Cardiovascular Diabetology

REVIEW

Open Access

Caloric restriction and its mimetics in heart failure with preserved ejection fraction: mechanisms and therapeutic potential

Alexander Fuerlinger[1,2], Alina Stockner[1], Simon Sedej[1,2,3] and Mahmoud Abdellatif[1,2,4,5*]

Abstract

The global increase in human life expectancy, coupled with an unprecedented rise in the prevalence of obesity, has led to a growing clinical and socioeconomic burden of heart failure with preserved ejection fraction (HFpEF). Mechanistically, the molecular and cellular hallmarks of aging are omnipresent in HFpEF and are further exacerbated by obesity and associated metabolic diseases. Conversely, weight loss strategies, particularly caloric restriction, have shown promise in improving health status in patients with HFpEF and are considered the gold standard for promoting longevity and healthspan (disease-free lifetime) in model organisms. In this review, we implicate fundamental mechanisms of aging in driving HFpEF and elucidate how caloric restriction mitigates the disease progression. Furthermore, we discuss the potential for pharmacologically mimicking the beneficial effects of caloric restriction in HFpEF using clinically approved and emerging caloric restriction mimetics. We surmise that these compounds could offer novel therapeutic avenues for HFpEF and alleviate the challenges associated with the implementation of caloric restriction and other lifestyle modifications to reduce the burden of HFpEF at a population level.

Keywords Aging, HFpEF, Obesity, Fasting, Caloric restriction mimetics, SGLT2, GLP-1A

Introduction

Human life expectancy is increasing globally, shifting the demographic landscape towards an aged population [1]. This demographic shift is accompanied by a rising prevalence and socioeconomic burden of cardiovascular diseases, which are the primary causes of morbidity and mortality worldwide [2]. Cardiovascular diseases, irrespective of their aetiology, often culminate in the development of heart failure (HF) with either preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF). Currently, over 56 million people worldwide are diagnosed with HF, [3] and at least half of them have HFpEF [4]. The prevalence of HFpEF has increased disproportionately compared to HFrEF, primarily due to population aging, [5, 6] making HFpEF a leading cause of hospitalisation in the elderly, with 29% of discharged patients readmitted within 90 days [7]. Long-term studies have also revealed alarmingly high mortality rates in patients with HFpEF that surpass many types of cancer [5].

Despite recent advances in the quest for effective therapies, the heterogeneous and complex pathophysiology

*Correspondence:
Mahmoud Abdellatif
mahmoud.abdellatif@medunigraz.at
[1]Department of Cardiology, Medical University of Graz, 8036 Graz, Austria
[2]BioTechMed-Graz, 8010 Graz, Austria
[3]Faculty of Medicine, University of Maribor, 2000 Maribor, Slovenia
[4]Metabolomics and Cell Biology Platforms, Institut Gustave Roussy, 94805 Villejuif, France
[5]Centre de Recherche des Cordeliers, Equipe labellisée par la Ligue contre le cancer, Université de Paris, Sorbonne Université, INSERM U1138, Institut Universitaire de France, Paris 75006, France

of HFpEF limit the effectiveness of emerging treatments to selected patient groups, and thus the burden of morbidity and mortality remains unacceptably high [8]. In this regard, HFpEF is increasingly recognized as an age-related disease, with the age-dependent risk of HFpEF substantially exceeding that of HFrEF, especially in women [9, 10]. Additionally, HFpEF is closely associated with the global pandemics of obesity and metabolic syndrome, as the majority of patients with HFpEF are either overweight or obese [11]. Thus, aging and associated systemic comorbidities appear to actively contribute to HFpEF and its prognosis by driving numerous pathogenic cardiac and noncardiac processes [12]. Consequently, HFpEF manifests as a multifaceted syndrome affecting various organs besides the heart, [13] highlighting the potential of anti-aging and metabolic therapies that beneficially impact multiple organ systems.

In this review, we elucidate the fundamental mechanisms of aging that are implicated in the development of HFpEF and examine how caloric restriction (CR), the gold-standard metabolic and anti-aging intervention, mitigates the progression of HFpEF. Furthermore, we explore the potential for pharmacologically mimicking the beneficial effects of CR using emerging CR mimetics (CRM), which could offer novel therapeutic possibilities for combating HFpEF. Ultimately, we address the challenges associated with implementing CR and other lifestyle modifications at a population level.

Pathophysiology of HFpEF

Recent years have seen a significant progress in understanding the pathophysiology of HFpEF, leading to the recognition of HFpEF as a multi-organ syndrome rather than an isolated disease of the heart [12]. The burden of non-cardiac comorbidities is remarkably higher in HFpEF compared to HFrEF [14]. Furthermore, patients with HFpEF are more likely to die from non-cardiovascular events than those with HFrEF [14]. Consequently, it is widely accepted that addressing both cardiac and extra-cardiac factors might be necessary for improving outcomes in patients with HFpEF. This view, however, adds to the complexity of HFpEF pathophysiology, as it encompasses the molecular and cellular changes not only in the heart but also in other organs, such as the lungs, kidneys, skeletal muscle, adipose tissue, as well as the vascular and immune system [12]. Thus, there remains a critical unmet need to identify unifying mechanisms that could pave the way for the development of novel and more efficient evidence-based therapies for HFpEF [15].

HFpEF as an age-related condition

Although HFpEF prevalence is increasing in both older and younger individuals, it remains predominantly a disease of the elderly, with only 14% of all HF diagnoses in patients under 40 years being HFpEF [16]. Furthermore, the incidence and prevalence of HFpEF increase later and more drastically with age compared to HFrEF [6]. Indeed, the most crucial risk factor for the development of HFpEF is advanced age, making the disease increasingly viewed as an age-related condition. As such, HFpEF is a leading cause of morbidity, hospitalization and mortality in adults over the age of 65 [17]. Notably, although old age alone may not cause HFpEF, age-associated systemic and cardiac changes, including arterial stiffness, cardiac fibrosis, ventricular stiffening, hypertrophy and diastolic dysfunction, provide an ideal substrate for the development of HFpEF [18]. Thus, the combination of genetic predisposition, environmental factors (e.g., unhealthy nutrition, sedentariness, and smoking) and comorbidities accelerates and exacerbates age-related systemic and cardiac changes at the molecular, cellular and whole-organ level, thereby substantially increasing the risk of HFpEF [10, 19–21].

It is important to note that the majority of HFpEF-promoting comorbidities, including obesity, diabetes mellitus (DM), hypertension, metabolic syndrome, chronic kidney disease (CKD), atrial fibrillation and amyloidosis are also predominantly age-related. For instance, the prevalence of DM significantly increases with age, with the number of patients over 65 years old projected to increase by more than 50% by 2030, making them the age group with the highest prevalence of DM in the future [22]. Similarly, age-related arterial stiffness increases the prevalence of hypertension by more than two folds in individuals over 80 years compared to those aged 40 to 59 years (76.5% vs. 32.4%, respectively) [23, 24]. CKD also drastically increases with age with a third of all patients being between 70 and 79 years of age, and over half being above 80 years [25]. Notably, 88% of patients with CKD also exhibit hypertension, 17% display DM, and 40% have at least two comorbidities [26]. This underscores the complexity of HFpEF, as age-associated comorbidities are highly interconnected. Irrespectively, amyloidosis is another relevant age-related risk factor for HFpEF, which almost exclusively affects those older than 60 years [27]. The age-associated deposition of amyloid-beta in the heart and vasculature is associated with cardiomyocyte dysfunction, vascular stiffening and increased inflammation, further connecting cardiovascular diseases with age-associated neurodegenerative diseases such as Alzheimer's disease [28].

Beyond epidemiological associations, emerging evidence from human and experimental studies indicate that the molecular and cellular hallmarks of aging are accentuated in HFpEF and might be mechanistically involved in its pathogenesis [29]. Among these, disabled macroautophagy, loss of proteostasis, genomic instability, epigenetic alterations, mitochondrial dysfunction,

dysregulated neurohormonal signalling, cell senescence and inflammation are particularly relevant for the cardiovascular system and might serve as potential entry points for the treatment of HFpEF.

The hallmarks of cardiovascular aging in HFpEF

Macroautophagy, herein referred to as autophagy, is a degradative pathway essential for cellular survival and homeostasis [30]. Autophagy progressively declines with age, [31, 32] and multiple studies have shown that genetic reinforcement of such decline causes accelerated cardiac and vascular aging [33–38]. For instance, cardiomyocyte-specific autophagy protein (ATG) 5 knockout mice exhibit left ventricular systolic and diastolic dysfunctions, exaggerated cardiac hypertrophy, pronounced effort intolerance, reduced cardiopulmonary functional capacity and shortened lifespan, coupled to disrupted sarcomere structure, dysfunctional mitochondria and increased oxidative stress [34]. Specifically in HFpEF, myocardial gene expression analysis of septal biopsies from non-failing and failing human hearts identified autophagy as a uniquely downregulated pathway in patients with HFpEF compared to those with HFrEF and to non-failing controls [39]. Conversely, pharmacological activation of autophagy via the natural polyamine spermidine prevented the development of HFpEF in *Dahl* salt-sensitive rats fed a high-salt diet [40]. Similarly, the autophagy inducer rapamycin effectively attenuated classical signs of HFpEF, like left ventricular hypertrophy, fibrosis and diastolic dysfunction, in mouse models of aging and pressure overload [41, 42].

Along similar lines, the efficiency of cellular **proteostasis** declines with age [43]. Particularly in cardiomyocytes, sarcomeres rely on the continuous removal of misfolded and aggregated proteins via the ubiquitin–proteasome system and chaperone-mediated autophagy [44–46]. Proteasomal functional analysis of cardiac tissue from human non-failing donor hearts and hearts with dilated or hypertrophic cardiomyopathy (HCM) revealed markedly reduced proteasomal proteolytic activity in failing and HCM hearts compared to controls [47]. The latter points towards a likely involvement in the pathophysiology of HFpEF, which is prevalent among patients with HCM [48].

Besides impaired protein and organelle quality control, DNA damage and **genomic instability** are intimately linked to advanced age and increased exposure to oxidative stress. Indeed, inefficient DNA damage response can lead to cellular senescence and inflammation– both of which are hallmarks of aging [49]. The analysis of human myocardia from patients with aortic stenosis, which resembles many features of HFpEF, showed elevated markers of DNA damage in cardiomyocytes, [50] potentially contributing to cardiomyocyte hypertrophy and myocardial fibrosis, and ultimately predisposing the heart to the development of HFpEF. Intriguingly, age-related mutations with significant effects on the cardiovascular system primarily occur in the blood and bone marrow, and not in the heart [29]. Carriers of these mutations—otherwise known as clonal haematopoiesis of indeterminate potential (CHIP)—are typically aged but otherwise healthy individuals. Among these, *Tet2* mutations have been identified as an independent risk factor for HFpEF in a large prospective cohort study, with 8090 participants [51]. A smaller study consisting of 81 patients with HFpEF further showed exacerbated diastolic dysfunction, higher N-terminal pro b-type natriuretic peptide (NT-proBNP) levels and worse prognosis in association with *Tet2*-mediated CHIP [52]. Along similar lines, an aggravated HFpEF phenotype was reported in bone marrow-specific *Tet2*-deficient mice subjected to high-fat diet (HFD) and L-NAME [52]. Mechanistically, *Tet2* mutations have been found to induce a pro-inflammatory phenotype through activation of the NLR family pyrin domain containing 3 (NLRP3)/interleukine-1β (IL-1β) axis [53]. Besides somatic mutations, age-related shifts in gene expression can also be caused by a variety of **Epigenetic factors**, including DNA methylation, histone modifications and non-coding RNAs (ncRNAs). In HFpEF, histone modifications through genetic or pharmacological interventions targeting histone deacetylases (HDACs) have been shown to attenuate diastolic dysfunction in clinically relevant rodent and feline models, [54–56] while other epigenetic factors are less understood and will require further investigations.

Mitochondrial dysfunction is a key characteristic of aging and a major pathophysiological mechanism underlying HFpEF [29, 57]. Impaired mitochondrial quality control is among the proposed mechanisms of mitochondrial dysfunction in HFpEF [58], leading to the accumulation of mitochondrial damage and a mismatch between ATP production and demand [57]. Supporting this notion, non-invasive cardiac imaging using ^{31}P-MRS revealed significantly reduced cardiac energy reserve [59]. In addition, reduced cardiac energy reserve and ATP production have been reported in various preclinical models of HFpEF [60, 61]. Of note, treatment of ZSF1 obese rats with an FDA-approved HFpEF therapeutic, the sodium-glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin, increased mitochondrial oxygen consumption via restabilising the mitochondrial electron transfer chain [62]. Besides energy metabolism, mitochondria play a crucial role in the intracellular calcium signalling, redox balance, anabolic and catabolic processes, inflammation and cellular death. Therefore, mitochondria are considered central organelles for multiple HFpEF-relevant pathological processes that go beyond impaired ATP production [29].

Another key aspect of aging is **cell senescence** or the permanent arrest of cell cycle, with pro-inflammatory phenotypic alterations. Available evidence implicates the accumulation of senescent cells in age-dependent cardiac structural and functional changes [63, 64]. Specifically in HFpEF, endothelial cellular senescence exacerbated HFpEF development in senescence-accelerated mice fed a high-fat/high-salt Western diet [65]. Compared to chow diet-fed controls, senescence-accelerated mice fed a Western diet showed worse left ventricular diastolic function and hypertrophy as well as left atrial dilatation, myocardial fibrosis, lung congestion and exercise intolerance, coupled to impaired vascular function and increased inflammation [65].

Furthermore, **neurohormonal signalling**, including the renin–angiotensin–aldosterone system (RAAS), β-adrenergic signalling and growth hormone signalling, is progressively dysregulated with aging [29]. RAAS and β-adrenergic signalling, in particular, play a central role in the pathophysiology and treatment of numerous age-related cardiovascular diseases. With aging, RAAS-dependent cardiovascular stiffening and decreased β-adrenergic reserve might predispose the heart to HFpEF [66]. Indeed, angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists (MRAs) and β-blockers are all commonly used in the treatment of several underlying comorbidities of HFpEF, including hypertension, ischemic heart disease and arrhythmia, among others [67]. However, with the exception of mineralocorticoid receptor antagonism, [68] clinical trials investigating the impact of RAAS modulation and β-adrenergic blockade in HFpEF failed to meet their primary endpoints [67, 69]. Nevertheless, subgroup analyses suggest that HFpEF patients on the lower end of the ejection fraction (EF) spectrum might still benefit from ARNI, ARB and MRA treatment to decrease hospitalizations [70]. Importantly, finerenone, a non-steroidal MRA, has been shown to improve major cardiovascular outcomes in patients with HFpEF [68]. Unlike other age-related neurohormonal dysregulations, insulin/insulin-like growth factor-1 (IGF-1) signalling exhibits a biphasic age-dependent relationship to cardiovascular health [71]. While IGF-1 signalling is indispensable in early life, it is detrimental in aging [71]. In that regard, old mice with cardiac-specific overexpression of the IGF-1 receptor (IGF-1R) have aggravated cardiac aging, accelerated HF development and reduced lifespan [71]. Conversely, genetic ablation or pharmacological inhibition of IGF-1R reduced cardiac hypertrophy, fibrosis, inflammation, and extends lifespan in aged mice [72, 73]. Importantly, although circulating plasma levels of IGF-1 decline in HFpEF, cardiac expression of IGF-1R increases, at least on a transcriptional level [74]. The down-stream effects of IGF-1 signalling include disabled autophagy, mitochondrial dysfunction, impaired oxidative metabolism and myocardial bioenergetics, all of which are relevant pathophysiological mechanisms contributing to HFpEF [71].

Finally, increased **inflammation** integrates all these aging mechanisms and their consequences in HFpEF pathogenesis. In fact, among the initial attempts to establish a unifying pathological mechanism underlying HFpEF, it was postulated that comorbidities induce systemic and coronary microvascular inflammation as a potential cause of HFpEF [75]. Indeed, circulating inflammatory markers, in particular, high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), are significantly associated with incident HFpEF [76, 77]. Besides circulating inflammatory markers, inflammation of the myocardium itself was observed in cardiac biopsies from patients with HFpEF, revealing increased infiltration of macrophages, dendritic cells and $CD3^+$ T-cells, which were closely associated with increased fibrosis and extracellular matrix remodelling [78, 79]. In this vein, inhibition of the NLRP3/IL-1β axis ameliorated cardiac dysfunction, fibrosis and inflammation in preclinical models of HFpEF [80, 81]. Notably, however, only a few clinical trials investigating immunomodulating therapies in HFpEF have been reported, with mixed outcomes. In the DHART trial, IL-1 receptor inhibition with anakinra reduced systemic inflammation and increased exercise capacity [82]. However, a slightly larger follow-up trial failed to reproduce the effects on exercise capacity, despite reducing hsCRP and NT-proBNP levels [83]. Notably, the extent of systemic inflammation is associated with phenotypic differences between HFpEF patients, [84] indicating that immunomodulating therapies might prove more beneficial in patients with elevated inflammatory markers. Regardless, outcomes of future and ongoing trials, like COLpEF, which is investigating the anti-inflammatory effects of colchicine in HFpEF, [85] will elucidate whether and how HFpEF can be optimally treated using anti-inflammatory interventions.

Taken together, the hallmarks of cardiovascular aging are markedly pronounced in HFpEF, suggesting accelerated biological aging in affected individuals. Although the pathophysiological relevance of each mechanism may vary in HFpEF, compelling evidence suggests that impaired autophagy, mitochondrial dysfunction, neurohormonal signalling, and inflammation are key drivers of HFpEF. Given the intricate interconnections among these aging hallmarks and their direct or indirect contributions to the systemic derangements observed in HFpEF, 29] each hallmark– either alone or in combination with

others– could represent a potential mechanistic target for novel therapeutic interventions in HFpEF.

Caloric restriction: the unattainable holy grail of longevity

CR is defined as a reduction of calorie intake without malnutrition. This can be implemented by reducing meal sizes without prolonged fasting periods, aiming for a CR of around 20–30%, or with time-restricted eating periods (i.e. intermittent fasting [IF]), such as: (i) alternate-day fasting (ADF), with eating only every other day; (ii) periodic fasting or arrhythmic IF, with two consecutive or dispersed fasting days per week; or (iii) time-restricted eating (TRE), with defined daily eating windows [86]. Rodent model organisms are commonly calorically restricted by being offered pre-weighed food allotments aimed at a 10–50% CR, which is much simpler than counting the actual amount of calories in rigorously conducted human studies [87]. However, rodents offered one meal per day are most likely to indulge in the provided food portion quickly, resulting in prolonged fasting periods between consecutive meals, mimicking IF. Besides that, the potential of overeating in periods with access to food has to be considered in human and rodent studies [86]. Irrespective of the regimen of CR or fasting, dietary restriction remains the gold standard to increase lifespan and promote healthy aging [86, 88–90]. CR extends lifespan up to 28% in mice, independently of genetic background, and this can be further prolonged through circadian alignment of feeding and fasting periods [91–93]. CR also prolongs lifespan and prevents the development of age-related morbidities in non-human primates [94, 95]. CR in humans has been also shown to attenuate signs of cardiovascular aging, including reduced ventricular and vascular stiffness, lowered blood pressure, and improved cardiac function in the form of alleviated diastolic dysfunction [96, 97].

Nutrient deprivation during CR and fasting induces a metabolic switch towards catabolic pathways, particularly autophagy induction, via several nutrient-sensing pathways, such as AMP-activated kinase (AMPK). AMPK is a key sensor of the cellular energy status and is activated by an increased AMP-to-ATP ratio upon reduced nutrient supply [98, 99]. Active phospho-AMPK inhibits the mechanistic target of rapamycin (mTOR) by direct phosphorylation of the mTORC1 subunit, [100] which is crucial in the regulation of cell growth by integrating anabolic signals like insulin or IGF-1 [101]. Inhibition of the mTOR signalling pathway has been shown to promote longevity in yeast, [102] flies, [103] nematodes [104] and in mice [105, 106]. In the fasted state, AMPK activation and mTOR inhibition also culminate in the activation of autophagy through AMPK-mediated phosphorylation and activation of unc-51 like autophagy activating kinase 1 (ULK1), which otherwise can be counteracted by active mTORC1 [107]. Furthermore, mTOR can inhibit the transcription factor EB (TFEB) and thereby suppress the expression of lysosomal and autophagy-related genes [108–110]. In addition, the insulin/IGF-1 pathway is involved in the regulation of autophagy, [111, 112] as it mediates the phosphatidylinositol-3-kinase (PI3K)/AKT signalling cascade, [111, 113, 114] known to activate mTORC1 [115, 116]. Besides attenuated mTORC1 activation, reduced IGF-1 signalling during CR or fasting exerts pro-autophagic actions by activating transcriptional activators of autophagy, including TFEB and forkhead-box O (FOXO) [117–119]. Alternatively, autophagy can be initiated through the nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase Sirtuin-1 (SIRT-1), which is activated by CR [120, 121]. In fact, CR upregulates SIRT-1 expression, [121–123] thereby activating autophagic flux through the deacetylation of essential autophagy machinery proteins, like ATG5, ATG7 or ATG8 [122]. Accordingly, mice lacking SIRT-1 do not show lifespan extension upon CR [124].

Mechanistically, downstream activation of autophagy is especially important in the clearance of dysfunctional mitochondria (i.e. mitophagy) that accumulate during aging [125]. Enhanced production of reactive oxygen species (ROS) in aged mitochondria, or accumulating mitochondrial DNA (mtDNA) released from leaky organelles can trigger inflammatory responses or, in the case of released caspases or nucleases can even lead to cell death [19]. In the model organism *C. elegans*, CR and IF restored the age-related imbalance in mitochondrial network remodelling via AMPK and increased mitochondrial fatty acid oxidation [126]. Besides autophagy, chronic low-grade inflammation in aging, known as inflammaging, [127] is also improved upon CR and fasting [116, 128]. Recently, analysis of transcriptional changes demonstrated that CR in aged rats rejuvenates the age-related pro-inflammatory state [129]. Specifically, the polarization to pro-inflammatory M1 macrophages is redirected towards anti-inflammatory M2, as well as reduced neutrophil migration into peripheral tissues and attenuated pro-inflammatory signalling (e.g. TNFα, IL1β, IL-6) in calorically restricted animals [129, 130]. Prolonged 25% CR has been also shown to lower the age-related increase in circulating pro-inflammatory cytokines, an effect that correlated with improved diastolic dysfunction in humans [96].

Caloric restriction in HFpEF

Patients with metabolic syndrome, who are typically at risk of HFpEF, exhibit reduced body weight and improved blood pressure, lipid profile and glucose homeostasis in response to CR and TRE [131, 132]. Specifically in obese, aged patients with HFpEF, CR (either alone or in

combination with physical exercise) improved quality of life, enhanced exercise capacity and lowered LV mass, body weight, body fat mass and inflammation [133, 134].

Mechanistically, it is plausible to speculate that CR protects from HFpEF, at least in part, through autophagy induction because autophagy-related genes and proteins are downregulated in humans and rodents with HFpEF, respectively [34, 39, 135, 136]. In support of this assumption, CR improved diastolic dysfunction, coinciding with suppressed mTOR and increased ratio of LC3B-II/LC3B-I (microtubule-associated protein 1 light chain 3B) in aged rats [137]. Among autophagy subroutines, impaired mitophagy might be particularly relevant in the pathogenesis of HFpEF due to associated mitochondrial dysfunction [29]. Recent studies show that although global cardiac autophagy is reduced in response to HFpEF risk factors, like obesity and increased afterload, ULK1-dependent alternative mitophagy is activated—albeit insufficiently—to counteract severe cardiac decline in preclinical models of diabetic and hypertrophic cardiomyopathy [138, 139]. However, experimental HFpEF, induced by a two-hit model combining obesity and hypertension, displayed blunted cardiac mitophagy, coupled with impaired metabolic adaptation due to inadequate fatty acid oxidation (FAO) and mitochondrial dysfunction, which could be counteracted by reactivating mitophagy or stimulating FAO [58, 140]. Since both mitophagy and FAO are upregulated during fasting and CR, [141–146] these findings highlight the potential involvement of mitophagy/autophagy and FAO in the anti-HFpEF effects of fasting and CR. Indeed, fasting appears to mechanistically depend on polyamine-induced autophagy and mitophagy to promote healthspan and lifespan in aged mice [147]. Since damaged mitochondria can also elicit significant inflammatory responses, the anti-inflammatory effects of CR are possibly mediated through mitochondrial quality control. Using a 3-hit mouse model HFpEF induced by obesity, aging and hypertension, a vicious cycle of enhanced NLRP3-inflammasome activation and mitochondrial dysfunction could be counteracted by supplementation of the ketone body β-hydroxybutyrate that also ameliorated HFpEF in these mice [81]. Notably, CR and fasting are known to significantly upregulate ketone body production and increase their consumption as an alternative fuel for cellular energy homeostasis [148]. Indeed, ADF attenuated age-related cardiac inflammation and remodelling in aged rats, [149, 150] whereas in humans, the cardioprotective actions of CR correlated with reduced inflammatory markers [96, 151].

In sum, accumulating evidence strongly suggests that CR and fasting can positively impact various aging mechanisms to improve cardiac health in HFpEF and associated risk factors, like aging, obesity, and hypertension (Fig. 1). However, implementing restrictive dietary regimens could potentially entail adverse effects such as reduced immunity, body temperature, bone density and lean mass, which can subsequently increase the risk of infections, falls and frailty, especially in older patients [86, 152, 153]. Additionally, CR has been associated with a decrease in sex hormone levels in sedentary and obese post-menopausal women, [154] who are at high risk for HFpEF [155]. Similarly, healthy middle-aged men who underwent long-term CR (with a mean duration of 7.4 years) had lower levels of total testosterone compared to controls, [156] which might favour HFpEF development due to the associated adverse effects on metabolic health [157]. That said, the effect of CR on testosterone levels appears to be dependent on body weight, as multiple studies have reported an increase in testosterone levels in obese men who underwent CR [158]. Furthermore, a recent study investigating the impact of 25% CR and TRE in males and females with obesity did not detect significant changes in any sex hormones, including in pre- and post-menopausal women, relative to controls [159]. This highlights the need for further studies investigating the impact of CR on sex hormones, preferably in the context of HFpEF.

Irrespectively, even though modified fasting regimens and concomitant resistance or endurance training and food supplements are increasingly proposed to resolve these issues, [160–164] poor adherence to fasting and CR undermines the feasibility of dietary interventions as a long-term treatment option [165, 166]. Thus, pharmacological alternatives that can mimic the benefits of CR and fasting, especially in old and obese patients with HFpEF, are needed.

Caloric restriction mimetics

CRMs are natural and synthetic pharmacological compounds capable of replicating certain metabolic effects of CR without the need to reduce food intake [167]. Specifically, CRMs converge on their ability to induce autophagy and counteract obesity through different mechanisms (Table 1). These include protein deacetylation via acetyl-CoA depletion, acetyltransferases inhibition or deacetylases activation, suppression of appetite and nutrient-sensing signalling and stimulating ketogenesis, among others [168].

Experimental caloric restriction mimetics

Inhibitors of acetyl-CoA synthesis

Protein acetylation can occur enzymatically via lysine acetyltransferases (KATs) or through a non-enzymatic reaction, with acetyl-CoA serving as the sole acetyl-group donor. Accordingly, a reduction in cytosolic acetyl-CoA decreases protein acetylation, thereby inducing autophagy [169]. Hydroxycitric acid (HCA) lowers the cytosolic

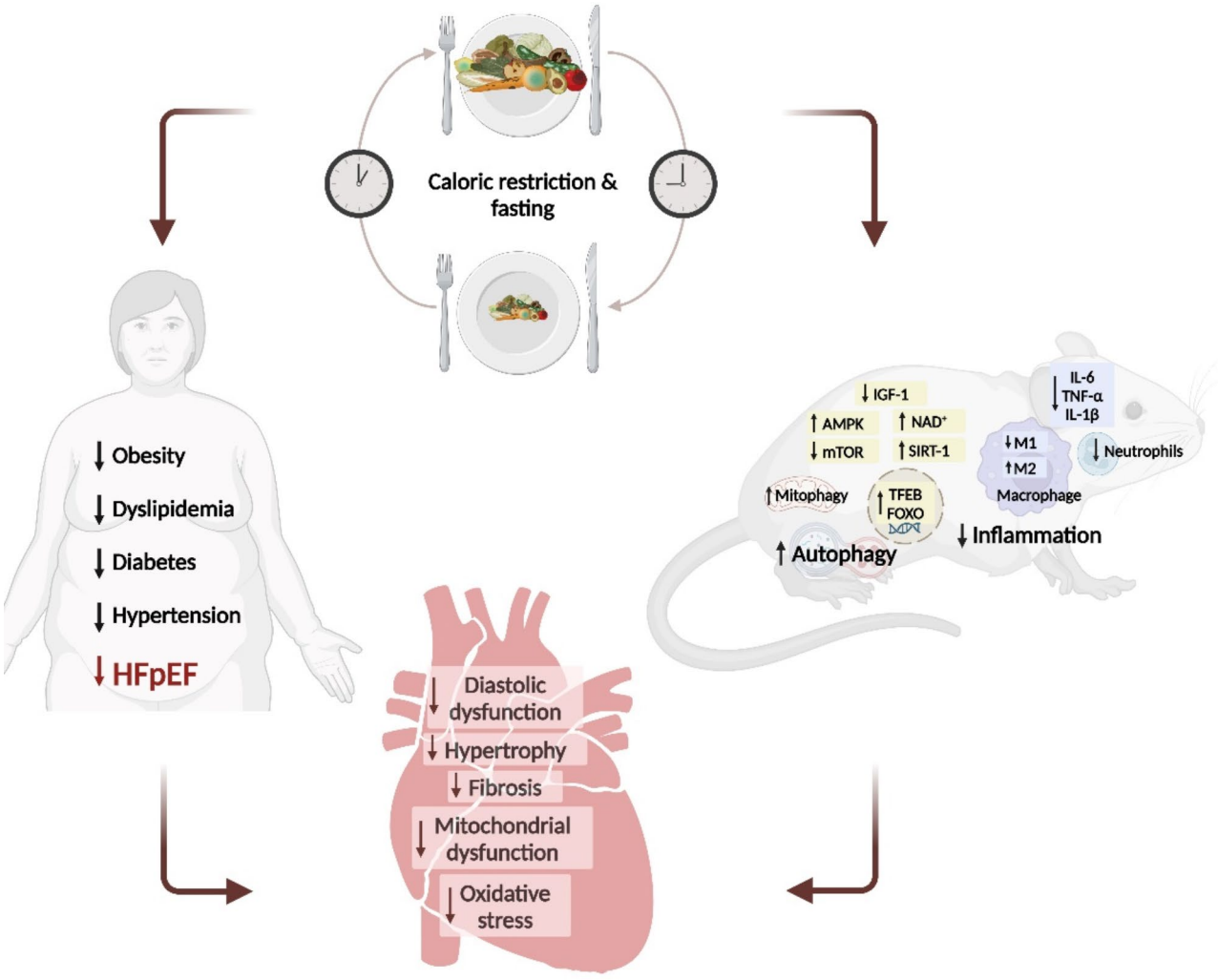

Fig. 1 Molecular targets and mechanisms involved in the systemic and cardiac health-promoting effects of caloric restriction (CR) and fasting. Abbreviations: AMPK, AMP-activated kinase; FOXO, forkhead-box O; HFpEF, heart failure with preserved ejection fraction; IGF-1, insulin-like growth factor-1; IL-1β, interleukin-1β; IL-6, interleukin-6; M1/M2, pro-/anti-inflammatory macrophage polarization; mTOR, mechanistic target of rapamycin; NAD^+, nicotinamide adenine dinucleotide (oxidized form); SIRT-1, sirtuin 1; TFEB, transcription factor EB; TNF-α, tumour necrosis factor-α; Created with BioRender.com

acetyl-CoA pool by competitive inhibition of ATP citrate lyase, leading to autophagy induction in multiple tissues and cell types, including the myocardium [169]. Furthermore, HCA reduced the body weight of mice in an autophagy-dependent fashion [169]. Beyond weight loss, HCA treatment elicited multiple systemic and cardiometabolic benefits in male obese Zucker rats, [170] known to develop a HFpEF-like phenotype [171]. Specifically, HCA-treated rats had lower body weight, insulin resistance and oxidative stress compared to non-treated controls. Notably, HCA treatment also decreased circulating levels of inflammatory markers, such as CRP and IL-6, which are typically elevated in HFpEF [170]. Along similar lines, another study reported salutary effects of HCA in male rats with pulmonary hypertension, including reduced right ventricular pressures and remodelling, along with reduced inflammatory markers and oxidative stress [172]. Nonetheless, direct studies investigating the effects of HCA on cardiac parameters in genuine models of HFpEF are lacking. Similarly, future HFpEF studies should investigate the impact of bempedoic acid, another ATP citrate lyase inhibitor that lowers acetyl-CoA levels. Given its established safety and efficacy profile in cardiovascular patients, [173] bempedoic acid might be even a more promising CRM candidate than HCA.

Perhexiline and its derivative perhexiline maleate reduce acetyl-CoA levels via inhibiting carnitine O-palmitoyl transferase 1, thereby decreasing mitochondrial fatty acid uptake and inducing autophagy [168, 174]. Perhexiline, which can also activate autophagy through mTOR suppression, is an already established pharmacological intervention for angina [175]. Moreover,

Table 1 Caloric restriction mimetics and their effects in animal models with or at risk of HFpEF

Condition	Compound	Molecular target(s)	Model(s)	Treatment effect(s)	Ref
At risk of HFpEF	Hydroxycitric acid	ACLY	ZDF obese rats Monocrotaline/hypoxia induced pulmonary hypertension in rats	Reduced obesity, insulin resistance, oxidative stress and inflammation Reduction in right ventricular pressures/hypertrophy, reduced inflammation	[170, 172]
HFpEF	Curcumin	EP300/AMPK	*Dahl* salt-sensitive rats	Reduced cardiac hypertrophy	[183]
	Spermidine	EP300	*Dahl* salt-sensitive rats	Reduced blood pressure, cardiac hypertrophy, diastolic dysfunction, inflammation and pulmonary congestion; Nephroprotection	[40]
	Berberine	DRP1/mTOR/SIRT-1	Mice fed HFD and L-NAME	Improved cardiac and mitochondrial function, improved Ca^{2+} handling	[207]
	Resveratrol	SIRT-1/GATA	Mice subjected to uninephrectomy and aldosterone	Improved cardiac dysfunction and reduced hypertrophic signalling	[209]
	Nicotinamide	NAD^+/Sirtuins	ZSF1 obese rats Mice fed HFD and L-NAME	Improved cardiac function and metabolism, and decreased cardiomyocyte stiffness	[60, 190]
	Nicotinamide riboside	NAD^+/Sirtuins	Mice fed HFD and L-NAME	Improved cardiac function and increased fatty acid oxidation	[191, 192]

Abbreviations: ACLY, ATP citrate lyase; AMPK, AMP-activated kinase; DRP1, dynamin-related protein 1; EP300, E1A binding protein p300; HFD, high-fat diet; HFpEF, heart failure with preserved ejection fraction; GATA, GATA binding protein; L-NAME, $N^{[\omega]}$-nitro-l-arginine methyl ester; mTOR, mechanistic target of rapamycin; SIRT-1, sirtuin-1; NAD^+, nicotinamide adenine dinucleotide (oxidized form)

perhexiline has shown promise in treating patients with HCM, [176] as it improved myocardial bioenergetics, denoted by an increased PCr/ATP ratio, reduced diastolic dysfunction, enhanced exercise capacity and attenuated symptomatic burden. These improvements were accompanied by reduced plasma glucose and fatty acid levels, suggesting increased cardiac substrate utilization by perhexiline. This might be particularly beneficial in the HFpEF myocardium, where energy metabolism and metabolic flexibility are impaired [61, 176]. Thus, given that patients with HCM often progress to clinically evident HFpEF, testing perhexiline in patients with HFpEF is warranted.

Inhibitors of Acetyltransferases

Inhibition of acetyltransferases, in particular E1A binding protein p300 (EP300), activates autophagy not only by reducing the acetylation status of proteins involved in autophagosome formation, [168] but also through inhibiting mTOR [177]. Besides its effect on autophagy, EP300 is involved in the regulation of cardiac hypertrophic and pro-fibrotic gene expression by interacting with myocyte enhancer factor 2 (MEF2), GATA and SMAD [178]. EP300 overexpression in transgenic mice induced dose-dependent cardiac hypertrophy and premature death due to heart failure [179]. Notably, failing human hearts with ischemic or dilated cardiomyopathy had an increased EP300 activity compared to non-failing controls [179]. Thus, EP300 inhibition might exert cardioprotective effects through simultaneous activation of autophagy and reduction of hypertrophic and pro-fibrotic gene expression.

Indeed, the natural polyamine spermidine, which inhibits EP300, extends the lifespan and cardiac healthspan in mice [40, 168]. Late-in-life administration of spermidine reduced age-dependent cardiac hypertrophic remodelling and diastolic dysfunction, rejuvenated cardiomyocyte composition and reduced inflammation [40]. Furthermore, spermidine improved mitochondrial morphology, biogenesis and function in cardiomyocytes from aged mice and rats [180, 181]. Aged rats treated with spermidine also exhibited SIRT-1 activation, leading to increased mitochondrial biogenesis via downstream deacetylation of PPARγ coactivator 1 alpha (PGC1-α) [180]. This resulted in improved mitochondrial oxidative phosphorylation and lower ROS production, and coincided with a reduced number of senescent cells [180]. Along similar lines, aged mice treated with spermidine had more mitochondria and a smaller degree of mitochondrial disorganisation [181]. Notably, spermidine levels progressively decrease in the human myocardium with aging and obesity, [29, 182] and are negatively associated with inflammation, oxidative stress, hypertension, cardiac remodelling and dysfunction [182]. These findings indicate that a reduction in cardiac spermidine levels due to aging or concomitant comorbidities might contribute to the development of HFpEF. Indeed, spermidine supplementation protected from HFpEF development in male *Dahl* salt-sensitive rats fed a high-salt diet [40]. Specifically, spermidine delayed the onset of hypertension and reduced cardiac hypertrophy, diastolic dysfunction, lung congestion and circulating inflammatory markers. Additionally, spermidine-treated *Dahl* rats had increased renal autophagy along with less severe hypertensive kidney injury, supporting the notion that extra-cardiac

effects might be beneficial, if not required, for HFpEF treatment [40]. Notably, the cardioprotective effects of spermidine appear to be largely dependent on autophagy, since they were absent in autophagy-deficient mice [40].

Curcumin is another natural compound that inhibits EP300, induces autophagy and can protect from HFpEF [177, 183]. Both curcumin and its active metabolite, tetrahydrocurcumin, have shown benefits in models of HFpEF risk factors, including obesity and aging. For instance, curcumin exerted cardioprotective effects, while activating autophagy and inhibiting apoptosis in a model of diabetic cardiomyopathy induced by streptozotocin and HFD [184]. Cardiac autophagy in these mice was induced through AMPK activation and the downstream phosphorylation of BCL-2 and BIM, reducing their binding to BECLIN1, thereby making it available for autophagy induction [184]. This highlights the potential of curcumin to activate autophagy via alternative targets to acetyltransferases. Mice fed tetrahydrocurcumin also exhibited an extended lifespan compared to controls when treated from a young age [185]. Beyond HFpEF risk factors, curcumin has been shown to reduce cardiac hypertrophy and protect against HFpEF development in *Dahl* salt-sensitive rats [183]. Notably, this effect was independent of blood pressure modulation, but was attributed to reduced GATA4 acetylation, which diminished the transcription of hypertrophic genes, such as ANF and β-MHC. Furthermore, EP300 levels were elevated in *Dahl* salt-sensitive rats, supporting the involvement of EP300 in hypertensive heart disease and related HFpEF in these rats [183]. Despite these promising preclinical results, a clinical trial investigating the effects of curcumin in hypertensive heart disease with preserved EF resulted in neutral outcomes. The primary endpoint of diastolic dysfunction, measured by E/e', was not improved after curcumin treatment for 24 weeks, although curcumin prevented an increase in BNP levels [186].

Activators of deacetylases

Major HFpEF risk factors, including aging, obesity and hypertension are all associated with a decline in cellular levels of nicotinamide adenine dinucleotide (NAD^+), [187] and this decline is further exacerbated after the onset of HFpEF both in animals and humans [60, 188, 189]. Since NAD^+ is the rate-limiting substrate for sirtuin deacetylases, its replenishment represents another strategy to reduce protein deacetylation, induce autophagy and attenuate age- and obesity-related cardiometabolic disorders, including HFpEF [187]. Indeed, oral supplementation with the NAD^+ precursor nicotinamide effectively elevated cardiac NAD^+ levels and prevented the development of HFpEF in preclinical models involving single and multiple hits of aging, obesity and hypertension [60, 190]. Both female and male rats and mice treated with nicotinamide exhibited improved diastolic function, reduced myocardial hypertrophy and lung congestion, along with enhanced exercise tolerance and cardiopulmonary function capacity. In ZSF1 obese rats with HFpEF, nicotinamide reduced body weight and induced a metabolic shift from glycolysis to FAO, restoring myocardial energy reserves. Furthermore, nicotinamide reinstated SIRT-1 expression and reduced SERCA2a and titin acetylation, resulting in reduced myocardial stiffness [60]. Nicotinamide riboside is another NAD^+ precursor that showed efficacy in murine HFpEF models induced by the combination of HFD and L-NAME (two-hit model) or by HFD, aging and desoxycorticosterone pivalate (three-hit model) [191, 192]. Nicotinamide riboside reduced the acetylation of enzymes involved in FAO and restored their functional capacity, possibly due to increased activity of the mitochondrial deacetylase SIRT-3 [191]. However, a study performed in SIRT-3 knockout mice suggested that the cardioprotective effect of nicotinamide riboside might be independent of SIRT-3-mediated mitochondrial protein deacetylation, at least in models of pressure overload-induced HFrEF [193]. Notably, NAD^+ repletion seems more efficacious in reversing experimental HFpEF induced by HFD and L-NAME than dietary intervention to reduce weight, [189] suggesting that restoring NAD^+ levels exerts beneficial effect beyond improving comorbidities. Thus, more research is warranted to elucidate the molecular mechanisms that underpin the cardioprotective benefits of NAD^+ replenishment. Similarly, although sirtuins have been shown to play a crucial role in the regulation of cardiac autophagy, [194, 195] the extent to which autophagy contributes to the beneficial effects of NAD^+ precursors in HFpEF remains to be elucidated.

Other CRMs in this class include polyphenols, such as berberine and resveratrol, which are proposed to act as sirtuin activators. However, it is important to note that the specificity of these nutraceuticals is uncertain, and they have been shown to interact with other molecular targets [196–200]. Irrespectively, berberine has shown efficacy in delaying aging, [201–203] and its metabolite tetrahydroberberrubine has been shown to enhance cardiac autophagy, thereby improving cardiac dysfunction in mice with accelerated aging induced by D-galactose as well as in mice and rats exposed to pressure overload [204–206]. Berberine treatment protected from HFpEF development in mice subjected to HFD and L-NAME [207]. In doing so, berberine activated cardiac autophagy, leading to improved mitochondrial function, cardiomyocyte calcium handling and mechanical properties during diastole. Along similar lines, resveratrol has been shown to induce autophagy, delay aging and extend the lifespan of metabolically-stressed mice [121, 208]. Furthermore,

resveratrol treatment prevented the development of diastolic dysfunction and attenuated myocardial hypertrophy, fibrosis, inflammation and ROS damage in a murine model of HFpEF induced by uninephrectomy and aldosterone administration [209]. Mechanistically, these cardioprotective effects were attributed to SIRT-1-dependent deacetylation of SMAD3, counteracting the profibrotic activation of TGF-β signalling [209].

Clinically approved caloric restriction mimetics

SGLT2 inhibitors

The clinical management of HFpEF has dramatically evolved in recent years, largely due to sodium-glucose cotransporter 2 inhibitors (SGLT2i) [210]. The SGLT2i dapagliflozin and empagliflozin have both demonstrated efficacy in reducing the rate of cardiovascular death or HF hospitalisation in patients with HFpEF [211, 212]. Importantly, these beneficial effects are observed regardless of diabetes status, [213] suggesting that the underlying mechanisms extend beyond lowering plasma glucose levels. While the exact molecular mechanisms underlying the cardioprotective actions of SGLT2i remain to be fully elucidated, evidence indicates that they recapitulate key aspects of caloric restriction, positioning them as putative CRMs [214]. Of note, SGLT2 inhibition results in glucose excretion that is equivalent to an estimated loss of 150–350 kcals per day, [215] roughly 5–10% reduction in the average daily caloric intake [216]. This caloric deficit, albeit modest, appears to trigger a metabolic shift toward increased ketone body production, characterized by body weight loss and nutrient-deprivation signalling, coupled to induced autophagy and mitochondrial biogenesis– all of which are bona fide hallmarks of CR [217].

Mechanistically, although higher ketone body availability is associated with cardioprotection, [218] including in HFpEF models, [81] the rise in ketone bodies induced by SGLT2i is modest and per se cannot entirely explain the benefits of SGLT2i treatment [219, 220]. Various reports have suggested a direct interaction of SGLT2i with mTOR, SIRT-1 and SIRT-3, [221–223] while others proposed an indirect suppression through ketone body-dependent signalling [219]. Furthermore, available evidence suggests that SGLT2i inhibit the glucose transporter GLUT1 in cardiomyocytes, reducing glucose uptake and leading to mTOR inhibition and AMPK activation. Thus, SGLT2i modulate the activity of major nutrient-sensing pathways, [219] which are disrupted in HFpEF due to accumulating metabolic intermediates [224]. In parallel, SGLT2i promote fatty acid uptake and oxidation, further reducing the accumulation of intermediate metabolites and restoring the balance between glycolysis and oxidative phosphorylation [219, 225]. Activation of AMPK and sirtuins and inhibition of mTOR subsequently increases autophagic flux, [223, 226, 227] and induces mitochondrial biogenesis through PGC1-α [219, 228]. SGLT2i also exhibit anti-inflammatory properties involving reduced NLRP3 activation, NF-κB signalling and IL-1β/IL-6 secretion, which have been linked to AMPK activation and the anti-inflammatory properties of ketone bodies [229]. Of note, disrupted mitophagy has been shown to aggravate the activation of NLRP3 inflammasome through the cytosolic escape of mtDNA that triggers cGAS/STING pathway [230, 231]. This finding points towards an anti-inflammatory mechanism of SGLT2i via increasing mitophagy, [232] and supports the observation that mitophagy is not adequately activated in HFpEF [58]. Notably, SGLT2 inhibition also increases the clearance of senescence cells, indicating that SGLT2i also delay aging like CR and other CRMs [233, 234].

Taken together, SGLT2i exert cardioprotective effects through multiple mechanisms reminiscent of CR, including weight loss, ketogenesis and nutrient-deprivation signalling, which converge on autophagy induction and improved mitochondrial quality control. Indeed, the protective effects of SGLT2i were absent, at least in the kidneys, of autophagy-deficient mice [235]. However, as the majority of these mechanistic studies were not conducted in HFpEF, further research is warranted to systematically examine the relevance and contribution of these different mechanisms in genuine models of HFpEF. Besides, SGLT2i have been associated with an increased risk of genital and urinary tract infections as well as hypotension in patients with HFpEF [212]. These risks could potentially be mitigated in the future by leveraging novel mechanistic insights to develop more targeted and refined interventions.

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1RA) have demonstrated efficacy in lowering body weight and improving outcomes in obesity-related HFpEF, thereby mimicking aspects of CR. A pooled analysis of the STEP-HFpEF, STEP-HFpEF DM, SELECT and FLOW trials, including 3743 participants, showed that the GLP-1RA semaglutide significantly reduced the risk of cardiovascular death or HF worsening, [236] independent of diabetes status. Follow-up subgroup analyses revealed greater benefits in patients with severe obesity (BMI ≥ 35 kg/m^2). However, although greater weight loss was associated with more pronounced HF improvements, the observed benefits cannot be attributed to weight reduction alone. Despite comparable weight loss, patients with more severe HF exhibited stronger treatment effects than those with less severe disease. Moreover, female patients and those without diabetes achieved more weight loss than males and diabetic patients but exhibited comparable improvements in outcomes. Kaplan–Meier analysis also indicate that cardiovascular benefits emerge

before significant weight loss [236]. Along similar lines, the GLP-1RA albiglutide significantly reduced the risk of major adverse cardiovascular events in diabetic patients without a significant effect on bodyweight [237]. More recently, tirzepatide, a dual agonist of both GLP-1R and glucose-dependent insulinotropic peptide (GIP) receptors that has a more pronounced weight-lowering effect than classical GLP-1RAs [238] improved major outcomes in patients with HFpEF in the SUMMIT trial [239].

GLP-1RAs lower body weight by modulating satiety and ingestion through central hypothalamic effects as well as peripheral mechanisms, such as delayed gastric emptying and reduced nutrient absorption [240]. Consequently, the adverse effects associated with modern long-acting GLP-1RAs primarily revolve around gastrointestinal discomfort [241]. Regardless, the reduction in caloric intake varied between trials, ranging between 16–39% [242]. This significant decrease in nutrient availability inevitably affects nutrient-sensing pathways. Indeed, administration of GLP-1RA or increasing endogenous GLP-1 activated AMPK signalling and inhibited mTOR activation with a subsequent increase in autophagic flux across multiple tissues, including the heart [243–250]. For instance, liraglutide protected against diabetic cardiomyopathy in ZDF rats in an autophagy-dependent manner [245]. Furthermore, increasing GLP-1 availability activated autophagy in the perivascular adipose tissue and improved vascular function, while reducing inflammatory signalling, potentially contributing to the blood pressure-lowering properties of GLP-1RA [246].

It is becoming increasingly clear that GLP-1RA induce systemic metabolic changes similar to CR, including improved glucose homeostasis, enhanced lipid profile, reduced blood pressure and inflammation with pleiotropic effects across organs relevant for HFpEF, such as adipose tissue, liver, kidneys, blood vessels and the heart [240]. Notably, semaglutide treatment exerts more pronounced cardioprotective effects than CR in a murine model of HFpEF induced by aging, obesity and hypertension, [251] denoting additional GLP-1R-mediated effects independent of weight loss and reduced caloric intake. This is supported by the broad expression of GLP-1R in various cell types and tissues [252]. However, available evidence indicates that GLP-1R signalling may have limited relevance for the heart, since GLP-1R-deficient mice were still protected against cardiac dysfunction by liraglutide, at least in the setting of myocardial infarction [253].

In sum, mounting preclinical and clinical evidence indicates that GLP-1RAs, which act through mechanisms reminiscent of CR, is another CRM drug class with proven efficacy especially in patients with obesity-related HFpEF.

Future perspectives and concluding remarks

Extensive research efforts over the past decade have transformed our understanding of the biology of aging and its role in HF. Considering that traditional risk factors account for only about 53% of the attributable risk for HF in the elderly, [254] the hallmarks of aging are becoming increasingly recognized as potential therapeutic targets in HFpEF. The ability to modify the molecular and cellular hallmarks of aging to alter the pathophysiology of HFpEF offers the exciting possibility that aging itself could represent a new area for therapeutic target discovery in HFpEF. Indeed, experimental CRMs with healthspan-promoting effects have gained traction in the field. While the mechanisms mediating the benefits of these experimental compounds in HFpEF are multifactorial and remain to be fully elucidated, their CR-like effects have spurred efforts to specifically target metabolic remodelling in HFpEF for therapeutic benefits. This knowledge has yielded novel targets to prevent, delay or even treat HFpEF (Fig. 2), but ensuring their translation to patients is needed and requires investments into further drug discovery and large-scale outcome trials.

In this regard, controlled randomized HFpEF studies, considering careful dose adaptation from rodent to human studies, are needed to allow comparisons of clinically effective CRMs (i.e. SGLT2i and GLP-1RA) with emerging CRMs that have been experimentally validated. In particular, mounting evidence indicates that NAD^+ precursors might become an alternative or an addition to SGLT2i and GLP-1RA, pending future studies identifying potential subgroups of patients with HFpEF, who are most likely to benefit from these putative CRMs. Moving forward, careful monitoring of any potential long-term adverse effects will be critical to ensure that they are clinically safe. Alternatively, repurposing currently used drugs with established safety profile and CR-like features might be worth considering. For example, metformin, which is a synthetic anti-diabetic biguanide and a CRM candidate drug, might be a viable option. Indeed, post-hoc analyses of clinical trials indicated that metformin potentially lowers mortality and hospitalisations in HFpEF, [255, 256] and two ongoing clinical trials are now testing metformin in patients with HFpEF [257, 258]. Collectively, progress in the development and testing of CRMs that impact shared biology of human aging and HFpEF will ultimately enhance their translational success rate and likely change the trajectory of HFpEF in older and obese adults.

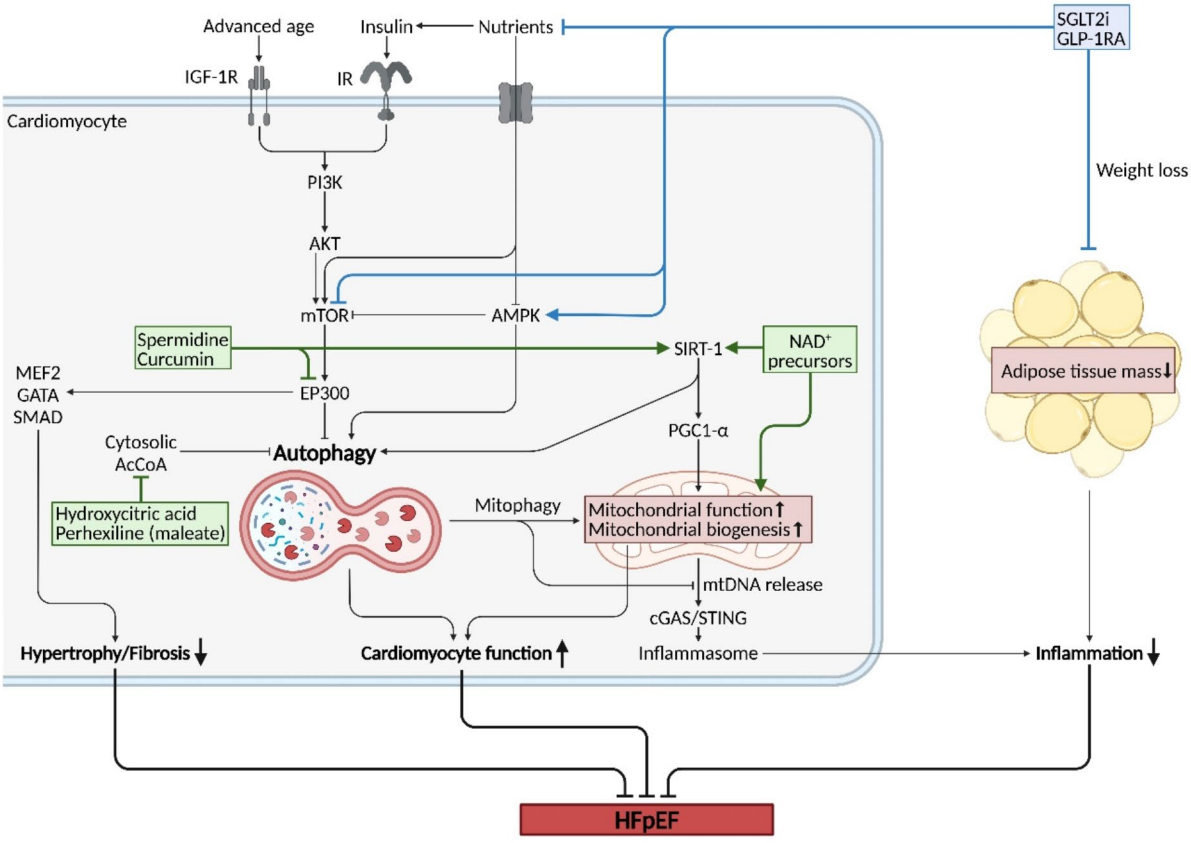

Fig. 2 Molecular targets and key mechanisms of caloric restriction mimetics in HFpEF. Abbreviations: AcCoA, acetyl-coenzyme A; AKT, AKT serine/threonine kinase; AMPK, AMP-activated protein kinase; cGAS, cyclic GMP-AMP synthase; EP300, E1A binding protein p300; GATA, GATA binding protein; GLP-1RA, glucagon-like peptide-1 receptor agonists; HFpEF, heart failure with preserved ejection fraction; IGF-1R, insulin-like growth factor-1 receptor; IR, insulin receptor; MEF2, myocyte enhancer factor 2; mtDNA, mitochondrial DNA; mTOR, mechanistic target of rapamycin; NAD^+, nicotinamide adenine dinucleotide (oxidized form); PGC1-α, PPAR gamma coactivator 1-alpha; PI3K, phosphatidylinositol-3-kinase; SGLT2i, sodium/glucose co-transporter 2 inhibitor; SMAD, suppressor of mothers against decapentaplegic; STING, stimulator of interferon genes protein; Created with BioRender.com

Acknowledgements
M.A. and S.S. are grateful to the Austrian Science Fund (FWF) for the Excellence Cluster (10.55776/COE14), and acknowledge funding received from the Medical University of Graz (Excellence Cluster MetAGE and Flagship Project VASC-HEALTH), and BioTechMed-Graz (Flagship Project INTERACD$^+$ to S.S., and Young Researcher Group to M.A.). M.A. acknowledge additional funding received from the FWF (DOI: 10.55776/P34926) as well as (DOI: 10.55776/I6931) under the umbrella of the Partnership Fostering a European Research Area for Health (ERA4Health) (GA N° 101095426 of the EU Horizon Europe Research and Innovation Program).

Author contributions
MA conceived the review. AF and AS conducted literature research and created figures. All authors contributed to writing and reviewing the manuscript.

Data availability
No datasets were generated or analysed during the current study.

Competing interests
M.A. and S.S. hold a patent related to the cardiometabolic effects of nicotinamide and spermidine. The other authors report no conflicts of interest.

Received: 25 November 2024 / Accepted: 26 December 2024
Published online: 18 January 2025

References

1. Kontis V, et al. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. Lancet. 2017;389:1323–35.
2. Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The global burden of cardiovascular diseases and risk. J Am Coll Cardiol. 2022;80:2361–71.
3. Yan T, et al. Burden, trends, and inequalities of heart failure globally, 1990 to 2019: a secondary analysis based on the global burden of disease 2019 study. JAHA. 2023;12: e027852.
4. Gladden JD, Chaanine AH, Redfield MM. Heart failure with preserved ejection fraction. Annu Rev Med. 2018;69:65–79.
5. Owan TE, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355:251–9.
6. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14:591–602.
7. Fonarow GC, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50:768–77.
8. Peikert A, Solomon SD. Contemporary treatment options in heart failure with preserved ejection fraction. Eur Heart J - Cardiovascular Imaging. 2024. https://doi.org/10.1093/ehjci/jeae201.
9. Ceia F, et al. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. Eur J Heart Fail. 2002;4:531–9.
10. Abdellatif M, Kroemer G. Heart failure with preserved ejection fraction: An age-related condition. J Mol Cell Cardiol. 2022;S0022–2828(22):00052–9. https://doi.org/10.1016/j.yjmcc.2022.03.008.

11. Borlaug BA, et al. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. Cardiovasc Res. 2023;118:3434–50.
12. Mishra S, Kass DA. Cellular and molecular pathobiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2021;18:400–23.
13. Shah SJ, et al. Research priorities for heart failure with preserved ejection fraction: national heart, lung, and blood institute working group summary. Circulation. 2020;141:1001–26.
14. Streng KW, et al. Non-cardiac comorbidities in heart failure with reduced, mid-range and preserved ejection fraction. Int J Cardiol. 2018;271:132–9.
15. Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart failure with preserved ejection fraction: JACC scientific statement. J Am Coll Cardiol. 2023;81:1810–34.
16. Wong CM, et al. Heart failure in younger patients: the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). Eur Heart J. 2014;35:2714–21.
17. Savarese G, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2022;118:3272–87.
18. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part ii: the aging heart in health: links to heart disease. Circulation. 2003;107:346–54.
19. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. Cell. 2023;186:243–78.
20. Yang K, et al. Lifestyle effects on aging and CVD: A spotlight on the nutrient-sensing network. Ageing Res Rev. 2023;92: 102121.
21. Withaar C, Li S, Meems LMG, Silljé HHW, de Boer RA. Aging and HFpEF: Are we running out of time? J Mol Cell Cardiol. 2022;168:33–4.
22. Whiting DR, Guariguata L, Weil C, Shaw J. IDF Diabetes Atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011;94:311–21.
23. Sun Z. Aging, Arterial Stiffness, and Hypertension. Hypertension. 2015;65:252–6.
24. Mozaffarian, D. *et al.* Heart Disease and Stroke Statistics—2015 Update: A Report From the American Heart Association. *Circulation***131**, (2015).
25. Kampmann JD, et al. Prevalence and incidence of chronic kidney disease stage 3–5– results from KidDiCo. BMC Nephrol. 2023;24:17.
26. Fraser SDS, et al. The burden of comorbidity in people with chronic kidney disease stage 3: a cohort study. BMC Nephrol. 2015;16:193.
27. Papingiotis', 'Georgios, Basmpana', 'Lamprini & Farmakis', 'Dimitrios. Cardiac amyloidosis: epidemiology, diagnosis and therapy. https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-19/cardiac-amyloidosis-epidemiology-diagnosis-and-therapy.
28. Stakos DA, et al. The Alzheimer's disease amyloid-beta hypothesis in cardiovascular aging and disease. J Am Coll Cardiol. 2020;75:952–67.
29. Abdellatif M, Rainer PP, Sedej S, Kroemer G. Hallmarks of cardiovascular ageing. Nat Rev Cardiol. 2023;20:754–77.
30. Abdellatif M, Sedej S, Carmona-Gutierrez D, Madeo F, Kroemer G. Autophagy in cardiovascular aging. Circ Res. 2018;123:803–24.
31. Rubinsztein DC, Mariño G, Kroemer G. Autophagy and aging. Cell. 2011;146:682–95.
32. Kaushik S, et al. Autophagy and the hallmarks of aging. Ageing Res Rev. 2021;72: 101468.
33. Taneike M, et al. Inhibition of autophagy in the heart induces age-related cardiomyopathy. Autophagy. 2010;6:600–6.
34. Ljubojević-Holzer S, et al. Loss of autophagy protein ATG5 impairs cardiac capacity in mice and humans through diminishing mitochondrial abundance and disrupting Ca2+cycling. Cardiovasc Res. 2022;118:1492–505.
35. Michiels CF, Fransen P, De Munck DG, De Meyer GRY, Martinet W. Defective autophagy in vascular smooth muscle cells alters contractility and Ca2+ homeostasis in mice. Am J Physiol - Heart Circul Physiol. 2015;308:H557–67.
36. Grootaert MOJ, et al. Defective autophagy in vascular smooth muscle cells accelerates senescence and promotes neointima formation and atherogenesis. Autophagy. 2015;11:2014–32.
37. Torisu T, et al. Autophagy regulates endothelial cell processing, maturation and secretion of von Willebrand factor. Nat Med. 2013;19:1281–7.
38. Hsieh PN, et al. A conserved KLF-autophagy pathway modulates nematode lifespan and mammalian age-associated vascular dysfunction. Nat Commun. 2017;8:1–12.
39. Hahn VS, et al. Myocardial gene expression signatures in human heart failure with preserved ejection fraction. Circulation. 2021;143:120–34.
40. Eisenberg T, et al. Cardioprotection and lifespan extension by the natural polyamine spermidine. Nat Med. 2016;22:1428–38.
41. Gu J, et al. Rapamycin inhibits cardiac hypertrophy by promoting autophagy via the MEK/ERK/Beclin-1 pathway. Front Physiol. 2016;7: 184300.
42. Quarles E, et al. Rapamycin persistently improves cardiac function in aged, male and female mice, even following cessation of treatment. Aging Cell. 2020;19: e13086.
43. Alberti S, Hyman AA. Biomolecular condensates at the nexus of cellular stress, protein aggregation disease and ageing. Nat Rev Mol Cell Biol. 2021;22:196–213.
44. Hofmann C, Katus HA, Doroudgar S. Protein misfolding in cardiac disease. Circulation. 2019;139:2085–8.
45. McLendon PM, Robbins J. Proteotoxicity and cardiac dysfunction. Circ Res. 2015;116:1863–82.
46. Martin TG, et al. Cardiomyocyte contractile impairment in heart failure results from reduced BAG3-mediated sarcomeric protein turnover. Nat Commun. 2021;12:1–16.
47. Predmore JM, et al. Ubiquitin proteasome dysfunction in human hypertrophic and dilated cardiomyopathies. Circulation. 2010;121:997–1004.
48. Chen Q-F, et al. Clinical characteristics and prognosis of patients with hypertrophic cardiomyopathy and heart failure with preserved ejection fraction. Clin Res Cardiol. 2024;113:761–9.
49. Pezone A, et al. Inflammation and DNA damage: cause, effect or both. Nat Rev Rheumatol. 2023;19:200–11.
50. Stadiotti I, et al. Pressure overload activates dna-damage response in cardiac stromal cells: A novel mechanism behind heart failure with preserved ejection fraction? Front Cardiovas Med. 2022;9: 878268.
51. Schuermans A, et al. Clonal hematopoiesis and incident heart failure with preserved ejection fraction. JAMA Netw Open. 2024;7:E2353244.
52. Cochran JD, et al. Clonal hematopoiesis in clinical and experimental heart failure with preserved ejection fraction. Circulation. 2023;148:1165–78.
53. Sano S, et al. Tet2-mediated clonal hematopoiesis accelerates heart failure through a mechanism involving the IL-1β/NLRP3 inflammasome. J Am Coll Cardiol. 2018;71:875–86.
54. Ranjbarvaziri S, et al. Targeting HDAC6 to treat heart failure with preserved ejection fraction in mice. Nat Commun. 2024;15:1–17.
55. Jeong MY, et al. Histone deacetylase activity governs diastolic dysfunction through a nongenomic mechanism. Sci Transl Med. 2018;10:eaao0144.
56. Wallner M, et al. HDAC inhibition improves cardiopulmonary function in a feline model of diastolic dysfunction. Sci Transl Med. 2020;12:7205.
57. Kumar AA, Kelly DP, Chirinos JA. Mitochondrial dysfunction in heart failure with preserved ejection fraction. Circulation. 2019;139:1435–50.
58. Yoshii A, et al. Blunted cardiac mitophagy in response to metabolic stress contributes to HFpEF. Circ Res. 2024;135:1004–17.
59. Phan TT, et al. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. J Am Coll Cardiol. 2009;54:402–9.
60. Abdellatif, M. *et al.* Nicotinamide for the treatment of heart failure with preserved ejection fraction. *Science Translational Medicine***13**, (2021).
61. Sun Q, et al. Mitochondrial fatty acid oxidation is the major source of cardiac adenosine triphosphate production in heart failure with preserved ejection fraction. Cardiovasc Res. 2024;120:360–71.
62. Schauer A, et al. Empagliflozin improves diastolic function in HFpEF by restabilizing the mitochondrial respiratory chain. Circul Heart Failure. 2024;17:e011107.
63. Luan Y, et al. Cardiac cell senescence: molecular mechanisms, key proteins and therapeutic targets. Cell Death Discov. 2024;10:1–15.
64. Anderson R, et al. Length-independent telomere damage drives post-mitotic cardiomyocyte senescence. EMBO J. 2019. https://doi.org/10.1161/CIRCHEARTFAILURE.116.003806.
65. Gevaert AB, et al. Endothelial senescence contributes to heart failure with preserved ejection fraction in an aging mouse model. Circ Heart Fail. 2017. https://doi.org/10.1161/CIRCHEARTFAILURE.116.003806.
66. Jia G, Aroor AR, Hill MA, Sowers JR. Role of renin-angiotensin-aldosterone system activation in promoting cardiovascular fibrosis and stiffness. Hypertension. 2018;72:537–48.
67. McDonagh TA, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599–726.
68. Solomon SD, et al. Finerenone in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2024;391:1475–85.
69. Matsumoto S, et al. Calcium channel blocker use and outcomes in patients with heart failure and mildly reduced and preserved ejection fraction. Eur J Heart Fail. 2023;25:2202–14.
70. Heidenreich PA, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American college of cardiology/American

heart association joint committee on clinical practice guidelines. Circulation. 2022;145:E895–1032.
71. Abdellatif M, et al. Fine-tuning cardiac insulin-like growth factor 1 receptor signaling to promote health and longevity. Circulation. 2022;145:1853–66.
72. Ock S, et al. Deletion of IGF-1 receptors in cardiomyocytes attenuates cardiac aging in male mice. Endocrinology. 2016;157:336–45.
73. Mao K, et al. Late-life targeting of the IGF-1 receptor improves healthspan and lifespan in female mice. Nat Commun. 2018;9:2394.
74. D'Assante R, et al. Myocardial expression of somatotropic axis, adrenergic signalling, and calcium handling genes in heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. ESC Heart Failure. 2021;8:1681–6.
75. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: Comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62:263–71.
76. Tromp, J. *et al.* Biomarker profiles in heart failure patients with preserved and reduced ejection fraction. *Journal of the American Heart Association***6**, (2017).
77. Kalogeropoulos, A. *et al.* Inflammatory Markers and Incident Heart Failure Risk in Older Adults. The Health ABC (Health, Aging, and Body Composition) Study. *Journal of the American College of Cardiology***55**, 2129–2137 (2010).
78. Hahn VS, et al. Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. JACC Heart Failure. 2020;8:712–24.
79. Westermann D, et al. Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. Circul Heart Failure. 2011;4:44–52.
80. Shen S, et al. Colchicine alleviates inflammation and improves diastolic dysfunction in heart failure rats with preserved ejection fraction. Eur J Pharmacol. 2022;929: 175126.
81. Deng Y, et al. Targeting mitochondria-inflammation circuit by β-hydroxybutyrate mitigates HFpEF. Circ Res. 2021;128:232–45.
82. Van Tassell BW, et al. Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART pilot study). Am J Cardiol. 2014;113:321–7.
83. Van Tassell BW, et al. IL-1 blockade in patients with heart failure with preserved ejection fraction. Circ Heart Fail. 2018;11: e005036.
84. Sabbah MS, et al. Obese-inflammatory phenotypes in heart failure with preserved ejection fraction. Circ Heart Fail. 2020;13:E006414.
85. Bourcier L, et al. Effects of COLchicine on inflammation, myocardial damage and microvascular dysfunction in heart failure with Preserved Ejection Fraction– the COLpEF trial. Arch Cardiovasc Dis Suppl. 2023;15:53.
86. Hofer SJ, Carmona-Gutierrez D, Mueller MI, Madeo F. The ups and downs of caloric restriction and fasting: from molecular effects to clinical application. EMBO Mol Med. 2022;14: e14418.
87. Vaughan KL, et al. Caloric restriction study design limitations in rodent and nonhuman primate studies. J Gerontol: Series A. 2018;73:48–53.
88. Voglhuber J, Ljubojevic-Holzer S, Abdellatif M, Sedej S. Targeting cardiovascular risk factors through dietary adaptations and caloric restriction mimetics. Front Nutr. 2021;8: 758058.
89. Duan H, et al. Dietary strategies with anti-aging potential: Dietary patterns and supplements. Food Res Int. 2022;158: 111501.
90. Kapahi P, Kaeberlein M, Hansen M. Dietary restriction and lifespan: Lessons from invertebrate models. Ageing Res Rev. 2017;39:3–14.
91. Mitchell SJ, et al. Daily fasting improves health and survival in male mice independent of diet composition and calories. Cell Metab. 2019;29:221-228.e3.
92. Di Francesco A, et al. Dietary restriction impacts health and lifespan of genetically diverse mice. Nature. 2024;634:684–92.
93. Acosta-Rodríguez V, et al. Circadian alignment of early onset caloric restriction promotes longevity in male C57BL/6J mice. Science. 2022;376:1192–202.
94. Mattison JA, et al. Caloric restriction improves health and survival of rhesus monkeys. Nat Commun. 2017;8:14063.
95. Mattison JA, et al. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. Nature. 2012;489:318–21.
96. Meyer TE, et al. Long-term caloric restriction ameliorates the decline in diastolic function in humans. J Am Coll Cardiol. 2006;47:398–402.
97. Dengo AL, et al. Arterial destiffening with weight loss in overweight and obese middle-aged and older adults. Hypertension. 2010;55:855–61.
98. Xiao B, et al. Structure of mammalian AMPK and its regulation by ADP. Nature. 2011;472:230–3.
99. Cantó C, Auwerx J. Calorie restriction: Is AMPK a key sensor and effector? Physiology (Bethesda). 2011;26:214–24.
100. Gwinn DM, et al. AMPK phosphorylation of raptor mediates a metabolic checkpoint. Mol Cell. 2008;30:214–26.
101. Weichhart T. mTOR as regulator of lifespan, aging, and cellular senescence: a mini-review. Gerontology. 2018;64:127–34.
102. Yalcin G, Kim J, Seo D, Lee CK. FPR1 is essential for rapamycin-induced lifespan extension in Saccharomyces cerevisiae. Biochem Biophys Res Commun. 2023;653:76–82.
103. Su Y, et al. Alpha-ketoglutarate extends Drosophila lifespan by inhibiting mTOR and activating AMPK. Aging (Albany NY). 2019;11:4183–97.
104. Vidovic, T., Dakhovnik, A., Hrabovskyi, O., MacArthur, M. R. & Ewald, C. Y. AI-Predicted mTOR Inhibitor Reduces Cancer Cell Proliferation and Extends the Lifespan of C. elegans. *Int J Mol Sci***24**, (2023).
105. Ortega-Molina A, et al. A mild increase in nutrient signaling to mTORC1 in mice leads to parenchymal damage, myeloid inflammation and shortened lifespan. Nat Aging. 2024;4:1102–20.
106. Wu JJ, et al. Increased mammalian lifespan and a segmental and tissue-specific slowing of aging after genetic reduction of mTOR expression. Cell Rep. 2013;4:913–20.
107. Kim J, Kundu M, Viollet B, Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol. 2011;13:132–41.
108. Settembre C, et al. TFEB links autophagy to lysosomal biogenesis. Science. 2011;332:1429–33.
109. Roczniak-Ferguson A, et al. The transcription factor TFEB links mTORC1 signaling to transcriptional control of lysosome homeostasis. Sci Signal. 2012;5:ra42.
110. Napolitano G, et al. mTOR-dependent phosphorylation controls TFEB nuclear export. Nat Commun. 2018;9:3312.
111. Green CL, Lamming DW, Fontana L. Molecular mechanisms of dietary restriction promoting health and longevity. Nat Rev Mol Cell Biol. 2022;23:56–73.
112. Geffken SJ, et al. Insulin and IGF-1 elicit robust transcriptional regulation to modulate autophagy in astrocytes. Mol Metabolism. 2022;66: 101647.
113. Kenyon C. The first long-lived mutants: discovery of the insulin/IGF-1 pathway for ageing. Philos Trans R Soc Lond B Biol Sci. 2011;366:9–16.
114. Holzenberger M, et al. IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. Nature. 2003;421:182–7.
115. Bond P. Regulation of mTORC1 by growth factors, energy status, amino acids and mechanical stimuli at a glance. J Int Soc Sports Nutr. 2016;13:8.
116. Mercken EM, et al. Calorie restriction in humans inhibits the PI3K/AKT pathway and induces a younger transcription profile. Aging Cell. 2013;12:645–51.
117. Di Malta C, Cinque L, Settembre C. Transcriptional regulation of autophagy: mechanisms and diseases. Front Cell Dev Biol. 2019;7:114.
118. Mitchell SE, et al. The effects of graded levels of calorie restriction: II. Impact of short term calorie and protein restriction on circulating hormone levels, glucose homeostasis and oxidative stress in male C57BL/6 mice. Oncotarget. 2015;6:23213–37.
119. Kazemi A, Speakman JR, Soltani S, Djafarian K. Effect of calorie restriction or protein intake on circulating levels of insulin like growth factor I in humans: a systematic review and meta-analysis. Clin Nutr. 2020;39:1705–16.
120. Yessenkyzy A, et al. Polyphenols as caloric-restriction mimetics and autophagy inducers in aging research. Nutrients. 2020;12:1344.
121. Morselli E, et al. Caloric restriction and resveratrol promote longevity through the Sirtuin-1-dependent induction of autophagy. Cell Death Dis. 2010;1:e10–e10.
122. Lee IH, et al. A role for the NAD-dependent deacetylase Sirt1 in the regulation of autophagy. Proc Natl Acad Sci U S A. 2008;105:3374–9.
123. Wei Z, et al. Caloric restriction, Sirtuins, and cardiovascular diseases. Chin Med J (Engl). 2024;137:921–35.
124. Boily G, et al. SirT1 regulates energy metabolism and response to caloric restriction in mice. PLoS ONE. 2008;3: e1759.
125. Guo J, Chiang WC. Mitophagy in aging and longevity. IUBMB Life. 2022;74:296–316.
126. Weir HJ, et al. Dietary restriction and AMPK increase lifespan via mitochondrial network and peroxisome remodeling. Cell Metab. 2017;26:884-896.e5.
127. Fulop T, et al. Immunology of Aging: the Birth of Inflammaging. Clin Rev Allergy Immunol. 2023;64:109–22.
128. Dugan B, Conway J, Duggal NA. Inflammaging as a target for healthy ageing. Age Ageing. 2023. https://doi.org/10.1093/ageing/afac328.
129. Ma S, et al. Caloric restriction reprograms the single-cell transcriptional landscape of rattus norvegicus aging. Cell. 2020;180:984-1001.e22.

130. Ryu S, et al. The matricellular protein SPARC induces inflammatory interferon-response in macrophages during aging. Immunity. 2022;55:1609-1626.e7.
131. Kunduraci YE, Ozbek H. Does the energy restriction intermittent fasting diet alleviate metabolic syndrome biomarkers? A randomized controlled trial. Nutrients. 2020;12:3213.
132. Wilkinson MJ, et al. Ten-hour time-restricted eating reduces weight, blood pressure, and atherogenic lipids in patients with metabolic syndrome. Cell Metab. 2020;31:92-104.e5.
133. El Hajj EC, et al. Pragmatic weight management program for patients with obesity and heart failure with preserved ejection fraction. J Am Heart Assoc. 2021;10: e022930.
134. Kitzman DW, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: A randomized clinical trial. JAMA - J Am Med Assoc. 2016;315:36–46.
135. Abdellatif M, Schmid ST, Fuerlinger A, Kroemer G. Anti-ageing interventions for the treatment of cardiovascular disease. Cardiovasc Res. 2024;00:1–13.
136. Summer G, et al. A directed network analysis of the cardiome identifies molecular pathways contributing to the development of HFpEF. J Mol Cell Cardiol. 2020;144:66–75.
137. Shinmura K, et al. Impact of long-term caloric restriction on cardiac senescence: caloric restriction ameliorates cardiac diastolic dysfunction associated with aging. J Mol Cell Cardiol. 2011;50:117–27.
138. Tong M, et al. Alternative mitophagy protects the heart against obesity-associated cardiomyopathy. Circ Res. 2021;129:1105–21.
139. Nah J, et al. Ulk1-dependent alternative mitophagy plays a protective role during pressure overload in the heart. Cardiovasc Res. 2022;118:2638–51.
140. Shao D, et al. Increasing fatty acid oxidation prevents high-fat diet-induced cardiomyopathy through regulating parkin-mediated mitophagy. Circulation. 2020;142:983–97.
141. Mehrabani S, Bagherniya M, Askari G, Read MI, Sahebkar A. The effect of fasting or calorie restriction on mitophagy induction: a literature review. J Cachexia Sarcopenia Muscle. 2020;11:1447–58.
142. Li SJ, Lin YH, Chiang CH, Wang PY, Chen CY. Early-onset dietary restriction maintains mitochondrial health, autophagy and ER function in the left ventricle during aging. J Nutr Biochem. 2022;101: 108944.
143. Picca A, Faitg J, Auwerx J, Ferrucci L, D'Amico D. Mitophagy in human health, ageing and disease. Nat Metab. 2023;5:2047–61.
144. Davinelli S, De Stefani D, De Vivo I, Scapagnini G. Polyphenols as caloric restriction mimetics regulating mitochondrial biogenesis and mitophagy. Trends Endocrinol Metab. 2020;31:536–50.
145. Bruss MD, Khambatta CF, Ruby MA, Aggarwal I, Hellerstein MK. Calorie restriction increases fatty acid synthesis and whole body fat oxidation rates. Am J Physiol Endocrinol Metab. 2010;298:E108–16.
146. Wang L, et al. The effects of graded levels of calorie restriction: XIX. impact of graded calorie restriction on protein expression in the liver. J Gerontol Series A Biol Sci Med Sci. 2023;78:1125.
147. Hofer SJ, et al. Spermidine is essential for fasting-mediated autophagy and longevity. Nat Cell Biol. 2024;2024:1–14. https://doi.org/10.1038/S41556-024-01468-X.
148. Anton SD, et al. Flipping the metabolic switch: understanding and applying the health benefits of fasting. Obesity (Silver Spring). 2018;26:254–68.
149. Castello L, et al. Alternate-day fasting protects the rat heart against age-induced inflammation and fibrosis by inhibiting oxidative damage and NF-kB activation. Free Radic Biol Med. 2010;48:47–54.
150. Castello L, et al. Alternate-day fasting reverses the age-associated hypertrophy phenotype in rat heart by influencing the ERK and PI3K signaling pathways. Mech Ageing Dev. 2011;132:305–14.
151. Spadaro O, et al. Caloric restriction in humans reveals immunometabolic regulators of health span. Science. 2022;375:671–7.
152. Johnson ML, et al. Mechanism by which caloric restriction improves insulin sensitivity in sedentary obese adults. Diabetes. 2016;65:74–84.
153. Huang TH, Ables GP. Dietary restrictions, bone density, and bone quality. Ann N Y Acad Sci. 2016;1363:26–39.
154. de Roon M, et al. Effect of exercise and/or reduced calorie dietary interventions on breast cancer-related endogenous sex hormones in healthy postmenopausal women. Breast Cancer Res. 2018;20:1–16.
155. Sabbatini AR, Kararigas G. Menopause-related estrogen decrease and the pathogenesis of HFpEF: JACC review topic of the week. J Am Coll Cardiol. 2020;75:1074–82.
156. Cangemi R, Friedmann AJ, Holloszy JO, Fontana L. Long-term effects of calorie restriction on serum sex-hormone concentrations in men. Aging Cell. 2010;9:236–42.
157. Hamam A, Abou-Omar M, Rabah H, Khattab H, Alaarag A. Worsening effect of testosterone deficiency on males with heart failure with preserved ejection fraction. BMC Endocr Disord. 2022;22:321.
158. Smith SJ, Teo SYM, Lopresti AL, Heritage B, Fairchild TJ. Examining the effects of calorie restriction on testosterone concentrations in men: a systematic review and meta-analysis. Nutr Rev. 2022;80:1222–36.
159. Lin S, et al. Effect of time restricted eating versus daily calorie restriction on sex hormones in males and females with obesity. Eur J Clin Nutr. 2024;78:814–7.
160. Keenan S, Cooke MB, Belski R. The effects of intermittent fasting combined with resistance training on lean body mass: a systematic review of human studies. Nutrients. 2020;12:2349.
161. Weiss EP, et al. Lower extremity muscle size and strength and aerobic capacity decrease with caloric restriction but not with exercise-induced weight loss. J Appl Physiol. 2007;1985(102):634–40.
162. Brubaker PH, et al. A randomized, controlled trial of resistance training added to caloric restriction plus aerobic exercise training in obese heart failure with preserved ejection fraction. Circ Heart Fail. 2023;16: e010161.
163. Peng Y, Zhong Z, Huang C, Wang W. The effects of popular diets on bone health in the past decade: a narrative review. Front Endocrinol Lausanne. 2023;14:1287140.
164. Stekovic S, et al. Alternate day fasting improves physiological and molecular markers of aging in healthy. Non-obese Humans Cell Metabolism. 2020;31:878–81.
165. Dorling JL, et al. Changes in body weight, adherence, and appetite during 2 years of calorie restriction: the CALERIE 2 randomized clinical trial. Eur J Clin Nutr. 2020;74:1210–20.
166. Trepanowski JF, et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. JAMA Intern Med. 2017;177:930–8.
167. Madeo F, Pietrocola F, Eisenberg T, Kroemer G. Caloric restriction mimetics: towards a molecular definition. Nat Rev Drug Discovery. 2014;13:727–40.
168. Madeo F, Carmona-Gutierrez D, Hofer SJ, Kroemer G. Caloric restriction mimetics against age-associated disease: targets, mechanisms, and therapeutic potential. Cell Metab. 2019;29:592–610.
169. Mariño G, et al. Regulation of autophagy by cytosolic acetyl-coenzyme a. Mol Cell. 2014;53:710–25.
170. Asghar M, et al. Super CitriMax (HCA-SX) attenuates increases in oxidative stress, inflammation, insulin resistance, and body weight in developing obese Zucker rats. Mol Cell Biochem. 2007;304:93–9.
171. Mátyás C, et al. Prevention of the development of heart failure with preserved ejection fraction by the phosphodiesterase-5A inhibitor vardenafil in rats with type 2 diabetes. Eur J Heart Fail. 2017;19:326–36.
172. Wang S, et al. Hydroxycitric acid tripotassium hydrate attenuates monocrotaline and hypoxia-induced pulmonary hypertension in rats. Int Heart J. 2024;65:318–28.
173. Nissen SE, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. N Engl J Med. 2023;388:1353–64.
174. Renna M, Jimenez-Sanchez M, Sarkar S, Rubinsztein DC. Chemical inducers of autophagy that enhance the clearance of mutant proteins in neurodegenerative diseases. J Biol Chem. 2010;285:11061–7.
175. Phan TT, et al. Multi-centre experience on the use of perhexiline in chronic heart failure and refractory angina: old drug, new hope. Eur J Heart Fail. 2009;11:881–6.
176. Abozguia K, et al. Metabolic modulator perhexiline corrects energy deficiency and improves exercise capacity in symptomatic hypertrophic cardiomyopathy. Circulation. 2010;122:1562–9.
177. Pietrocola F, et al. Spermidine induces autophagy by inhibiting the acetyltransferase EP300. Cell Death Differ. 2015;22:509–16.
178. Ghosh AK. p300 in cardiac development and accelerated cardiac aging. Aging Dis. 2020;11:916–26.
179. Wei JQ, et al. Quantitative control of adaptive cardiac hypertrophy by acetyltransferase p300. Circulation. 2008;118:934–46.
180. Wang J, et al. Spermidine alleviates cardiac aging by improving mitochondrial biogenesis and function. Aging. 2020;12:650–71.
181. Messerer J, et al. Spermidine supplementation influences mitochondrial number and morphology in the heart of aged mice. J Anat. 2023;242:91–101.

182. Belin MAF, et al. Cardiac biogenic amine profile and its relationship with parameters of cardiovascular disease in obesity. Vascul Pharmacol. 2024;156: 107412.
183. Sunagawa Y, et al. Curcumin, an inhibitor of p300-hat activity, suppresses the development of hypertension-induced left ventricular hypertrophy with preserved ejection fraction in dahl rats. Nutrients. 2021;13:2608.
184. Yao Q, et al. Curcumin protects against diabetic cardiomyopathy by promoting autophagy and alleviating apoptosis. J Mol Cell Cardiol. 2018;124:26–34.
185. Kitani K, Osawa T, Yokozawa T. The effects of tetrahydrocurcumin and green tea polyphenol on the survival of male C57BL/6 mice. Biogerontology. 2007;8:567–73.
186. Funamoto M, et al. Effects of high-absorption curcumin for the prevention of hypertensive heart disease: a double-blind, placebo-controlled, randomized clinical study. Eur Heart J Open. 2022;2:1–9.
187. Abdellatif M, Sedej S, Kroemer G. NAD+ metabolism in cardiac health, aging, and disease. Circulation. 2021;144:1795–817.
188. Doan KV, et al. Cardiac NAD+ depletion in mice promotes hypertrophic cardiomyopathy and arrhythmias prior to impaired bioenergetics. Nat Cardiovas Res. 2024;3:1236–48.
189. Koay YC, et al. The efficacy of risk factor modification compared to NAD+ repletion in diastolic heart failure. JACC: Basic Transl Sci. 2024;9:733–50.
190. Wang Y-C, et al. Indole-3-propionic acid protects against heart failure with preserved ejection fraction. Circ Res. 2024;134:371–89.
191. Tong D, et al. NAD+ repletion reverses heart failure with preserved ejection fraction. Circ Res. 2021;128:1629–41.
192. Liu X, et al. Mitochondrial protein hyperacetylation underpins heart failure with preserved ejection fraction in mice. J Mol Cell Cardiol. 2022;165:76–85.
193. Walker MA, et al. Raising NAD+level stimulates short-chain dehydrogenase/reductase proteins to alleviate heart failure independent of mitochondrial protein deacetylation. Circulation. 2023;148:2038–57.
194. Lee IH, et al. A role for the NAD-dependent deacetylase Sirt1 in the regulation of autophagy. Proc Natl Acad Sci. 2008;105:3374–9.
195. Hariharan N, et al. Deacetylation of FoxO by Sirt1 plays an essential role in mediating starvation-induced autophagy in cardiac myocytes. Circ Res. 2010;107:1470–82.
196. Chen X, et al. Berberine attenuates cardiac hypertrophy through inhibition of mTOR signaling pathway. Cardiovasc Drugs Ther. 2020;34:463–73.
197. Zeng Z, et al. Myocardial hypertrophy is improved with berberine treatment via long non-coding RNA MIAT-mediated autophagy. J Pharm Pharmacol. 2019;71:1822–31.
198. Li C, et al. Berberine exerts protective effects on cardiac senescence by regulating the Klotho/SIRT1 signaling pathway. Biomed Pharmacother. 2022;151:113097.
199. Beher D, et al. Resveratrol is not a direct activator of sirt1 enzyme activity. Chem Biol Drug Des. 2009;74:619–24.
200. Moskalev A, et al. Targeting aging mechanisms: pharmacological perspectives. Trends Endocrinol Metab. 2022;33:266–80.
201. Dang Y, et al. Berberine ameliorates cellular senescence and extends the lifespan of mice via regulating p16 and cyclin protein expression. Aging Cell. 2020;19: e13060.
202. Xiao Y, et al. Berberine extends healthspan and delays neurodegenerative diseases in Caenorhabditis elegans through ROS-dependent PMK-1/SKN-1 activation. Arch Gerontol Geriatr. 2024;128: 105644.
203. Navrotskaya VV, Oxenkrug G, Vorobyova LI, Summergrad P. Berberine prolongs life span and stimulates locomotor activity of drosophila melanogaster. Am J Plant Sci. 2012;03:1037–40.
204. Wang L, et al. Tetrahydroberberrubine retards heart aging in mice by promoting PHB2-mediated mitophagy. Acta Pharmacol Sin. 2023;44:332–44.
205. Abudureyimu, M. *et al.* Berberine promotes cardiac function by upregulating PINK1/parkin-mediated mitophagy in heart failure. *Frontiers in Physiology***11**, (2020).
206. Li MH, et al. Berberine improves pressure overload-induced cardiac hypertrophy and dysfunction through enhanced autophagy. Eur J Pharmacol. 2014;728:67–76.
207. Abudureyimu M, et al. Berberine alleviates myocardial diastolic dysfunction by modulating Drp1-mediated mitochondrial fission and Ca2+ homeostasis in a murine model of HFpEF. Front Med. 2023;17:1219–35.
208. Baur JA, et al. Resveratrol improves health and survival of mice on a high-calorie diet. Nature. 2006;444:337–42.
209. Zhang L, et al. Resveratrol ameliorates cardiac remodeling in a murine model of heart failure with preserved ejection fraction. Front Pharmacol. 2021;12: 646240.
210. Paneni F, Costantino S, Hamdani N. Regression of left ventricular hypertrophy with SGLT2 inhibitors. Eur Heart J. 2020;41:3433–6.
211. Solomon SD, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387:1089–98.
212. Anker SD, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385:1451–61.
213. Teo YH, et al. Effects of sodium/glucose cotransporter 2 (Sglt2) inhibitors on cardiovascular and metabolic outcomes in patients without diabetes mellitus: a systematic review and meta-analysis of randomized-controlled trials. J Am Heart Assoc. 2021;10:1–18.
214. Hoong CWS, Chua MWJ. SGLT2 inhibitors as calorie restriction mimetics: insights on longevity pathways and age-related diseases. Endocrinology. 2021;162:1–20.
215. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: A predictable, detectable, and preventable safety concern with sglt2 inhibitors. Diabetes Care. 2015;38:1638–42.
216. FAO. Food balance sheets 2010–2022 Global, regional and country trends. *Food and Agricultural Organization of the United Nations* 1–11 (2024) https://doi.org/10.4060/cd1656en.
217. Packer M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis. Circulation. 2022;146:1383–405.
218. Nielsen R, et al. Cardiovascular effects of treatment with the ketone body 3-hydroxybutyrate in chronic heart failure patients. Circulation. 2019;139:2129–41.
219. Packer M. SGLT2 inhibitors: role in protective reprogramming of cardiac nutrient transport and metabolism. Nat Rev Cardiol. 2023;20:443–62.
220. Verma S, et al. Empagliflozin increases cardiac energy production in diabetes: novel translational insights into the heart failure benefits of SGLT2 inhibitors. JACC Basic Transl Sci. 2018;3:575–87.
221. Sun P, et al. Canagliflozin attenuates lipotoxicity in cardiomyocytes and protects diabetic mouse hearts by inhibiting the mTOR/HIF-1α pathway. iScience. 2021;24:102521.
222. Ying Y, et al. Phloretin protects against cardiac damage and remodeling via restoring SIRT1 and anti-inflammatory effects in the streptozotocininduced diabetic mouse model. Aging. 2019;11:2822–35.
223. Wang CY, et al. TLR9 binding to beclin 1 and mitochondrial SIRT3 by a sodium-glucose co-transporter 2 inhibitor protects the heart from doxorubicin toxicity. Biology. 2020;9:1–23.
224. Hahn VS, et al. Myocardial metabolomics of human heart failure with preserved ejection fraction. Circulation. 2023;147:1147–61.
225. Aragón-Herrera A, et al. Empagliflozin reduces the levels of CD36 and cardiotoxic lipids while improving autophagy in the hearts of Zucker diabetic fatty rats. Biochem Pharmacol. 2019;170: 113677.
226. Ren C, et al. Sodium-glucose cotransporter-2 inhibitor empagliflozin ameliorates sunitinib-induced cardiac dysfunction via regulation of AMPK–mTOR signaling pathway-mediated autophagy. Front Pharmacol. 2021;12: 664181.
227. Yu YW, et al. Sodium-Glucose Co-transporter-2 Inhibitor of Dapagliflozin Attenuates Myocardial Ischemia/Reperfusion Injury by Limiting NLRP3 Inflammasome Activation and Modulating Autophagy. Frontiers in Cardiovascular Medicine. 2021;8: 768214.
228. Qian L, et al. Peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) family in physiological and pathophysiological process and diseases. Signal Transduct Target Ther. 2024;9:1–44.
229. Elrakaybi A, Laubner K, Zhou Q, Hug MJ, Seufert J. Cardiovascular protection by SGLT2 inhibitors– Do anti-inflammatory mechanisms play a role? Mol Metab. 2022;64: 101549.
230. Jiménez-Loygorri JI, et al. Mitophagy curtails cytosolic mtDNA-dependent activation of cGAS/STING inflammation during aging. Nat Commun. 2024;15:1–15.
231. Kim J, Kim HS, Chung JH. Molecular mechanisms of mitochondrial DNA release and activation of the cGAS-STING pathway. Exp Mol Med. 2023;55:510–9.
232. Yang C, et al. Canagliflozin mitigates diabetic cardiomyopathy through enhanced PINK1-Parkin mitophagy. Int J Mol Sci. 2024;25:7008.
233. Katsuumi, G. *et al.* SGLT2 inhibition eliminates senescent cells and alleviates pathological aging. *Nature Aging* 1–13 (2024) https://doi.org/10.1038/s43587-024-00642-y.
234. Miller, R. A. *et al.* Canagliflozin extends life span in genetically heterogeneous male but not female mice. *JCI Insight***5**, (2020).

235. Matsui S, et al. Empagliflozin protects the kidney by reducing toxic ALB (albumin) exposure and preventing autophagic stagnation in proximal tubules. Autophagy. 2024. https://doi.org/10.1080/15548627.2024.2410621.
236. Kosiborod MN, et al. Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials. Lancet. 2024;404:949–61.
237. Hernandez AF, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018;392:1519–29.
238. Jastreboff AM, et al. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med. 2022;387:205–16.
239. Packer, M. *et al.* Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *New England Journal of Medicine***0**,.
240. Ussher JR, Drucker DJ. Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. Nat Rev Cardiol. 2023;20:463–74.
241. Filippatos TD, Panagiotopoulou TV, Elisaf MS. Adverse Effects of GLP-1 Receptor Agonists. Rev Diabet Stud. 2014;11:202–30.
242. Christensen S, Robinson K, Thomas S, Williams DR. Dietary intake by patients taking GLP-1 and dual GIP/GLP-1 receptor agonists: A narrative review and discussion of research needs. Obesity Pillars. 2024;11: 100121.
243. Zhang Y, et al. Liraglutide relieves myocardial damage by promoting autophagy via AMPK-mTOR signaling pathway in zucker diabetic fatty rat. Mol Cell Endocrinol. 2017;448:98–107.
244. He Q, Sha S, Sun L, Zhang J, Dong M. GLP-1 analogue improves hepatic lipid accumulation by inducing autophagy via AMPK/mTOR pathway. Biochem Biophys Res Commun. 2016;476:196–203.
245. Noyan-Ashraf MH, et al. A Glucagon-Like Peptide-1 Analog Reverses the Molecular Pathology and Cardiac Dysfunction of a Mouse Model of Obesity. Circulation. 2013;127:74–85.
246. Zhu B, et al. Alogliptin improves endothelial function by promoting autophagy in perivascular adipose tissue of obese mice through a GLP-1-dependent mechanism. Vascul Pharmacol. 2019;115:55–63.
247. Zheng R-H, et al. Exogenous supplement of glucagon like peptide-1 protects the heart against aortic banding induced myocardial fibrosis and dysfunction through inhibiting mTOR/p70S6K signaling and promoting autophagy. Eur J Pharmacol. 2020;883: 173318.
248. Yang S, et al. Glucagon-like peptide-1 alleviates diabetic kidney disease through activation of autophagy by regulating AMP-activated protein kinase-mammalian target of rapamycin pathway. Am J Physiol-Endocrinol Metabol. 2020;319:E1019–30.
249. Yu X, et al. Liraglutide ameliorates non-alcoholic steatohepatitis by inhibiting NLRP3 inflammasome and pyroptosis activation via mitophagy. Eur J Pharmacol. 2019;864: 172715.
250. Fang, Y. *et al.* Liraglutide alleviates hepatic steatosis by activating the TFEB-regulated autophagy-lysosomal pathway. *Front. Cell Dev. Biol.***8**, (2020).
251. Withaar C, et al. The cardioprotective effects of semaglutide exceed those of dietary weight loss in mice With HFpEF. JACC: Basic Transl Sci. 2023;8:1298–314.
252. Pyke C, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. Endocrinology. 2014;155:1280–90.
253. Ussher JR, et al. Inactivation of the cardiomyocyte glucagon-like peptide-1 receptor (GLP-1R) unmasks cardiomyocyte-independent GLP-1R-mediated cardioprotection. Mol Metabol. 2014;3:507–17.
254. Tromp J, et al. Age dependent associations of risk factors with heart failure: pooled population based cohort study. BMJ. 2021;372: n461.
255. Halabi A, Sen J, Huynh Q, Marwick TH. Metformin treatment in heart failure with preserved ejection fraction: a systematic review and meta-regression analysis. Cardiovasc Diabetol. 2020;19:124.
256. Li JZ, Li YR. Cardiovascular protection by metformin: latest advances in basic and clinical research. Cardiology. 2023;148:374–84.
257. University of California, San Francisco. *Phase II Trial of Metformin for Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction*. https://clinicaltrials.gov/study/NCT03629340 (2023).
258. Wake Forest University Health Sciences. *Metformin for Older Patients With Heart Failure With Preserved Ejection Fraction*. https://clinicaltrials.gov/study/NCT05093959 (2024).

Publisher's Note