances, chronic low-grade inflammation, sympathetic overactivity, and metabolic disorders that contribute to cardiovascular aging. Hyperactivity of the hypothalamic-pituitary-adrenal axis characterized by elevated basal cortisol levels and impaired circadian regulation, has been associated with VSMC proliferation, extracellular matrix accumulation, vascular inflammation, and reduced

endothelial NO production [34, 35]. These age-dependent changes may contribute to endothelial dysfunction, arterial stiffness, and hypertensive vascular remodeling.

The hypothalamic-pituitary-growth hormone/insulin-like growth factor 1 (GH/IGF-1) axis also undergoes age-related decline. Reduced GH secretion and lower IGF-1 availability may compromise endothelial repair and promote apoptosis in cardiomyocytes, VSMCs, and ECs, thereby contributing to cardiovascular dysfunction [36]. Likewise, progressive deterioration of the hypothalamic-pituitary-gonadal axis results in declining sex hormone levels. Depleted testosterone and estrogen may diminish their vasoprotective, anti-fibrotic, antioxidant effects, potentially rendering the aged cardiovascular system vulnerable to atherosclerosis, myocardial fibrosis, myocardial infarction, and cardiac arrhythmias [37, 38]. Collectively, dysfunction across these endocrine axes may reinforce inflammation, cellular senescence, and autonomic imbalance during cardiovascular aging.

Beyond autonomic dysregulation, other endocrine pathways have been implicated in cardiovascular aging. Brain-derived neurotrophic factor (BDNF), for example, appears closely linked to age-related neural remodeling. Compared to 3-month-old rats, 24-month-old rats exhibited reduced autonomic nerve density and lower expression of growth-associated protein 43 and BDNF in cardiac tissue [39]. Consistent findings were observed in *in vitro* experiments using serum collected from animals of different ages. In addition, increased activation of the renin–angiotensin–aldosterone system (RAAS) is a common feature of cardiovascular aging. A rat study suggested that RAAS activation promotes age-related cardiovascular remodeling through nicotinamide adenine dinucleotide phosphate oxidase (Nox2)-mediated increase in MMP activity, fibrosis, and cardiomyocyte hypertrophy [40]. Importantly, RAAS activation may be further amplified by hypothalamic-pituitary dysfunction, creating a self-enforcing cycle of cardiovascular deterioration.

2.4 Cardiac Conduction System Aging

The cardiac conduction system coordinates the propagation of electrical impulses from the sinoatrial node (SAN) through the atrioventricular conduction network to ensure synchronized myocardial contraction. Aging is associated with progressive degeneration of this system, including reductions in SAN pacemaker cell numbers and altered ion channel expression [41]. Age-related myocardial remodeling, atherosclerosis, and arterial stiffening further impair conduction function. Together, these changes reduce automaticity and slow impulse propagation, often manifesting clinically as bradyarrhythmias. Electrocardiographic findings may indicate mild prolongation of the PR interval and QRS complex, as well as leftward deviation of the QRS axis [42]. Connexin 43 (Cx43), the principal gap-junction protein in ventricular myocardium, also declines with age. Reduced Cx43 expression impairs intercellular electrical coupling, slowing conduction velocity and potentially increasing susceptibility to age-related arrhythmias [43].

3. Aging-Related Cardiovascular Diseases and Secondary Pathological Processes

This section summarizes major cardiovascular diseases associated with aging and key secondary pathological processes that arise during acute cardiovascular events, with particular emphasis on their epidemiology and underlying mechanisms.

3.1 Coronary Artery Disease and Peripheral Arterial Disease

CAD and peripheral arterial disease (PAD) are vascular manifestations of atherosclerosis occurring in different arterial beds [17, 44]. In CAD, atherosclerotic lesions narrow or obstruct blood flow, leading to myocardial ischemia or infarction. In PAD, systemic atherosclerosis primarily affects lower extremity arteries, causing tissue ischemia and functional impairment.

Aging is a major driver of atherosclerotic disease. Using the Coronary Heart Disease Policy Model and United States census data, one study projected that the prevalence of coronary heart disease would increase by 47% between 2010 and 2040, with a 56% increase in deaths among individuals aged 65-84 years [45]. Similarly, an integrated epidemiology review incorporating the Framingham, Rotterdam, and Women's Health and Aging studies reported that PAD prevalence is uncommon before age 50 but exceeds 10% among individuals aged 60-70 years and approaches 20% by age 80 [46]. The same review identified diabetes, hypertension, and dyslipidemia as major correlates of PAD, highlighting the interactions between aging and cardiometabolic risk factors [46].

Vascular calcification is an important pathological contributor to both CAD and PAD. Based on its anatomical location, vascular calcification is classified as either intimal or medial [44, 47]. Intimal calcification typically occurs within atherosclerotic plaques through processes resembling chondrogenic differentiation, whereas medial calcification develops independently of atherosclerosis through osteogenic signaling and contributes to arterial stiffening. Although both forms occur in CAD and PAD, medial calcification appears to play a dominant role in PAD [48].

3.2 Hypertensive Heart Disease

Hypertension is strongly associated with advancing age and remains a major contributor to cardiovascular morbidity worldwide. In the United States, hypertension prevalence progressively increases from 7.3% among adults aged 18–39 years to 65.6% among those aged ≥60 years [49]. Similar age-dependent trends have been reported in China, where prevalence rises from 7.7% among individuals aged 18–24 years to 74.0% among those aged ≥75 years [50]. This increasing burden of hypertension contributes substantially to the development of hypertensive heart disease (HHD).

HHD encompasses structural and functional cardiac alterations resulting from chronic elevation of blood pressure. Major features include left ventricular hypertrophy, myocardial fibrosis, and remodeling of the aorta and resistance arterioles. Ventricular wall thickening impairs diastolic filling and promotes diastolic dysfunction, while increased myocardial mass elevates cardiac workload. Over time, these pathological changes increase the risk of heart failure, particularly HFpEF [51]. Older adults with hypertension also experience higher rates of atrial fibrillation, ventricular arrhythmias [52], and myocardial ischemia [53], contributing to substantial morbidity and reduced quality of life.

3.3 Valvular Heart Disease

The prevalence of valvular heart disease increases markedly with age. In a population-based study of 11,911 participants, prevalence rose from 0.7% (95% CI 0.5–1.0) among individuals aged 18-44 years to 13.3% (95% CI 11.7–15.0) among those aged ≥75 years ($P < 0.0001$) [54]. Likewise, a prospective UK study involving 4,237 participants found that 28.2% had valvular heart disease, with age emerging as the strongest predictor of clinically significant disease (OR=1.07, 95% CI 1.05–1.09, $P < 0.001$) [55].

Degenerative valve disease, including aortic stenosis and mitral annular calcification, represents the predominant form of age-related valvular disease. Similar to atherosclerosis, its pathology is characterized by basement membrane disruption, inflammatory cell infiltration, and lipid accumulation [56, 57]. These changes are mediated by valve interstitial cells (VICs), the principal cellular component of cardiac valves. Bone morphogenetic proteins (BMPs), particularly BMP-2 and BMP-4, promote osteogenic differentiation of VICs and contribute to valvular fibrosis and calcification [58]. Extracellular matrix remodeling further accelerates calcification, partly through Cadherin-11 signaling [59] and increased expression of fibronectin and laminin [60].

3.4 Diabetic Cardiomyopathy

Diabetic cardiomyopathy (DbCM) is a diabetes-associated myocardial disorder whose prevalence increases with age. Aging not only increases cardiovascular risk but also promotes the development of T2DM, thereby amplifying the burden of diabetes-associated cardiac dysfunction.

A population-based study of 2,900 diabetic patients (mean age 72, range 40–85) reported that more than 60% were older than 70 years [61]. Compared with patients aged 40–60 years, DbCM prevalence was 25%, 15%, and 7% higher among those older than 70 years under the least restrictive, intermediate, and most restrictive criteria, respectively [61]. Consistent with these findings, another study reported heart failure prevalence rates of 3.2% in normoglycemic individuals, 6.0% in those with abnormal glucose regulation (AGR), and 11.8% in T2DM patients. Corresponding odds ratios for heart failure were 1.7 (95% CI 1.4–2.1) and 2.8 (95% CI 2.2–3.6) for AGR and T2DM patients, respectively [62].

Pathologically, DbCM is characterized by myocardial remodeling and impaired diastolic relaxation that progressively evolves into systolic dysfunction and heart failure [63]. These abnormalities may be more pronounced in older diabetic patients with concurrent hypertension, in whom overactivation of the RAAS, especially elevated angiotensin II levels, may exacerbate cardiomyocyte oxidative stress and injury [64].

3.5 Ischemia-Reperfusion Injury: A Secondary Pathological Cascade

Ischemia-reperfusion injury (IRI) is not a distinct cardiovascular disease but a secondary pathological process that occurs when blood flow is restored following a period of ischemia. It frequently complicates multiple age-related cardiovascular disorders, particularly acute myocardial infarction.

IRI develops via two sequential phases. During ischemia, reduced blood flow induces cellular stress and metabolic dysfunction. Subsequent reperfusion paradoxically triggers further tissue injury through mechanisms including oxidative stress, mitochondrial dysfunction, opening of the mitochondrial permeability transition pore (mPTP), inflammatory activation involving nuclear factor kappa B (NF-κB), immune cell infiltration, and apoptosis [65]. Although studied most in the heart, IRI also affects the brain, kidneys, and other organs. Direct epidemiological evidence linking aging to IRI remains limited. Nevertheless, experimental studies consistently demonstrate that aging increases both susceptibility to IRI [66] and the severity of tissue injury following ischemia-reperfusion events [67-70].

4. Metformin and Age-Related Metabolic-Hemodynamic Dysregulation

The pleiotropic metabolic and cardiovascular effects of metformin are largely mediated through activation of AMPK. By inhibiting mitochondrial respiratory chain complex I, metformin decreases cellular ATP production, increases the AMP/ATP ratio, and activates AMPK, a central regulator of cellular energy homeostasis [71, 72]. Because aging is frequently accompanied by hyperglycemia, dyslipidemia, and insulin resistance, metformin may mitigate age-associated metabolic disturbances while conferring additional cardiovascular benefits through coordinated regulation of glucose and lipid metabolism. Key mechanisms are summarized in Figure 2.

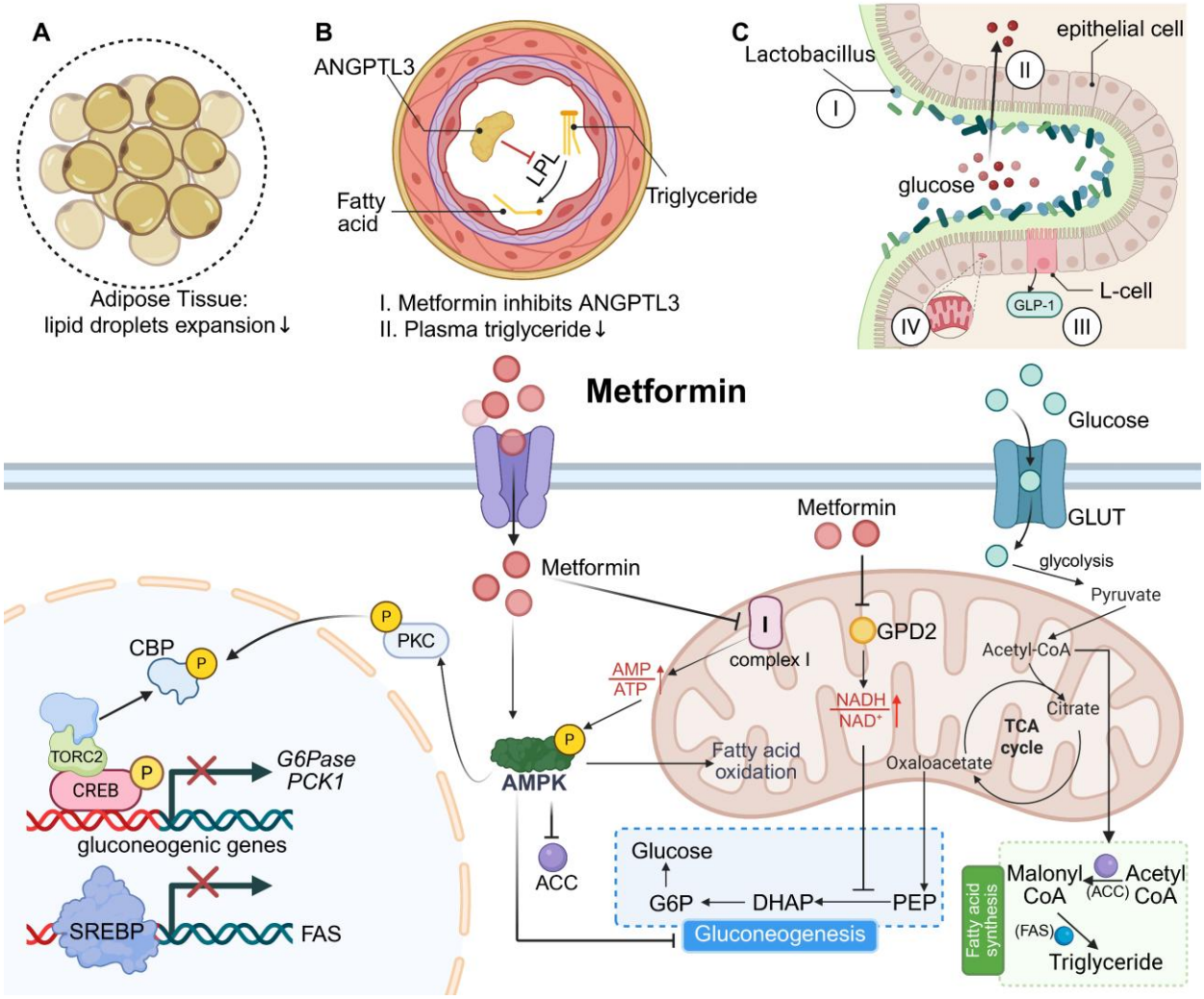

Figure 2. Mechanisms of metformin in blood glucose and lipid regulation. The figure categorizes metformin's effects into systemic level modulation (A-C) and intracellular molecular signaling (bottom). **Systemic Regulation (A-C): (A) Adipose tissue:** Metformin inhibits lipid droplet fusion and lipolysis, thereby reducing the release of free fatty acids. **(B) Circulation:** Metformin lowers plasma triglyceride levels by enhancing lipoprotein lipase (LPL) by inhibiting angiopoietin-like protein 3 (ANGPTL3). **(C) Gut:** In the intestine, metformin (I) increases *Lactobacillus* abundance (II) inhibits glucose transport; (III) promotes glucagon-like peptide-1 (GLP-1) secretion; and (IV) enhances local enterocyte glucose metabolism. **Intracellular signaling (bottom):** The central mechanism involves metformin inhibition of mitochondrial complex I, thus reducing ATP production and elevating the cellular AMP/ATP ratio. The elevated AMP/ATP ratio activates **AMP-activated protein kinase (AMPK)-dependent pathways: In the nucleus,** AMPK phosphorylates the CREB-CBP-TORC2 complex, disrupting its assembly and suppressing the expression of hepatic gluconeogenic enzyme (G6pase, Pck1) genes. AMPK also downregulates SREBP-1 and fatty acid synthase (FAS), thereby inhibiting lipogenesis. **In the cytosol:** activated AMPK inhibits ACC activity via phosphorylation, leading to reduced malonyl-CoA synthesis, thereby promoting fatty acid oxidation, and suppressing fatty acid synthesis. **At the membrane:** Activated AMPK accelerates GLUT4 translocation. **Redox-dependent pathway:** independent of AMPK, metformin inhibits mitochondrial glycerol-3-phosphate dehydrogenase (GPD2), which increases the NADH/NAD^+ ratio, leading to inhibition of gluconeogenesis. AMP = Adenosine Monophosphate, AMPK = AMP-Activated Protein Kinase, ANGPTL3 = Angiopoietin-like protein 3, ATP = Adenosine Triphosphate, G6pase = Glucose-6-Phosphatase, G6P = glucose-6-phosphate, Pck1 = Phosphoenolpyruvate

Carboxykinase 1, CREB = cAMP Response Element-Binding Protein, PKC = Protein Kinase C, CBP = CREB-Binding Protein, TORC2 = Transducer of Regulated CREB Activity 2, GLUT4 = Glucose Transporter Type 4, GPD2 = Glycerol-3-Phosphate Dehydrogenase 2, NADH = Nicotinamide Adenine Dinucleotide (Reduced), ACC = Acetyl-CoA Carboxylase, SREBP-1 = Sterol Regulatory Element-Binding Protein-1, FAS = Fatty Acid Synthase, LPL = Lipoprotein Lipase, GLP-1 = Glucagon-Like peptide-1, DHAP = Dihydroxyacetone phosphate, PEP = Phosphoenolpyruvate, TCA cycle = Tricarboxylic acid cycle, NAD^+ = Nicotinamide adenine dinucleotide (Oxidized).

4.1 Glucose Regulation

Metformin maintains glucose homeostasis through both AMPK-dependent and complementary AMPK-independent mechanisms that act across the liver, peripheral tissues, and intestine.

In the liver, suppression of hepatic gluconeogenesis is a principal mechanism. Intraduodenal metformin infusions activate AMPK in the duodenal mucosa and decrease hepatic gluconeogenesis in insulin resistant rats [73]. AMPK activation suppresses transcription of gluconeogenic genes, including glucose-6-phosphatase (G6pase) and phosphoenolpyruvate carboxykinase 1 (PCK1), through a pathway dependent on liver kinase B1 (LKB1) [74]. Metformin also inhibits gluconeogenesis via AMPK-independent pathways, including disruption of the CREB-CBP-TORC2 transcriptional complex via atypical protein kinase C (PKC) activation [75] and inhibition of mitochondrial glycerol-3-phosphate dehydrogenase (GPD2) which catalyzes conversion of glycerol-3-phosphate to dihydroxyacetone phosphate (DHAP), altering hepatocellular redox status [76, 77]. Additionally, GPD2 inhibition increases cytosolic $NADH/NAD^+$ ratio which limits glucose production from substrates such as lactate and glycerol [77].

In peripheral tissues, such as adipose and muscle, metformin enhances glucose uptake by promoting glucose transporter type 4 (GLUT4) translocation to the plasma membrane through AMPK-dependent signaling [78, 79]. Consistent with this mechanism, *in vitro* studies have shown increased GLUT4 abundance and glucose uptake in skeletal muscle cells treated with metformin [80].

The intestine is another important target of metformin-induced glucose regulation. Metformin increases intestinal glucose utilization through upregulation of glycolytic genes and glucose transporter type 1 (GLUT1) [81, 82], while suppressing transcellular glucose transport and enhancing glucagon-like peptide 1 (GLP-1) secretion [83, 84]. Additionally, metformin influences the gut microbiota and may restore intestinal glucose sensing through increases in *Lactobacillus* abundance and sodium-glucose cotransporter 1 (SGLT1) expression [85].

Collectively, metformin lowers glucose levels by: (1) suppressing hepatic gluconeogenesis; (2) enhancing peripheral glucose utilization; (3) modulating intestinal glucose handling; (4) promoting GLP-1 secretion; and (5) altering the gut microbiota composition.

4.2 Lipid Regulation

Metformin also regulates lipid metabolism primarily through AMPK signaling. Activation of AMPK inhibits acetyl-CoA carboxylase (ACC), reducing malonyl-CoA synthesis, and relieving inhibition of carnitine palmitoyltransferase 1, thereby facilitating fatty acid transport into mitochondria and enhancing β-oxidation [86]. AMPK activation additionally suppresses sterol regulatory element-binding protein 1 (SREBP-1) and downstream fatty acid synthase (FAS) expression, reducing lipid synthesis [86, 87].

In adipocytes, metformin limits lipid droplet expansion through downregulation of cell death-inducing DFFA-like effector c and related regulatory pathways via AMPK activation [88]. It also suppresses adipose tissue lipolysis in patients with T2DM [89], reducing the availability of substrates for hepatic gluconeogenesis. Moreover, metformin has been shown to lower plasma triglyceride levels through inhibition of angiopoietin-like protein 3 (ANGPTL3) and subsequent modulation of lipoprotein lipase (LPL) activity [90]. Together, these effects support a broader role for metformin in correcting age-related metabolic and hemodynamic disturbances that contribute to cardiovascular disease.

5. Cardiovascular Protective Mechanisms of Metformin

The longevity regulatory network proposed by North and Sinclair consists of four interconnected signaling axes: AMPK, mTOR (mechanistic target of rapamycin), sirtuins (SIRTs), and IGF-1 [91]. Interactions among these pathways may underlie the pleiotropic cardiovascular effects of metformin. Their downstream actions can be grouped into six functional domains: mitochondrial protection, antioxidant defense, autophagy modulation, anti-inflammatory effects, maintenance of genomic stability, and epigenetic remodeling (Fig. 3).

5.1 Mitochondrial Protection

Mitochondrial dysfunction is a hallmark of cardiovascular aging and contributes to endothelial dysfunction, myocardial remodeling, and ischemia-reperfusion injury. Consequently, preservation of mitochondrial integrity has emerged as a potential strategy for mitigating cardiovascular aging.

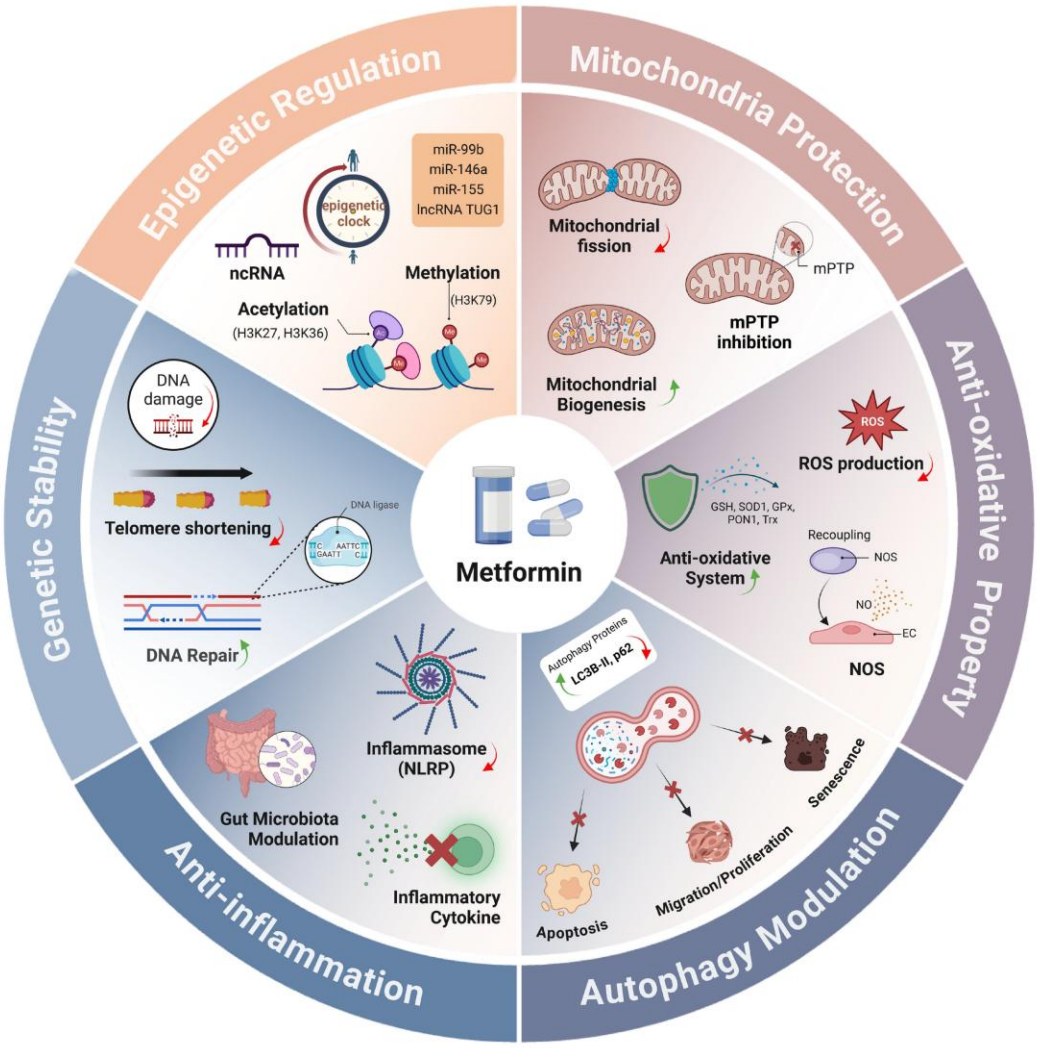

Figure 3. Multifaceted mechanisms of metformin in cardiovascular cell protection. Metformin exerts cardioprotective effects through six interconnected pathways (outer ring): **Mitochondrial Protection:** Metformin protects mitochondria by increasing mitochondrial biogenesis, suppressing mitochondrial fission, and inhibiting mPTP opening. **Antioxidant Properties:** Metformin maintains redox homeostasis by reducing ROS production via complex I inhibition, upregulating the expression of antioxidant enzymes (SOD1, GPx, PON1) and antioxidant proteins (Trx), and promoting NOS recoupling. **Autophagy Modulation:** Metformin mitigates apoptosis, senescence, and pathological migration/proliferation of cardiovascular-related cells by controlling the expression of autophagy-related proteins (increasing LC3-II and decreasing p62). **Anti-inflammatory Effects:** Metformin reduces inflammatory cytokine release, inhibits the NLRP3 inflammasome, and modulates gut microbiota to attenuate systemic inflammation. **Genetic Stability:** Metformin alleviates oxidative DNA damage, slows telomere shortening, and enhances DNA repair capacity, among which the activation of DNA ligases has great potential via the elevation of NAD^+ levels (lack of direct experimental evidence). **Epigenetic Regulation:** Metformin modulates gene expression via histone modifications (e.g., methylation of H3K79, acetylation of H3K27/H3K36) and the regulation of noncoding RNAs (ncRNAs) (miR-99b, miR-146a, lncRNA TUG1) to delay vascular aging. AMPK = AMP-activated protein kinase, mPTP = mitochondrial permeability transition pore, ROS = reactive oxygen species, NLRP3 = NOD-like receptor pyrin domain-containing protein 3, NAD^+ = nicotinamide adenine dinucleotide (Oxidized), Trx = thioredoxin, NOS = nitric oxide synthase, DNA = deoxyribonucleic acid, RNA = ribonucleic acid, EC = endothelial cell, GSH = glutathione, SOD1 = superoxide dismutase 1, GPx = glutathione peroxidase, PON1 = paraoxonase 1, TUG1 = taurine upregulated 1.

Metformin modulates mitochondrial respiration, reducing oxygen consumption and mitochondrial membrane potential, thereby decreasing metabolic stress under conditions of oxidative overload [92]. It also promotes mitochondrial biogenesis through AMPK-dependent pathway. In endothelial cells, metformin

activated the SIRT1-DOT1L (DOT1-like methyl-transferase)-SIRT3 axis, increasing H3K79me3 levels and enhancing mitochondrial biogenesis and delaying cellular senescence [93]. Long-term low-dose metformin treatment similarly attenuated vascular aging and atherosclerotic plaque development in mice [93]. Additional studies demonstrated that metformin mitigates diabetes-accelerated atherosclerosis through inhibiting AMPK-dependent dynamin-related protein 1 (Drp1)-mediated mitochondrial fission in human umbilical vein endothelial cells (HUVECs), suggesting another mechanism by which metformin may preserve mitochondrial function [94].

Regulation of the mPTP represents a second major mechanism of metformin. Excessive mPTP opening contributes to apoptosis, ischemia-reperfusion injury and heart failure. Experimental studies have shown that metformin inhibits mPTP opening through suppressing mitochondrial complex I activity, reducing endothelial and cardiomyocyte injury, and improves mitochondrial tolerance to calcium-induced stress [95-98]. Metformin also attenuates endoplasmic reticulum (ER) stress and improves mitochondrial function in aging murine hearts via AMPK activation [99, 100].

Several preclinical studies suggest cardioprotective effects during ischemia-reperfusion. Metformin reduced infarct size from 37% to 15% and improved ventricular function in isolated hearts and regional ischemia-reperfusion models [99, 101]. Notably, some benefits appeared independent of AMPK activation [99, 101], indicating that additional mechanisms may contribute. However, these findings remain largely preclinical, and clinical efficacy in ischemia-reperfusion injury has yet to be established.

5.2 Antioxidant Properties

Oxidative stress is a major driver of cardiovascular aging leading to the gradual deterioration of vascular function and the onset of age-related cardiovascular diseases. Metformin exhibits antioxidant effects through both reduction of ROS production and enhancement of endogenous antioxidant defenses. One key mechanism involves inhibition of mitochondrial complex I, which decreases mitochondrial ROS generation [101]. In rotenone-treated rats, metformin decreased oxidative stress and improved cellular antioxidant capacity [102], improving transport protein function and reducing erythrocyte osmotic fragility.

Metformin may also strengthen endogenous antioxidant systems. Increased paraoxonase-1 (PON1) activity has been observed in both diabetic animal models and patients with T2DM receiving metformin [103, 104], which may provide antioxidant and cardiovascular protection through inhibiting low-density lipoprotein (LDL) oxidation while enhancing high-density lipoprotein functions. Other studies reported increased glutathione peroxidase and superoxide dismutase activity, accompanied by reductions in markers of oxidative damage, including malondialdehyde and nitric oxide (NO) activity [105, 106]. Regulation of SIRT3-dependent pathways has similarly been implicated in lowering mitochondrial ROS levels [107].

At the cellular level, metformin activates forkhead box O3 (FOXO3) and FOXO1 signaling via AMPK activation, increasing thioredoxin (Trx) expression and reducing intracellular ROS accumulation [108, 109]. These effects appear to involve suppression of thioredoxin-interacting protein, an important regulator of redox homeostasis [109].

Nitric oxide synthase (NOS) represents another relevant target of metformin-induced antioxidant mechanisms. Metformin enhances endothelial NOS activity and NO bioavailability, improving vascular relaxation and limiting vascular calcification [110]. However, NOS uncoupling, a pathological state in which NOS produces superoxide anions (O_2^-) instead of NO, contributes significantly to cardiac remodeling, promoting hypertrophy, dilation, and functional decline [111]. Metformin may prevent NOS uncoupling by upregulating GTP cyclohydrolase 1 and tetrahydro-biopterin availability via AMPK activation, while suppressing nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation [112]. Collectively, these actions support the antioxidant and vasoprotective properties of metformin.

5.3 Autophagy Modulation

Autophagy is an essential cellular quality-control mechanism that removes damaged proteins and organelles into autophagosomes for lysosomal degradation, thereby limiting apoptosis, senescence, and inflammation. Impaired autophagy is increasingly recognized as a contributor to cardiovascular aging.

Multiple studies have demonstrated that metformin regulates autophagic activity in cardiovascular cells. In mesenchymal stem cells (MSCs), metformin increased microtubule-associated protein 1 light chain 3 (LC3) II/I ratio, and upregulated Klotho, poly ADP–ribose polymerase 1 (PARP-1), and SIRT-1 expression, delaying cellular senescence and descreasing cardiomyogenic differentiation [113]. Enhanced metformin-mediated autophagy has also been associated with improved cardiac function, reduced myocardial fibrosis, and attenuation of pathological hypertrophy in animal models [114].

Additional studies have linked metformin-induced autophagy to reduced apoptosis, increased Cx43

expression, protection against doxorubicin (DOX)-induced cardiotoxicity, attenuation of lipopolysaccharide (LPS)-induced myocardial injury, and suppression of VSMC proliferation and migration [115-118]. However, not all findings are consistent. Some studies reported that metformin reduced autophagic and mitophagic flux and protected cardiomyocytes from doxorubicin toxicity through apparent autophagy inhibition [119, 120]. Differences in experimental models, dosing regimens, observation periods, and methods used to assess autophagic flux likely contribute to these discrepancies [116, 119].

Beyond direct effects on cellular homeostasis, metformin-induced autophagy may also suppress inflammation. For example, metformin-induced activation of the autophagy-ROS-NLRP3 (NOD-like receptor pyrin domain-containing 3) axis in macrophages has been reported to reduce inflammatory injury to ischemic cardiomyocytes [121].

5.4 Inflammation

Chronic inflammation is a key driver of cardiovascular aging and contributes to the progression of atherosclerosis, heart failure, and other age-related cardiovascular disorders [122, 123]. Additionally, our group previously reported an association between elevated dietary inflammatory index and accelerated biological aging in multi-organ, including cardiovascular system [124]. Metformin exerts an anti-inflammatory effect through multiple pathways, many of which converge on AMPK activation.

In experimental models of atherosclerosis and DbCM, metformin suppresses inflammatory signaling through the Sestrin2-AMPK-mTOR pathway and inhibition of the NLRP3 inflammasome, resulting in reduced cytokine production and improved cardiac function [125, 126]. Synergistic anti-inflammatory effects have also been observed when metformin is combined with compounds such as curcumin or gallic acid [127, 128].

At the cellular level, metformin suppresses TNF-α-induced cyclooxygenase-2 expression, inducible NOS activity, and NF-κB signaling in cardiac and vascular cells through AMPK-mediated pathways [129-132]. Similar effects have been reported in aortic VICs, where metformin reduced NF-κB activation and calcification [133].

Inhibition of NF-κB signaling may also attenuate the senescence-associated secretory phenotype (SASP) by reducing the expression of pro-inflammatory genes [134]. In addition, metformin-induced changes in gut microbiota composition may contribute to lower systemic inflammation and potentially influence progression of aging-related CVDs [135, 136].

5.5 Genetic Stability

Accumulation of DNA damage and genomic instability is increasingly recognized as a contributor to cardiovascular aging and diseases. For example, genomic instability can promote endothelial-to-mesenchymal transition, a process implicated in aneurysm formation and atherosclerosis [137]. Current evidence suggests that metformin may support genomic stability through two complementary mechanisms: reducing DNA damage and enhancing DNA repair [138].

A significant source of DNA damage in cardiovascular cells is metabolism-associated oxidative stress, highlighting the relevance of metformin's antioxidant properties in limiting genomic injury [139]. Telomere maintenance may represent another protective mechanism, as telomere shortening is strongly associated with age-related CVDs [140, 141]. In individuals with mild age-related type 2 diabetes (MARD), metformin use was independently associated with reduced telomere attrition (β=0.030, 95% CI 0.010–0.051, P=0.004), although the effect size was modest [142]. Supporting these findings, an *in vitro* study in rat VSMCs revealed that metformin enhanced telomerase activity and telomerase reverse transcriptase (TERT) expression through an AMPK-peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α)-dependent pathway. This cellular response reduced senescence marker p53 expression, restored autophagic flux, and attenuated cellular senescence [143].

Metformin may also enhance DNA repair pathways to support genomic stability. The DNA damage response kinase, ataxia telangiectasia mutated (*ATM*), plays a central role in DNA repair and cell-cycle regulation. Metformin has been shown to activate ATM and downstream effectors, including protein kinase checkpoint kinase 2, in epithelial tumor cell lines [144]. However, whether similar mechanisms operate in aging cardiovascular tissues remains unclear. Interestingly, the *ATM*-associated variant rs11212617 has been linked to enhanced glycemic response to metformin and lower plasma drug concentrations, suggesting that genetic variations may influence therapeutic efficacy [145].

Another potential mechanism involves NAD^+ levels, which support the activity of PARP enzymes and DNA ligases involved in DNA repair [146, 147]. Metformin may increase intracellular NAD^+ availability through AMPK-mediated upregulation of nicotinamide phosphoribosyl transferase to accelerate the conversion of nicotinamide to NAD^+ [148], with subsequent sirtuin signaling pathways [148]. Although direct evidence

linking metformin-induced NAD^+ elevation to improved DNA repair in cardiovascular tissues remains limited, this pathway warrants further investigation in the context of cardiovascular aging.

5.6 Epigenetic Regulation

Epigenetic regulation has emerged as an important mechanism in cardiovascular aging and related disorders, including atherosclerosis, heart failure, and CAD [149, 150]. Growing evidence suggests that metformin may influence these processes through effects on microRNAs, DNA methylation and histone modification.

In hypertensive rats, metformin normalizes the expression of miR-99b, miR-146a, and miR-155 through the AMPK-dependent signaling, alleviating hypertension-induced cardiac damage [151]. Metformin has also been linked to epigenetic regulation through histone modification. In atherosclerotic mice, it delayed endothelial senescence via AMPK-mediated H3K79 methylation [93]. Similarly, in diet-induced obese (DIO) mice, metformin reversed alterations in H3K36me2 associated with metabolic dysfunction [152]. Another study showed that metformin reduced H3K27 acetylation at the SIRT3 promoter via AMPK-mediated signaling while enhancing Nrf2 binding, resulting in increased SIRT3 expression and protection against vascular injury induced by excessive salt intake [153].

Evidence from human studies further supports a potential epigenetic role for metformin. A genome-wide DNA methylation analysis in T2DM patients identified associations between treatment response and specific DNA methylation signatures [154], consistent with previous observations linking epigenetic variation to metformin responsiveness [149]. These findings suggest that epigenetic profiling may help inform personalized treatment strategies.

Interest has also grown in the potential effects of metformin on biological aging. Notably, the TRIIM trial reported that a combination regimen containing growth hormone, dehydroepiandrosterone, and metformin was associated with a reversal of epigenetic age as estimated by DNA methylation clocks [155]. However, because metformin was administered as part of a multidrug intervention, its specific contribution remains difficult to determine.

6. Potential Targets of Metformin in the Cardiovascular System

The upstream longevity pathways discussed above, including AMPK, mTOR, SIRTs, and IGF-1, form the core signaling framework underlying cardiovascular effects of metformin. Beyond these pathways, several downstream effectors, including ribosomal protein S6 kinase 1/4E-binding protein 1, unc51-like-kinase 1, hypoxia-inducible factor-1α, and glycogen synthase kinase 3β, have emerged as potential mediators of cardiovascular aging. Unlike the broad cellular processes described in Section 5, these molecules may exert more specific effects in particular cell types and disease contexts, rendering them potential targets for precision interventions. Current evidence regarding their roles in cardiovascular aging and their potential interactions with metformin is summarized below.

6.1 Ribosomal protein S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1)

S6K1 and 4E-BP1 are major downstream effectors of mTOR complex 1 (mTORC1). Activation of mTORC1 promotes protein synthesis and cellular growth through phosphorylation of S6K1 (T389 site) and 4E-BP1, thereby regulating ribosome biogenesis and cap-dependent mRNA translation.

Accumulating evidence implicates both proteins in cardiovascular aging. In vascular endothelial cells, S6K1 and arginase-II (Arg-II) form a positive feedback loop in which each promotes the activity of the other, resulting in eNOS uncoupling, inflammation, and endothelial senescence [156]. Further studies demonstrated that S6K1, Arg-II, and p38 MAPK constitute a mutually reinforcing signaling network in senescent endothelial cells and aged murine cardiovascular tissues. Inhibition of any single component decreased the activity of the entire network, and Arg-II deficiency was associated with lower S6K1 activity and improved vascular function [157].

The role of 4E-BP1 appears more complex. In *Drosophila*, 4E-BP improved cardiac contractility and calcium homeostasis through interactions with sarco/endoplasmic reticulum Ca2+-ATPase (SERCA) and eIF4E [158]. In contrast, murine studies suggest that excessive 4E-BP1 may contribute to cardiac dysfunction. Cardiac-specific deletion of *mTOR* caused fatal dilated cardiomyopathy, whereas ablation of 4E-BP1 improved cardiomyocyte survival and cardiac function [159]. Simultaneous deletion of 4E-BP1 and 4E-BP2 further enhanced cardiac function and survival under pressure overload conditions [160].

Metformin has been shown to modulate S6K1 and 4E-BP1 signaling in several cancers and autoimmune diseases [161-165]. However, direct evidence linking these effects to cardiovascular aging process and metformin remains limited. Future studies should determine whether modulation of S6K1/4E-BP1 contributes to the cardiovascular benefits of metformin

and whether these pathways represent viable therapeutic targets in aging cardiovascular tissues.

6.2 Unc51-like-kinase 1 (ULK1)

ULK1 is a key initiator of autophagy and a major downstream target of AMPK and mTOR signaling. Given the importance of autophagy in maintaining cardiovascular homeostasis, ULK1 has attracted attention as a potential mediator of anti-aging interventions.

In pressure-overload mouse models, ULK1-dependent mitophagy has been shown to protect against pathological cardiac remodeling and heart failure [166]. Similarly, in a zebrafish cryoinjury model, metformin accelerated cardiac regeneration through AMPK-ULK1-dependent autophagy. Loss of the ULK1 homolog *ulk1b* abolished the regenerative effects of metformin, supporting a central role for ULK1 in mediating these benefits [167].

Despite these findings, direct evidence linking metformin-induced ULK1 activation to alleviate cardiovascular aging remains scarce. Future work across diverse models of aging and cardiovascular disease is needed to clarify the translational relevance of this pathway.

6.3 Hypoxia-inducible factor 1 alpha (HIF-1α)

HIF-1α is a shared downstream target of both the mTOR- and SIRT-related signaling and regulates cellular adaptation to hypoxia. Its roles in angiogenesis, metabolism and cell survival make it relevant to both cardiovascular disease and aging [168].

Emerging evidence suggests that HIF-1α exerts context-dependent effects within the cardiovascular system. In endothelial cells, HIF-1α promotes angiogenesis, a process that may be beneficial in conditions such as diabetes-associated PAD, where vascular regeneration is impaired [169]. Conversely, in models of cardiac hypertrophy, HIF-1α upregulation has been associated with increased cardiomyocyte size and expression of hypertrophic markers, including atrial natriuretic peptide and vascular endothelial growth factor A [170]. Reduced HIF-1α expression has also been observed in senescent endothelial cells and contributes to age-related endothelial dysfunction [171].

Interestingly, metformin appears to regulate HIF-1α in a disease-specific manner. In PAD models, metformin promotes angiogenesis through HIF-1α activation [169], whereas in cardiac hypertrophy models it suppresses HIF-1α signaling and attenuates pathological remodeling [170]. The mechanisms underlying these apparently opposing effects remain unclear and may depend on cellular context, disease state, or metabolic status. Further mechanistic and translational studies are essential before HIF-1α can be considered a therapeutic target for cardiovascular aging.

6.4 Glycogen synthase kinase 3β (GSK3β)

GSK3β is a ubiquitously expressed serine/threonine kinase whose activity is inhibited by mTOR-activated Akt-induced phosphorylation at Ser9 [172]. It participates in multiple processes relevant to cardiovascular aging, including cellular survival, metabolism, and stress responses.

Several studies suggest a protective role for GSK3β in cardiovascular disease. In hypertrophic cardiomyocytes and rat models of cardiac hypertrophy, GSK3β promoted FOXO1 activation and nuclear localization, leading to inhibition of pathological hypertrophy [173]. In myocardial infarction models, increased GSK3β expression in cardiac stem cells enhances cardiac function and decreases ventricular fibrosis, suggesting a beneficial role in myocardial repair [174].

Evidence regarding the interaction between metformin and GSK3β remains inconsistent. In high glucose-treated cardiomyocytes, metformin activated the AKT/GSK3β pathway, reducing apoptosis and improving cardiac function in diabetic mice [175]. Conversely, metformin inhibited GSK3β activity in a peritoneal dialysis model [176]. These findings suggest that the effects of metformin on GSK3β are highly context dependent. Additional studies are needed to determine how GSK3β signaling contributes to metformin-mediated cardioprotection during aging.

7. Sex Differences in Cardiovascular Protective Effects of Metformin

Sex is an important but often underrecognized biological variable that may influence the cardiovascular effects of metformin. Cardiovascular aging differs between males and females owing to variations in sex hormone profiles, pharmacokinetics, body composition, and the regulation of pathways involved in mitochondrial function, inflammation, fibrosis, and metabolism. Consequently, the efficacy and mechanisms of metformin may not be uniform across sexes. Understanding these differences may help optimize the use of metformin in strategies targeting cardiovascular aging.

7.1 Hormonal Mechanisms Underlying Sex-Specific Effects

Age-related changes in sex hormones may contribute substantially to sex differences in cardiovascular aging and in the response to metformin. In women, the decline

in estrogen post-menopause is associated with the loss of multiple cardioprotective effects. Estrogen enhances endothelial function through eNOS activation, supports mitochondrial function via estrogen receptor β signaling, reduces oxidative stress, and suppresses the differentiation of cardiac fibroblasts to myofibroblasts limiting fibrosis [177, 178]. Consequently, estrogen deficiency is associated with increased vascular stiffness, mitochondrial dysfunction, and proinflammatory remodeling, all hallmarks of cardiovascular aging [179].

Metformin may interact with these pathways via AMPK activation. Kvandova *et al*. proposed that modulation of the AMPK-estrogen axis may represent a therapeutic strategy for endothelial dysfunction and inflammation, particularly in postmenopausal women and other high-risk female populations [180]. These observations raise the possibility that metformin may partially compensate for estrogen deficiency through overlapping downstream signaling pathways, although direct evidence remains limited. In contrast, the incremental benefit of metformin may be less evident in premenopausal women, where endogenous estrogen already supports AMPK activity and mitochondrial homeostasis. Further research is warranted to clarify these hypotheses.

Age-related alterations in testosterone may also influence the cardiovascular effects of metformin. A meta-analysis reported that low testosterone levels in elderly men are associated with increased all-cause mortality and cardiovascular mortality [181]. Conversely, higher endogenous testosterone levels in females have been linked to more favorable cardiovascular outcomes in certain settings [182]. Metformin has been shown to suppress androgen production by targeting *HSD3B2* and *CYP17A1* and by inhibiting mTORC1 activity independently of AMPK signaling, thereby reducing circulating testosterone levels [183]. However, these effects may be most relevant in hyperandrogenic conditions rather than in aging male populations.

7.2 Sex-Specific Pharmacokinetics of Metformin

In addition to hormonal influences, sex-specific pharmacokinetic differences may affect metformin responses. Age-related physiological changes, discussed in the section in 'Pharmacokinetics and Frailty in Aging Populations', can alter drug absorption, distribution and clearance.

Because women aged over 60 years generally exhibit lower estimated glomerular filtration rate (eGFR) than age-matched men [184], metformin clearance may be reduced in older women, potentially resulting in greater systemic exposure and prolonged tissue retention. This has led to the hypothesis that metformin could exert stronger or more sustained anti-aging effects in elderly females. However, current experimental and clinical evidence remain insufficient to confirm this possibility.

7.3 Preclinical and Clinical Evidence of Sex-Differences

Evidence regarding sex-specific cardiovascular responses to metformin remains inconsistent across both preclinical and clinical trials.

Although the elderly women tend to have lower eGFR [184], theoretically this may lead to a pharmacokinetic advantage of greater drug exposure in women, animal studies have failed to demonstrate enhanced benefits. Zhu *et al*. found that metformin failed to improve cardiac function or extend lifespan in aged female mice. Instead, it promoted metabolic reprogramming characterized by reduced mitochondrial respiration, increased glycolysis, persistent inflammation, and lower ATP production [185]. In contrast, several studies have reported beneficial effects in males. Metformin reduced chronic inflammation and age-related fibrosis in the heart, lungs and kidneys of aging male monkeys [186]. However, metformin effects on females were not studied. Similarly, McNair *et al*. demonstrated that metformin alleviated right ventricular dysfunction secondary to pulmonary hypertension exclusively in male mice, independent of cardiac AMPK signaling [187].

Clinical findings are similarly heterogeneous. In an 8-week double-blind, randomized, placebo-controlled trial involving 33 non-diabetic women, metformin at a dosage of 500 mg twice daily improved microvascular function and exercise tolerance [188]. Another RCT involving 78 T2DM patients demonstrated sex-specific metabolic effects: metformin combined with rosiglitazone improved myocardial substrate metabolism in women (elevated fatty acid clearance, decreased circulating levels and myocardial fatty acid utilization), whereas metformin monotherapy produced less favorable alterations in several metabolic parameters among men [189]. In contrast, a Mendelian randomization study revealed that genetically proxied metformin use was associated with longer lifespan in both sexes without significant sex differences, whereas other cardiovascular medications (e.g., proprotein convertase subtilisin/kexin type 9 inhibitors, β-blockers) exhibited sex-specific longevity effects [190].

Collectively, these findings suggest that cardiovascular effects of metformin may differ by sex, although the direction and magnitude of these differences remain uncertain. Variability in study populations, disease status, treatment regimens, and outcome measures likely contribute to the inconsistent results. Future studies should incorporate prespecified sex-stratified analyses

and standardized endpoints to better define potential sex-specific effects.

In summary, estrogen status, age-related changes in androgen signaling, and sex-dependent pharmacokinetic differences may all influence the cardiovascular effects of metformin. Consideration of these factors may be important when designing future trials and developing individualized strategies targeting cardiovascular aging.

Table 1. Summary of clinical trials evaluating metformin in aging-related cardiovascular diseases.

Trial (NCT ID) Reference	Design		Population (sample size, n)	Intervention vs. Control	Primary outcome	Safety	Main results	Limitations
	Core Trial Design	Statistical & Follow-up Design						
TAYSIDE (NCT00473876) [191]	Randomized, double-blind, Phase 4	Lost follow-up: n=4, (3 in metformin group, 1 in placebo group withdrew); Primary outcome: Per-protocol; Safety: Intention-to-treat; Total follow-up: 4 months	Patients with compensated CHF in NYHA functional I-III and insulin resistance but non-diabetic patients (n=62)	Metformin (for 4 months with a target dose of 1000mg twice a day) vs. placebo	**Peak VO_2:** No difference between treatment groups	SAE: 2/39 vs 1/23 (5.13% vs 4.35%) (All three were diagnosed prior to starting on metformin or placebo) Other AE (diarrhea): (46.15% vs 13.04%)	Improved cardiopulmonary function in insulin resistance-related dysfunction	Small sample size; Single-center design; Short follow-up; Limited generalizability.
GIPS-III (NCT01217307) [192]	Randomized, double-blind, Phase 3	Lost follow up: n=1, (1 in placebo group withdrew); Primary outcome: Intention-to-treat; Safety: Per-protocol Total follow-up: 4 months	Post-STEMI patients (n=380)	Metformin (500mg twice daily for 4 months) vs. placebo	**LVEF:** 53.1% (95% CI, 51.6 to 54.6) vs 54.8% (95% CI, 53.5 to 56.1)	All-cause mortality: 1.57% vs 0.53% (P=0.327) SAE (total): 5.76% vs 3.19% (P=0.248); Reinfarction: 4.19% vs 2.66%; Cardiovascular death: 0.52% vs 0%; Target lesion revascularization: 2.62% vs 2.13%	No significant LVEF improvement post-STEMI	Short follow-up duration; Selection bias; Limited generalizability.
Horwich (NCT01573949)	Single arm, open label	No loss to follow-up; Total follow-up: 3 months	HF with prediabetes (n=7)	Metformin (500 mg PO BID and pending lab values may be titrated to 1000 mg PO BID at 1 month)	**LVEF:** 25%±8% → 26%±9%	Safety data not specified	Underpowered due to small sample size	Extremely small sample size; short follow-up.
REMOVAL (NCT01483560) [193]	Randomized, double-blind	Lost follow up: n=41 (26 in metformin group, 15 in the placebo group); Primary outcome: Intention-to-treat; Safety: Intention-to-treat; Total follow-up: 36 months	T1DM with atherosclerosis (n=428)	Metformin + insulin vs insulin + placebo (Oral metformin titrated from initial 500mg to target 2000mg daily)	**Mean cIMT** (0, 12, 24, 36 months): 0.773±0.14 → 0.782±0.147 → 0.792±0.145 → 0.793±0.134 vs 0.791±0.183 → 0.788±0.174 → 0.823±0.187 → 0.820±0.177 (P=0.1664)	Other AE (total): 51.14% vs 24.88%; Cardiovascular events: 0.46% vs 0.48%; Ophthalmic AEs: 8.22% vs 15.31%; Hypersensitivity to metformin: 2.28% vs 0.48%	No significant anti-atherosclerotic effect in T1DM	Short follow-up (3 years) for hard outcomes; high attrition rate.

Notes: All P values are derived from the original literature.
NYHA = New York Heart Association; AE = adverse event; BID = *bis in die (Latin)*; CHF = chronic heart failure; SAE = serious adverse event; LVEF = left ventricular ejection fraction; cIMT = carotid intima-media thickness; SD = Standard Deviation; CI = confidence interval; post-STEMI = post-ST segment elevated myocardial infarction; PO = *per os (Latin)*; HF = heart failure; T1DM = type 1 diabetes mellitus.

8. Clinical Evidence of the Effects of Metformin on the Cardiovascular System

Although extensive mechanistic studies support the potential cardioprotective effects of metformin, most evidence derives from *in vitro* or animal experiments. Consequently, the clinical relevance of these findings for

cardiovascular aging remains uncertain. This section summarizes clinical studies registered on ClinicalTrials.gov that have evaluated metformin in age-related cardiovascular conditions (Table 1).

The Metformin in Insulin-Resistant Left Ventricular Dysfunction (TAYSIDE) trial (NCT00473876) was a randomized, double-blind, parallel-assignment phase IV study involving 62 participants [191]. Four months of metformin treatment (target dose 1000 mg twice daily) significantly reduced the VE/VCO_2 slope (cardiopulmonary exercise testing ventilation efficiency) (P=0.034), suggesting improved cardiopulmonary efficiency. However, no significant change was observed in the primary endpoint of peak VO_2. The Metformin to Reduce Heart Failure After Myocardial Infarction (GIPS-III) trial (NCT01217307) enrolled 380 non-diabetic patients following ST-segment elevation myocardial infarction (STEMI) [192]. After four months, metformin did not improve the primary endpoint of left ventricular ejection fraction (LVEF), which was numerically lower in the metformin group than in the placebo group (53.1% vs. 54.8%). Whether longer treatment duration or earlier preventive use might produce different outcomes remains unknown.

The Horwich study (NCT01573949), an unpublished registry-reported trial involving seven patients with heart failure and prediabetes, found no meaningful change in quality of life, HbA1c, renal function, or LVEF following three months of treatment. Interpretation is limited by the very small sample size.

The Reducing with Metformin Vascular Adverse Lesions in Type 1 Diabetes (REMOVAL) trial (NCT01483560) was a randomized, double-blind trial of 428 individuals with Type 1 diabetes [193]. Metformin did not significantly reduce progression of mean carotid intima-media thickness (cIMT), the primary endpoint, but significantly slowed progression of maximal cIMT (P=0.0093). Improvements were also observed in HbA1c, LDL cholesterol, body weight, and eGFR. A prespecified subgroup analysis suggested that vascular benefits were confined to never-smokers (−0.012 mm/year, P=0.0137) [194].

The Genomic Outcomes of Metformin (GOMET) trial (NCT02986659) was a phase IV randomized crossover study involving 30 non-diabetic participants. Metformin modestly altered gene expression signatures associated with health and longevity. However, planned analyses of autophagy and mitochondrial function were not completed because of funding constraints.

Beyond these individual trials, additional clinical evidence supports potential benefits of metformin in conditions including atherosclerosis, IRI, and cardiac arrhythmias in both diabetic and non-diabetic populations [195].

Regarding safety, metformin has demonstrated a favorable safety profile. In TAYSIDE, there were two serious adverse events in the metformin group and one in the placebo group, none of which were judged treatment-related [191]. In the GIPS-III trial, mortality rates and serious adverse events were higher in the metformin group but did not differ significantly from placebo [192]. Moreover, studies examining heart failure patients with or without T2DM found no association between plasma metformin concentrations and markers of lactic acidosis, supporting its safety when prescribed [196].

In summary, available clinical trials suggest that metformin may improve selective measures of cardiometabolic health, vascular function, and exercise capacity. However, the relevant evidence is subject to numerous limitations, which will be elaborated in the subsequent section.

9. Limitations and Perspectives

Although substantial mechanistic evidence supports metformin as a potential intervention for cardiovascular aging, clinical studies have yet to demonstrate consistent benefits. Several challenges should therefore be addressed before metformin can be considered a therapeutic strategy for cardiovascular aging.

9.1 The Hormetic Dose-Response Challenge

Metformin exhibits a hormetic biphasic dose–response relationship. At low concentrations (typically 10–500 μM), mild inhibition of mitochondrial respiratory chain complex I induces adaptive metabolic stress, activating cytoprotective pathways such as AMPK and enhancing cellular resilience [197]. Contrastingly, higher concentrations (typically 1–50 mM) may cause excessive energetic stress, promote oxidative imbalance, and activate cell death pathways, including apoptosis and ferroptosis [198].

Importantly, these effects vary across cell types and disease contexts, highlighting the need for individualized dosing strategies [199]. For example, lower doses may support mitochondrial function and energy metabolism in age-related heart failure, whereas higher doses may reduce oxidative injury during IRI by suppressing mitochondrial ROS production. Defining the optimal therapeutic window for cardiovascular aging therefore remains an important research priority.

9.2 Pharmacokinetics and Frailty in Aging Populations

Metformin pharmacokinetics are particularly relevant in older adults. Because the drug is eliminated largely

unchanged through the kidneys, age-related declines in estimated glomerular filtration rate (eGFR) may increase drug exposure and, in susceptible individuals, the risk of lactic acidosis.

Another important consideration is frailty, a syndrome characterized by reduced physiological reserve and heightened vulnerability to stressors. A recent clinical study reported that metformin (500 mg daily) reduced frailty scores in prefrail hypertensive older adults with prediabetes after six months of treatment [200]. However, whether such benefits translate to better cardiovascular outcomes remains unknown.

Furthermore, the doses currently used in clinical practice were developed for glycemic control rather than anti-aging purposes. Whether these regimens achieve sufficient concentrations to influence cardiovascular aging while maintaining an acceptable safety profile in older adults has not been established.

Overall, although metformin-associated lactic acidosis is uncommon, the risk increases in individuals with impaired renal function. Careful dose adjustment based on eGFR and regular monitoring of renal function remain essential. Future research should include frail older adults and incorporate pharmacokinetic analyses to better define the efficacy and safety window of metformin in cardiovascular aging.

9.3 The 'Pyramid' of Evidence and Regulatory Hurdles

Despite encouraging mechanistic data, current clinical evidence remains insufficient to establish metformin as a therapy for cardiovascular aging. Existing studies are limited by small sample sizes, short follow-up periods, heterogeneous patient populations, and heavy reliance on surrogate endpoints.

Several trials were underpowered. For example, the Horwich trial enrolled only seven subjects, precluding meaningful statistical inference. Follow-up periods ranged from only three months to three years, limiting the ability to detect effects on slowly evolving age-related cardiovascular processes.

A critical methodological limitation is the reliance on surrogate outcomes such as cIMT, LVEF, and VE/VCO_2 slope. Although these measures provide useful information regarding vascular structure, cardiac function, and exercise capacity, they do not necessarily predict clinically meaningful outcomes. Improvements in surrogate markers may not translate into reductions in myocardial infarction, stroke, cardiovascular hospitalization, or mortality.

To address this challenge, aging-related biomarkers, including epigenetic and multi-omics clocks, have been proposed as potential endpoints. However, no consensus has been reached regarding their validity as surrogate measures of clinical benefit, particularly in healthy older adults [201]. Another limitation of the current literature is that much of the supporting evidence derives from experimental models or populations with established cardiometabolic disease. Consequently, the applicability of these findings to healthy aging populations remains uncertain.

Although diabetes and aging share several biological features, including chronic inflammation, oxidative stress, and metabolic dysregulation, important differences exist in their underlying pathophysiology [202]. Cardiovascular benefits observed in diabetic models may be partly attributable to glucose-lowering effects and therefore may not fully translate to non-diabetic individuals.

From an evidence-based perspective, current evidence presents a 'pyramid' structure. A large body of mechanistic research and observational data originates from diabetic models and populations, whereas randomized controlled trials specifically targeting non-diabetic older adults remain limited. Nevertheless, studies conducted in diabetic settings have provided valuable insights into the molecular mechanisms through which metformin may influence cardiovascular aging [203].

Translating these findings into clinical practice also faces regulatory challenges. Aging is not currently recognized as a disease indication, making trial design, endpoint selection, and regulatory approval more complex. Furthermore, the risk-benefit balance differs substantially between diabetic and non-diabetic populations. In patients with DM, the established metabolic and cardiovascular benefits outweigh its risk. Conversely, healthy or non-diabetic older adults may have a lower tolerance for adverse effects and require stronger evidence of clinical benefit.

Future research should therefore focus on validating metformin in non-diabetic aging models, developing robust aging-related cardiovascular endpoints, and conducting adequately powered randomized controlled trials in elderly populations [204].

Additional practical considerations include established contraindications, such as severe hepatic and renal impairment, and adverse effects including gastrointestinal intolerance, vitamin B12 deficiency, and, rarely, lactic acidosis [205]. Interindividual variability in treatment response further complicates implementation. Pharmacogenomic studies have identified several genetic polymorphisms affecting metformin disposition and efficacy, including polymorphisms in *SLC22A1*, which encodes an organic cation transporter [206, 207]. Variants in the organic cation transporter and multidrug and toxic compound extrusion transporter genes also influence metformin absorption and excretion [208, 209]. More

recently, genome-wide association studies identified genetic variants near *ENOSF1* and *OSMR* that were associated with differences in HbA1c reduction and weight loss following metformin treatment [210]. These findings support the potential value of precision medicine approaches in future anti-aging applications of metformin.

10. Conclusion

This review summarizes age-related changes in the cardiovascular system and evaluates the potential role of metformin in mitigating cardiovascular aging and related diseases. Evidence from preclinical studies suggests that metformin influences multiple biological processes implicated in aging, including cellular energy metabolism, oxidative stress, autophagy, inflammation, genomic stability, and epigenetic regulation. Together, these actions provide a biological rationale for its investigation as a candidate intervention for cardiovascular aging.

We further highlight several downstream targets associated with longevity-related pathways, including AMPK, mTOR, SIRT, and IGF-1, that may contribute to the cardiovascular effects of metformin. These mechanisms extend the potential relevance of metformin beyond its established role in glucose lowering and support continued investigation of its broader cardiometabolic effects.

However, the current clinical evidence remains inconclusive. While studies such as TAYSIDE reported improvements in cardiopulmonary exercise parameters, the clinical significance of these findings is uncertain because of short follow-up periods and reliance on surrogate endpoints. Conversely, trials such as GIPS-III did not demonstrate significant improvements in cardiac function following myocardial infarction. Overall, existing studies support biological plausibility but do not establish definitive clinical efficacy.

The discrepancy between robust mechanistic evidence and inconsistent clinical outcomes highlights the challenges of translating geroscience-based interventions into practice. Factors such as sex differences, genetic variability, pharmacokinetics, frailty, and dose-dependent effects are likely to influence treatment response and should be incorporated into future study designs.

In summary, metformin remains an attractive candidate for targeting cardiovascular aging because of its well-characterized safety profile, broad mechanistic actions, and extensive clinical experience. Nevertheless, its role in cardiovascular aging has yet to be established. Large-scale, long-term randomized controlled trials incorporating cardiovascular hard outcomes, validated aging biomarkers, and stratification by sex and metabolic status will be essential to determine whether metformin can meaningfully improve cardiovascular health in aging populations.

Acknowledgment

The authors would like to express their sincere gratitude to Prof Lim Weiwen (National Heart Center Singapore) for language editing and proofreading this manuscript.

Author contributions

Yan Miao wrote the original draft, conducted formal analysis, and created visualizations. Wenting Wang contributed to investigation, writing - review & editing, and visualization. Ye Liu contributed to the revised manuscript, writing - review & editing, and visualization. Shumai Zhu contributed to investigation, writing - review & editing, and visualization. Ye Li contributed to investigation, writing - review & editing, and visualization. Xuehong Zheng was responsible for writing - review & editing and supervision. Dongye Zhuo was responsible for writing - review & editing and supervision. Jiaxin Hua contributed to writing - review & editing and project administration. Lihan Zhu contributed to investigation, and content curation. Jing Zhang contributed to methodology and data curation. Wenli Gu contributed to methodology and investigation. Lin Zhang contributed to methodology and visualization. Jun Zhang, Xiang Gu and Yuanzheng Ye contributed to writing - review & editing. Fang Wang, Peng Yu and Xiao Liu conceptualized the study, wrote the review & editing section, supervised the work, and provided funding acquisition. All authors reviewed and approved the final manuscript.

Supplementary Materials

The Supplementary data can be found online at: www.aginganddisease.org/EN/10.14336/AD.2026.1308.

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