ASIA PAC J SURG EXP & PATHOL

OPEN ACCESS AMP Asian Medical Press

REVIEW ARTICLE

Received 12 Jan 2025 | Accepted 20 Mar 2025 | Published Online 30 Mar 2025 https://doi.org/10.32948/ajsep.2025.03.20

Aging-related comorbidities, life-style interventions and therapeutic strategies in heart failure

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Cite this article: Phan NN, Yunus FN: Aging-related comorbidities, life-style interventions and therapeutic strategies in heart failure. Asia Pac J Surg Exp & Pathol 2025, 2: 38-47. https://doi.org/10.32948/ajsep.2025.03.20

Abstract

Aging is a key risk factor for heart failure which significantly contributes to progressive structural and functional deteriorations in the heart, such as increased incidence of left ventricular hypertrophy, decline in left ventricle diastolic function, left atrial dilation, atrial fibrillation, myocardial fibrosis and cardiac amyloidosis, all contributing to compromised cardiac performance and leading to heart failure. Concurrently, aging-induced systemic changes in key organs, including liver, adipose tissue, kidneys, and skeletal muscles, further aggravate heart failure by disrupting endocrine signaling, energy balance and metabolic homeostasis. Aging-related comorbidities, including obesity, diabetes, coronary artery disease, atherosclerosis, hypertension and chronic kidney disease, also exacerbate the burden on failing heart through complex metabolic, inflammatory, and oxidative pathways. Lifestyle interventions, like dietary plans and physical activity, offer potential to counteract aging-related cardiovascular decline. Plant-based diets, calorie restriction and micronutrient supplementation are key dietary intervention to support cardiovascular health. Exercise mitigates oxidative stress and inflammation as well as promotes mitochondrial biogenesis and cardiac autophagy, improving overall heart function. Evolving therapeutic approaches, such as senolytics, senomorphics, sirtuin activators and anti-inflammatory agents, offer promising avenues to target senescent cells, enhance metabolic and mitochondrial efficiency and modulate inflammatory responses, thereby alleviating aging-related cardiac dysfunction. This review discusses the role of aging-related systemic decline and comorbidities in heart failure, highlighting the potential of integrative strategies combining lifestyle interventions and anti-aging therapies. Active translation of these strategies into clinics as targeted and personalized therapies offer potential to mitigate the global burden of aging-related heart failure and improve quality of life for aging populations.

Key words heart failure, aging, aging-related comorbidities, exercise, anti-aging therapy

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Introduction

Aging is a major risk factor for heart failure and other cardiovascular diseases. After the age of 50, the occurrence of heart failure rises sharply with each advancing decade in human life, becoming one of the primary causes of death among older adults [1, 2]. Therefore, the aging population represents a significant challenge to global healthcare systems. The age-related functional decline in liver, adipose tissue, kidneys, and skeletal muscles plays a critical role in heart dysfunction. This systemic decline is primarily driven by changes in endocrine signaling, which affect the body's overall metabolic balances and heart health [3, 4]. On the other hand, aging-related comorbidities, commonly seen in older adults, such as obesity, diabetes, coronary artery disease, atherosclerosis, hypertension, and chronic kidney disease, further complicate the situation by increasing the damage to cardiac tissue, resulting in heart failure [5]. Evolving understanding of aging as a process of varying degree and rate of degeneration across species, individuals, and even different organs, has positioned it as a process that can be influenced and altered. This notion has opened gateway to target aging to slow down or even reverse the structural and functional changes that contribute to age-related diseases, including heart failure [6, 7]. Lifestyle changes, particularly physical activity, have emerged as protective factors against the decline of physiological functions, potentially extending cardiovascular health. Exercise combats age-associated intermediate phenotypes such as oxidative stress, cellular aging, and inflammation, playing a crucial role in preventing the cardiac deterioration that precedes the onset of heart failure [8]. Ongoing investigations are exploring a variety of aging-targeted therapeutic approaches in the context of heart failure, such as inhibition of senescence and inflammation, and SIRT activation mediated metabolic harmony. The future holds great potential for personalized treatments targeting aging processes in individuals with heart failure [9, 10]. In this review, we present aging as a primary factor driving heart failure with aging-related comorbidities worsening the situation. Furthermore, we emphasize the role of exercise and dietary interventions as potential strategies to modify aging processes, aiming to alleviate heart dysfunction in individuals with heart failure. Finally, we explore ongoing therapeutic innovations that may target the systemic mechanisms of aging in relation to heart failure.

Aging heart

The mass-to-volume ratio of the left ventricle increases with age, resulting in a reduction in stroke volume due to both systolic and diastolic dysfunction [11]. Diastolic dysfunction, which is rare in younger adults, becomes more common and severe with advancing age [12]. Aging also leads to a decrease in maximal heart rate, which can be attributed to a reduced intrinsic heart rate as well as a diminished responsiveness to β-adrenergic stimulation [13]. This reduction, combined with impaired relaxation and compliance of the left ventricle, raises left ventricular filling pressure and results in a decreased maximal cardiac output [14], ultimately compromising cardiac reserve [15]. Aging myocardium undergoes changes in its electrophysiological properties, influenced by the cardiac autonomic nervous system, which increases susceptibility to arrhythmias [16]. Elderly individuals often show signs of degenerative changes, especially in cases of severe aortic stenosis [17]. Age-related increases in both the maximal and minimal volumes of the left atrium have been observed, accompanied by a decline in longitudinal strain and radial motion during the reservoir and conduit phases [18]. This left atrial dilation and mechanical dysfunction become key contributors to the risk of atrial fibrillation and heart failure [19]. Aging also brings mild increases in pulmonary artery pressure and vascular resistance, which affect the right ventricle. Although the ejection fraction of both the left and right ventricles tends to remain stable, diastolic dysfunction in the right ventricle develops over time [20]. The volume of the right atrium increases with age, and older adults often experience more frequent disturbances in right atrial flow [21]. Aging process is also associated with myocardial fibrosis, characterized by excessive collagen deposition, which contributes to impaired cardiac function and elevates the risk of heart failure [22]. Cardiac amyloid deposition also rises with age, leading to thickened ventricular walls and increased myocardial stiffness, both of which contribute to the risk of heart failure [23].

Systemic decline during aging aggravates heart failure

Progressive accumulation of cellular and molecular alterations across various tissues, including organs such as the liver, adipose tissue, kidneys, and skeletal muscles, profoundly influence energy metabolism, hormonal balance, and overall physiological stability (**Figure 1**) [3]. As organisms age, alterations in the molecular mechanisms governing homeostasis within these tissues play a critical role in the development of heart failure [4]. The liver, as a central metabolic organ, undergoes age-associated alterations that contribute to heart failure. Insulin resistance in the liver, which intensifies gluconeogenesis, results in elevated free fatty acids (FFAs) in circulation, disrupting glucose and lipid homeostasis [24]. The impairment of insulin signaling in the liver involves the release of hepatokines, such as fibroblast growth factor 21 (FGF21), which affects systemic metabolic regulation and could play a role in the metabolic disturbances observed in heart failure [25]. The liver-heart interaction is reciprocal, with increased cardiac sympathetic activity potentially stimulating the liver to release glucose, which exacerbates insulin resistance throughout the body [26]. The interplay between adipose tissue and cardiac cells involves the secretion of adipokines such as adiponectin, leptin, resistin, and fibroblast growth factor 21 (FGF21), which collectively shape the metabolic environment of the heart [27]. Dysfunctional adipose tissue, particularly in visceral depots, becomes more pronounced with aging, and significantly influences the pathophysiology of heart failure. Elevated levels of adiponectin in the serum are linked with the severity of heart failure and are indicative of a poor clinical prognosis [28]. Circulating resistin contributes to the progression of myocardial fibrosis and apoptosis by inducing DNA damage, which results in maladaptive cardiac responses that drive heart failure [29]. Aging-related impairment of brown adipose tissue further raises plasma concentrations of trimethylamine N-oxide, which causes mitochondrial dysfunction by inhibiting cytochrome c oxidase 1 (COX1), thereby reducing ATP availability in cardiac cells, a key factor in heart failure development [30].

In the kidneys, aging leads to glomerular dysfunction, decreased renal blood flow, and compromised sodium handling, all of which contribute to the development of hypertension, an important risk factor for heart failure [31]. Systemic inflammation, oxidative damage, and imbalances in electrolytes in the kidneys accelerate the progression of heart failure [32]. The metabolic alterations in skeletal muscle due to aging also exacerbate heart failure. Altered secretion of myostatin (a myokine) adds to the complex network of metabolic and systemic changes associated with aging [33]. Accompanied by disrupted AMPK signaling and activation of the NF-κB pathway, sarcopenia impair mitochondrial function, reduce energy production, and promote systemic inflammation, all of which contribute to the development of cardiac diseases [34]. Reduced physical activity resulting from sarcopenia or muscle dysfunction exacerbates metabolic disturbances, accelerating the progression of heart failure [35]. Interestingly, the heart's

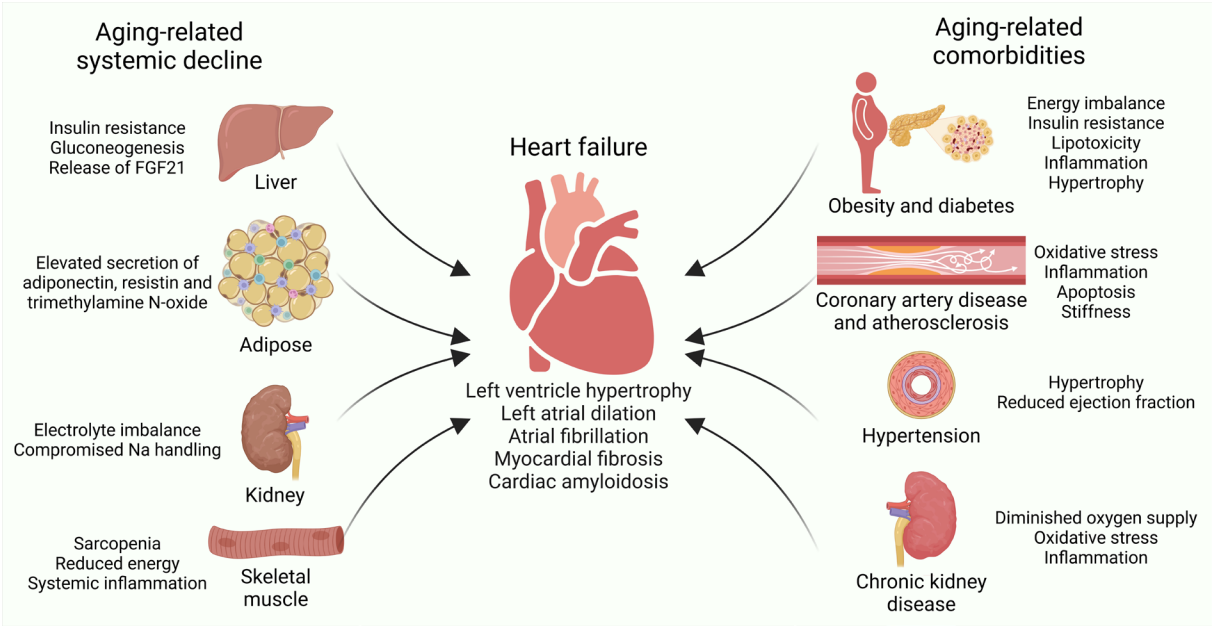

Figure 1. Aging-related systemic decline and comorbidities foster heart failure. Aging-related systemic decline in liver, adipose tissue, kidneys, and skeletal muscles, as well as aging-related comorbidities, such as obesity, diabetes, coronary artery disease, atherosclerosis, hypertension and chronic kidney disease, introduce structural and functional changes in the heart leading to heart failure.

altered release of myostatin in chronic heart failure may stimulate proteolysis in an ActIIB/Smad-dependent manner, leading to skeletal muscle wasting [36]. In conclusion, the bidirectional communication between the heart and other organs underscores the impact of aging-related systemic decline during heart failure.

Comorbidities of aging exacerbate heart failure

Aging-related obesity and diabetes significantly influence cardiovascular health and drive the progression of heart failure (**Figure 1, Table 1**). In obesity and diabetes, insulin resistance disrupts glucose regulation, leading to hyperglycemia, metabolic imbalance and oxidative stress within heart cells [37, 38]. Chronic hyperglycemia, a hallmark of diabetes, initiates a series of molecular events that generate oxidative stress through pathways such as protein kinase C (PKC) activation and the formation of advanced glycation end products. These processes are instrumental in promoting endothelial dysfunction, inflammation, and fibrosis within the cardiovascular system [39]. Dyslipidemia, marked by increased levels of fatty acids and triglycerides, promotes cardiac lipotoxicity and intensifies inflammatory processes [40]. Diabetes-related dyslipidemia plays a significant role in accelerating atherosclerosis and worsening cardiac dysfunction [41]. Obesity-induced epigenetic changes, including modifications in DNA methylation and histone structures, alter the expression of genes linked to metabolism, inflammation, and cardiac function [42]. The chronic inflammatory state associated with obesity, fueled by pro-inflammatory cytokines like TNF-α and IL-6, exacerbates immune activation and negatively affects cardiac function [43]. Mitochondrial dysfunction in obesity and diabetes generates excessive reactive oxygen species, resulting in oxidative stress that damages cells and impairs heart performance [44]. Persistent inflammation and oxidative stress contribute to fibrosis, which stiffens the heart muscle and diminishes its ability to contract efficiently [45]. Insulin resistance further contributes to a pro-inflammatory environment that aggravates cardiovascular complications [37]. Adaptive cardiac hypertrophy, triggered by the increased workload due to obesity, further accelerates the progression to heart failure [46]. Resistance to leptin, alongside imbalances in other adipokines such as adiponectin, resistin, and visfatin, further shapes the molecular pathways contributing to heart failure in older individuals with obesity [47].

Aging-related development of coronary artery disease begins with the formation of atherosclerotic plaques, which can rupture and lead to thrombus formation (Figure 1, Table 1). The thrombus can obstruct the coronary arteries either partially or completely, resulting in myocardial ischemia, which is a key cause of heart failure [48, 49]. Ischemic conditions activate various molecular mechanisms, including the release of ATP and potassium ions due to cellular stress. These actions stimulate purinergic receptors and exacerbate inflammation. Simultaneously, the ischemic myocardium releases damage-associated molecular patterns that further intensify the inflammatory response [50, 51]. Chronic inflammation and oxidative stress significantly contribute to the progression of heart failure, promoting cardiomyocyte apoptosis, necrosis, and adverse cardiac remodeling. These processes are driven by hypertrophic signaling pathways, particularly those involving Akt and mTOR [52, 53]. The fibrotic response, regulated by transforming growth factor-beta (TGF-β) and collagen deposition, leads to increased myocardial stiffness. This ongoing stress, combined with maladaptive remodeling and dysfunction of the heart, ultimately results in heart failure [54]. Aging-related onset of hypertension put strain on both the heart and blood vessels, resulting in harmful structural and functional alterations that increase the risk of heart failure [55]. As individuals age, the regulation of the renin-angiotensin-aldosterone system (RAAS), a critical hormonal network involved in managing blood pressure, becomes disrupted. This disruption leads to an overproduction of angiotensin II, a powerful vasoconstrictor, which in turn triggers the hypertrophy of vascular smooth muscle cells, inflammation, and oxidative stress. These molecular processes contribute to endothelial dysfunction and are central to the development of

Table 1. Comorbidities of aging exacerbate heart failure.

Comorbidity	Key molecular mechanisms	Systemic impact	Ref.
Obesity	Insulin resistance, chronic inflammation, mitochondrial dysfunction, and oxidative stress.	Promotes lipotoxicity, cardiac fibrosis, and energy imbalance.	[37, 40-47]
Diabetes	Advanced glycation end-products, endothelial dysfunction, oxidative stress, and inflammation.	Drives metabolic imbalance, cardiac fibrosis, and remodeling.	[37-39]
Coronary artery disease (CAD)	Atherosclerosis, plaque rupture, chronic inflammation, and thrombus formation.	Leads to ischemia, myocardial infarction, and heart failure.	[48-54]
Hypertension	RAAS activation, oxidative stress, and vascular inflammation.	Causes cardiac hypertrophy, endothelial dysfunction, and fibrosis.	[55-57]
Chronic kidney disease (CKD)	Uremic toxin accumulation, fluid retention, and systemic inflammation.	Contributes to hypertension, oxidative stress, and heart failure.	[58-61]

hypertension [56]. Hypertension further drives detrimental changes in the heart through the activation of neurohormonal systems, particularly angiotensin II and the sympathetic nervous system. This activation initiates signaling pathways that promote cardiac hypertrophy, including the mitogen-activated protein kinase (MAPK) pathway, phosphoinositide 3-kinase (PI3K)/Akt signaling, p38-MAPK, and c-Jun N-terminal kinase (JNK) pathways, which lead to hypertrophy of cardiomyocytes and interstitial fibrosis [57].

Aging-related chronic kidney disease is characterized by a gradual decline in kidney function, including a reduced glomerular filtration rate and impaired sodium regulation, which creates a biochemical environment that accelerates the development of heart failure (**Figure 1, Table 1**) [58]. Dysfunction in sodium regulation leads to electrolyte imbalances, promoting sodium retention and fluid accumulation. This fluid retention activates the RAAS, resulting in the release of angiotensin II and aldosterone. Angiotensin II induces vasoconstriction, while aldosterone facilitates increased sodium and water reabsorption, together raising blood volume and systemic blood pressure, thereby imposing greater stress on the heart, and resulting in heart failure progression [59]. The accumulation of uremic toxins in advanced stages of chronic kidney disease contributes to heart failure through systemic inflammation and oxidative stress. These toxins impair endothelial function, reducing vasodilatory capacity and fostering a proinflammatory state that adversely affects cardiac health [60]. Elevated levels of cytokines, including IL-1β, IL-6, and TNF-α marks the chronic inflammatory milieu associated with chronic kidney disease, driving detrimental cardiac remodeling processes linked to heart failure [61]. In summary, aging-related obesity, diabetes, coronary artery disease, hypertension, and chronic kidney disease create a complex interplay of molecular, metabolic and inflammatory disturbances that accelerate the progression of heart failure.

Lifestyle interventions mitigating aging in heart failure

A plant-based diet is associated with a reduced risk of heart failure [62]. Advanced heart failure studies in both patients and animal models, using metabolomic and proteomic approaches, reveal a metabolic shift characterized by diminished fatty acid oxidation and increased dependence on ketones as an energy source [63]. Dietary modifications that alter substrate availability, such as ketogenic diets, may help restore energy balance in failing hearts (**Figure 2, Table 2**) [61]. In the same way, caloric restriction has shown promise as a therapeutic approach for overweight individuals with heart failure, as it improves heart function by reducing adiposity. However, for underweight heart failure patients, extreme dietary restriction may increase mortality risk [64]. Nutritional deficiencies, both micro- and macronutrient-related, may also influence heart failure development and outcomes. Specifically, iron deficiency is associated with poor heart failure prognosis, and ongoing clinical trials are investigating the effects of intravenous iron supplementation in heart failure patients [65]. Macronutrient supplementation, particularly with unsaturated fatty acids like omega-3 polyunsaturated fatty acids (n-3 PUFA), has been shown to enhance ejection fraction and reduce heart failure-related hospitalizations [66]. However, recent meta-analyses have raised concerns about the potential risk of atrial fibrillation in individuals with cardiovascular risk factors [67].

Physical activity, recognized for its antioxidative properties, may partially mitigate pathological cardiac remodeling in older adults by addressing several processes linked to age-related heart failure (**Figure 2, Table 2**). These include mitochondrial dysfunction, chronic inflammation, cellular aging (senescence), and reduced cardiomyocyte regeneration [8, 68, 69]. Studies have shown that aerobic exercise training, conducted over a duration of three to six months, enhances peak oxygen consumption and exercise efficiency in individuals aged 65 to 79 [70]. Engaging in progressive and intense endurance training can lead to physiological remodeling of the left ventricle in previously sedentary individuals over 65, characterized by an increase in ventricular mass while maintaining the mass-volume ratio [71]. Exercise has also been shown to promote mitochondrial biogenesis in the heart, improving energy metabolism and bolstering the antioxidant defense system in heart failure patients [72]. Physical activity also promotes cardiac autophagy, which, in turn, stimulates mitochondrial biogenesis, reduces local tissue inflammation, and improves heart function [72, 73]. Research shows that 21 days of voluntary running in mice increases telomerase activity and prevents cellular aging in the heart, demonstrating the geroprotective properties of regular exercise [74]. In aged myostatin knockout mice, cardiac structure and function are notably better preserved. Interestingly, exercise training reduces myostatin levels in the skeletal muscles of both chronic heart failure patients and animal models, highlighting the potential advantages of exercise in addressing age-related cardiac alterations [75]. Exercise protects against apoptotic cell death by suppressing the calcineurin/nuclear factor of activated

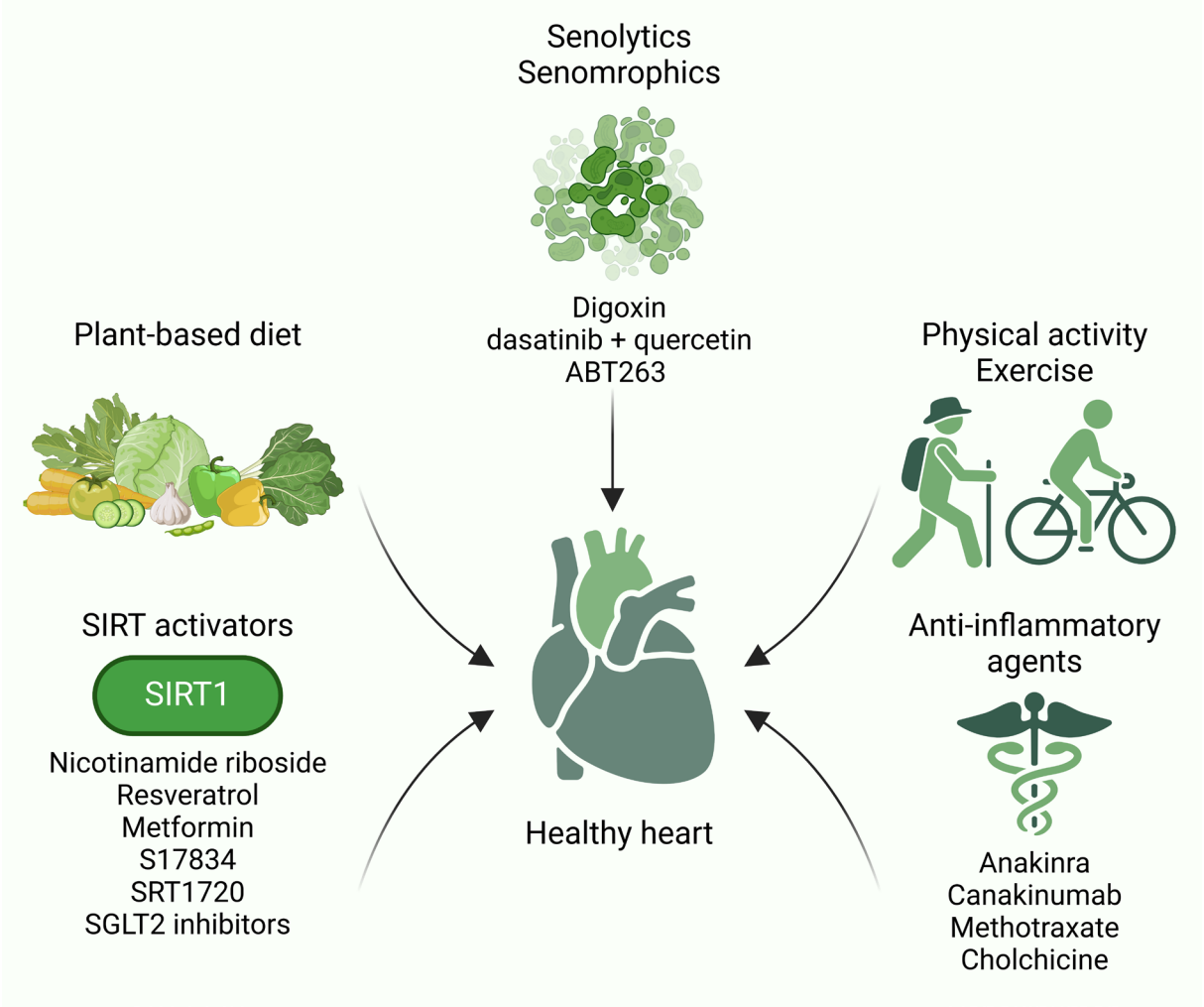

Figure 2. Lifestyle interventions and aging-targeted therapeutics counteract heart failure. Lifestyle interventions, such as plant-based diet, physical activity and exercise, as well as aging-targeted therapeutics including senolytics, senomorphics, SIRT activators and anti-inflammatory agents counteract heart failure.

T cells (NFAT) signaling pathway responsible for pathological hypertrophy, thereby preventing maladaptive remodeling in heart failure [76]. Moderate physical activity also reduces myocardial apoptosis and encourages cardiac regeneration through the activation of Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling, pathways often suppressed in heart failure [77]. On a molecular level, exercise enhances SIRT3 expression in aging hearts, which helps mitigate mitochondrial stress [78]. Exercise also promotes the cardiac-specific production of insulin-like growth factor 1 (IGF-1), triggering PI3K/Akt signaling that fosters angiogenesis, reduces apoptosis and fibrosis, and supports physiological hypertrophy, ultimately improving cardiac performance in heart failure [79]. Exercise-induced cell division cycle 42 (Cdc42) functions as a negative modulator of physiological hypertrophy, limiting excessive heart enlargement. In Cdc42-deficient models, animals display exaggerated exercise-induced cardiac hypertrophy, which can progress to heart failure [80]. Aerobic exercise and combined training effectively reduce pro-inflammatory markers like IL-6 and TNF-α, addressing chronic inflammation in overweight heart failure patients [81]. These findings underscore the therapeutic potential of diet and exercise in heart failure management.

Therapeutic strategies targeting aging in heart failure

The removal of p16Ink4a-positive senescent cells not only halts aging-associated characteristics but also sustains cardioprotective mechanisms, decreases cardiac hypertrophy and fibrosis, enhances cardiomyocyte proliferation, and consequently extends lifespan [82, 83]. These findings underscore the significance of advancing senomorphic and senolytic therapies for heart failure (**Figure 2, Table 2**). Recent studies suggest that digoxin, due to its senomorphic capabilities, such as modifying the T-cell pool to mitigate the senescence-associated secretory phenotype, holds potential as a geroprotective agent for individuals with frailty and multiple chronic conditions, including heart failure [84]. The senolytic combination of dasatinib and quercetin (D+Q) has shown efficacy in improving endothelial-dependent and independent vasomotor function, reducing fibrosis, and alleviating left ventricular systolic dysfunction in aged mice [83, 85]. Quercetin alone has been found to prevent cardiac lipid accumulation and attenuate high-fat diet-induced cardiac fibrosis, systolic dysfunction, oxidative stress, and hypertrophy [86]. A two-week treatment with the senolytic agent ABT263, a BCL2 inhibitor, in two-year-old mice resulted in the clearance of senescent cells and ameliorated age-related cardiac fibrosis and hypertrophy [87]. In a

Table 2. Lifestyle interventions and therapeutic strategies to counteract aging-related heart failure.

Intervention/Strategy	Mechanisms of action	Clinical benefits	Ref.
Plant-based diet	Improves metabolic balance, reduces inflammation, and enhances ketone utilization.	Lowers heart failure risk and improves overall heart health.	[62, 63]
Caloric restriction	Reduces adiposity, improves metabolic efficiency, and supports cardiac function.	Benefits overweight patients; not suitable for underweight individuals.	[64]
Micronutrient supplementation	Provides essential nutrients (e.g., iron, omega-3 fatty acids) to improve heart efficiency and function.	Reduces hospitalization and improves ejection fraction.	[65-67]
Physical activity	Enhances mitochondrial biogenesis, reduces inflammation, promotes autophagy, and boosts energy metabolism.	Improves cardiac function and reduces pathological remodeling.	[8, 68-81]
Senolytics (e.g., Dasatinib and Quercetin)	Targets and clears senescent cells, reduces fibrosis, and enhances cardiomyocyte regeneration.	Improves cardiac function and lifespan.	[83-88]
Sirtuin activators (e.g., Resveratrol)	Activates mitochondrial pathways, reduces oxidative stress, and supports endothelial function.	Enhances heart health and promotes longevity.	[9, 90-94]
SGLT2 inhibitors	Activates autophagy and reduces oxidative stress through AMPK/SIRT1 pathways.	Reduces hospitalizations and mortality in diabetic patients.	[95-98]
Anti-inflammatory agents	Reduces systemic and cardiac inflammation via cytokine modulation (e.g., IL-1 blockers, Methotrexate).	Prevents cardiac remodeling and improves exercise capacity.	[99-105]

model of angiotensin II (AngII) infusion, ABT263 improved left ventricular ejection fraction and prevented the accumulation of senescent cells, thereby reducing cardiac fibrosis, hypertrophy, and inflammation [88].

In human hearts, a decline in NAD+ levels is commonly observed with aging [89]. NAD+ is essential as it is the precursor for several enzymes, including SIRTs, which are vital for managing cardiomyocyte survival and mitochondrial membrane stability via histone deacetylation. Restoring NAD+ levels using nicotinamide riboside supplementation holds promise as a strategy to combat the effects of cardiac aging and to mitigate cardiovascular diseases, including heart failure (Figure 2, Table 2) [90]. A study administering 1,000 mg of nicotinamide riboside twice a day to clinically stable heart failure patients demonstrated its safety and tolerability, as well as its ability to nearly double NAD+ levels in whole blood [91]. Resveratrol, known to activate SIRT1, holds promise in alleviating oxidative and inflammatory stress. It offers several vascular health benefits, such as reducing platelet aggregation and arterial stiffness, and protecting against conditions like atherosclerosis, hypertension, ischemia/reperfusion injury, and heart failure [9]. Metformin, which activates autophagy through SIRT1, has been shown to decrease the incidence and mortality of heart failure in individuals with cardiovascular diseases [92]. S17834, a SIRT1 activator, also demonstrates anti-inflammatory and anti-atherogenic properties in models of accelerated cardiovascular aging [93], SRT1720, another SIRT1 activator, has been shown to enhance endothelial function, decrease vascular oxidative stress and inflammation, and inhibit plaque formation associated with atherosclerosis, thereby contributing to improved health and lifespan in accelerated aging models [94]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, primarily used for managing blood glucose levels in diabetes, promote autophagy by activating the AMPK/SIRT1 pathway [95]. Treatment with SGLT2 inhibitors in diabetic patients have shown a reduction in cardiovascular mortality and hospitalizations related to heart failure [96-98].

Targeting IL-1β, a significant pro-inflammatory cytokine, has been shown to offer cardioprotective effects by reducing inflammation and enhancing cardiac function in heart failure (Figure 2, Table 2) [99]. Anakinra (an IL-1 blocker) treatment in heart failure patients with high plasma C-reactive protein (CRP) levels significantly improved the systemic inflammation and increased aerobic exercise capacity [100]. Canakinumab (an IL-1β inhibitor) treatment in patients with myocardial infarction and elevated CRP substantial reduced both heart failure-related hospitalizations and mortality risk [101]. Methotrexate, an established anti-rheumatic agent, offers cardiovascular benefits by curbing inflammation, reducing atherosclerosis, and preventing vascular aging. It has also been linked to a lower risk of heart failure in rheumatoid arthritis patients and can improve endothelial function, arterial stiffness, and hypertension [102, 103]. Colchicine, a drug traditionally used to treat gout by blocking NLRP3 inflammasome activation, has recently been recognized for its potential cardiovascular benefits, including anti-aging effects. Preclinical studies suggest that colchicine improves exercise capacity and mitigates cardiac diastolic dysfunction, oxidative stress, and fibrosis in a hypertensive heart failure mouse model [104]. However, a prospective, randomized trial involving stable chronic heart failure patients found that while colchicine effectively reduced inflammatory markers, it did not significantly impact functional status or the risk of death or hospitalization due to heart failure [105].

In summary, despite encouraging findings, uncertainties persist regarding the role of above discussed aging-targeted therapies

(senomorphics, senolytics, SIRT-activating and anti-inflammatory agents) against heart failure. Hence, comprehensive long-term clinical studies are necessary to confirm the enduring benefits of these therapies in maintaining cardiac function, and alleviating heart failure.

Conclusion

The rising incidence of heart failure in aging populations, along with as age-related comorbidities exacerbating the condition, underscores the urgent need for innovative treatment approaches. Lifestyle and dietary changes have emerged as key strategies, with exercise in particular showing promise in reducing the cardiac strain associated with aging while helping to identify potential therapeutic targets [106]. Identifying biomarkers plays a vital role in recognizing individuals at high risk and customizing interventions based on their unique molecular profiles [107]. Addressing the age-related comorbidities that accelerate heart failure progression could uncover common therapeutic pathways, offering widespread benefits and reducing the overall burden of heart failure [108]. Aging-targeted therapies, such as senomorphics, senolytics, anti-inflammatory and SIRT-activating agents, are being extensively tested as a treatment for heart failure. Together, these strategies have the potential to mitigate the key characteristics of age-related heart failure and lay the foundation for transformative approaches to heart failure management that may also have implications for other cardiovascular conditions.

Acknowledgments

No applicable.

Ethics approval

No applicable.

Data availability

This narrative review is based on previously published studies and publicly available data. No new datasets were generated or analyzed for the current review.

Funding

None.

Authors' contribution

Nam Nhut Phan contributed to the design, writing of this review article and final submission online. Fakhar-un-Nisa Yunus cellected data and drew figures for the manuscript.

Competing interests

The authors declare no competing interests.

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