Duan *et al. Cardiovascular Diabetology* (2025) 24:186
https://doi.org/10.1186/s12933-025-02750-4

Cardiovascular Diabetology

REVIEW Open Access

The landscape of novel antidiabetic drugs in diabetic HFpEF: relevant mechanisms and clinical implications

Xiangling Duan[1,2†], Xiaomeng Zhang[3†] and Bao Sun[1,2*]

Abstract

As a heterogeneous syndrome, heart failure with preserved ejection fraction (HFpEF) has become the leading form of heart failure worldwide. Increasing evidence has identified that diabetes mellitus (DM) increases the risk of HFpEF. Worse still, the coexistence of both diseases poses a great threat to human health by further worsening the cardiovascular system and accelerating the progression of diabetes. Although several studies have indicated that the novel antidiabetic drugs, including sodium glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase 4 inhibitors (DPP4i) provide the cardiovascular benefits in T2DM patients with HFpEF, the elaborated roles and mechanisms are not fully understood. In this review, we summarize the state-of-the-art evidence regarding the epidemiology and pathophysiology of diabetic HFpEF, and the landscape of the novel antidiabetic drugs in the treatment of diabetic HFpEF, as well as discuss the relevant mechanisms, aiming to broaden the understanding of diabetic HFpEF and gain new insight into the treatment of this disease.

Keywords HFpEF, T2DM, SGLT2i, GLP-1 RA, DPP4i

Introduction

The global prevalence of diabetes mellitus (DM) has been increasing for decades. According to a report published by the International Diabetes Federation, more than 530 million people are suffering from DM in 2021, and this number is expected to reach 780 million by 2040 [1]. Characterized by a persistent state of hyperglycemia, DM is a metabolic disease caused by an imbalance in insulin secretion [2]. Notably, previous evidence indicated that a persistent hyperglycemic state resulted in heart failure (HF) [3]. For instance, diabetes-induced chronic hyperglycemia, persistently-elevated free fatty acids and hyperinsulinemia all could lead to cardiac hypertrophy, intramyocardial inflammation, impaired mitochondrial function, and ultimately HF [4].

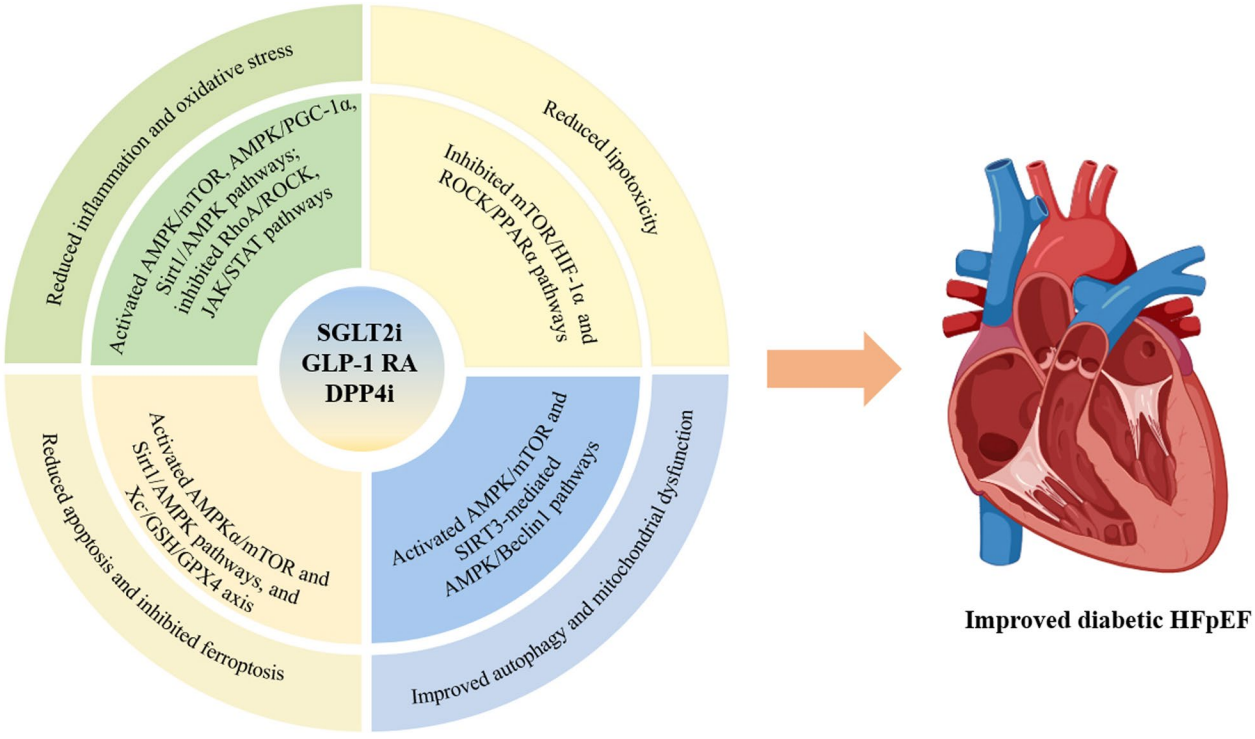
According to ejection fraction (EF), HF is divided into HF with reduced ejection fraction (HFrEF, EF < 40%) and HF with preserved ejection fraction (HFpEF, EF > 40%). Furthermore, HFpEF is subdivided into HF with mildly reduced ejection fraction (HFmrEF, 40% ≤ EF ≤ 60%) and HF with normal ejection fraction (HFnEF, EF ≥ 55% in men, EF ≥ 60% in women) [5]. Clinically, as currently the most common form of HF, HFpEF is characterized by ventricular hypertrophy and myocardial fibrosis, with signs of respiratory distress and congestion in most patients [6]. More importantly, it was estimated that approximately 45% of HFpEF patients had DM. The

†Xiangling Duan and Xiaomeng Zhang have contributed equally to this work.

*Correspondence:
Bao Sun
scy_csu2016@csu.edu.cn

Full list of author information is available at the end of the article

Graphical abstract



coexistence of both diseases not only induced a systemic pro-inflammatory state leading to coronary microvascular endothelial inflammation and resulting in myocardial dysfunction, but also induced a persistent pro-inflammatory state causing cardiac fibrosis that led to myocardial necrosis [7–10].

The novel antidiabetic drugs, such as sodium glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase 4 inhibitors (DPP4i), have demonstrated beneficial effects on cardiovascular outcomes in patients with DM [11]. There was evidence suggesting that SGLT2i could significantly reduce the hospitalization rate of diabetic HFpEF patients [12]. Incretin, encompassing endogenous GLP-1 RA and exogenous DPP4i, also attenuated the risk of cardiovascular diseases in HFpEF patients [13, 14]. However, the elaborated roles and mechanisms of these novel antidiabetic drugs in diabetic HFpEF were not fully understood.

In this review, we focus on the current evidence of the epidemiology and pathophysiology of diabetic HFpEF and then the landscape of the novel antidiabetic drugs in the treatment of diabetic HFpEF, as well as discuss the relevant mechanisms, aiming to broaden the understanding of diabetic HFpEF and provide new therapeutic options for the treatment of the disease.

The epidemiology and pathophysiology of diabetic HFpEF

DM, a common comorbidity in patients with HFpEF, is also the major risk factor for HFpEF [15]. It has been reported that the prevalence of HFpEF is steadily increasing due to the aging of population and the global prevalence of obesity and T2DM [16, 17]. Nevertheless, the prevalence of HFpEF varies across countries. For instance, REPORT-HF (an international longitudinal observational study aiming at evaluating the treatment of HF in clinical practice) revealed that 20.7% of 3,397 advanced HF patients had HFpEF [18]. A retrospective study involving 1,245 hospitalized patients with decompensated HF from 2013 to 2014 showed that 43% of them had LVEF ≥ 50% [19]. Meanwhile, there were also regional differences in the incidence of HF. In the study cohort of the Omstead County, Minnesota, USA, from 2000 to 2010, the incidence of HF decreased from 3.1 cases per 1,000 people to 2.2 cases. However, the decrease in the incidence of HFpEF was less than that of HFrEF [20]. In several US community-based studies from 1990 to 2009, the age- and sex-adjusted standardized incidence was 0.80 and 1.53 for HFrEF and HFpEF, respectively [21]. Furthermore, HFpEF also showed differences in terms of demographics. Among 1203 patients with HFpEF from 11 regions in Asia, 36% of the HFpEF patients were under 55 years old, 37% were under 65 years old,

and 16% were over 75 years old [22]. It was worth noting that the prevalence of HFpEF in the Portuguese community increased with age, with prevalence among females rather than males [23]. Furthermore, the registry data of HF patients by European Society of Cardiology (ESC) showed that HFpEF prevalence varied regionally: 18.4% in Southern Europe, 17.6% in Middle East, and 13.0% in Western regions [24]. Over time, the incidence of HF has decreased; however, the risk of HFpEF is increasing. According to current therapeutic guidelines, the recommended pharmacological regimen for HFpEF should include SGLT2i (empagliflozin), mineralocorticoid receptor antagonists (spironolactone), angiotensin receptor-neprilysin inhibitors (sacubitril/valsartan), and angiotensin II receptor blockers (candesartan) [25].

DM patients often showed early asymptomatic increased left ventricular (LV) stiffness, accompanied by abnormal natriuretic peptide (ANP) signal, which was the early phenomenon of HFpEF [26, 27]. Kristensen et al. analyzed the trial data of CHARM and found that the prevalence of HFpEF with DM was higher than those without diagnosed DM [28]. A survey indicated that diabetes HFpEF patients had longer hospital stays, lower discharge rates, and a higher risk of re-hospitalization due to HF [7]. Diabetic HFpEF patients also had greater burden in clinical symptoms, such as poor exercise ability and obstructive sleep apnea [9, 29]. Compared with patients without T2DM, diabetic HFpEF patients were younger, more obese and tended to be male, with higher body mass index and more risk for kidney diseases, anemia and congestion symptoms [9, 30, 31]. Although LVEF incidence was similar in diabetic patients and non-diabetic patients, diabetic HFpEF patients showed a more severe trend of concentric remodeling/hypertrophy, more serious impairment of LV diastolic function and more acute myocardial fibrosis [32, 33]. Diabetes and obesity, both of which are associated with the secretion of pro-inflammatory adipokines and the reduced availability of nitric oxide, may lead to the occurrence of HFpEF in young individuals due to myocardial remodeling and fibrosis [7, 34]. Supporting this view was the fact that compared with non-diabetic patients, the levels of white blood cells, creatinine and triglycerides in diabetic patients with HFpEF were higher [35]. Compared with patients without diabetes, patients with HFpEF, T2DM were associated with smaller LV volume, higher mitral valve E/e′ ratio and poorer prognosis [35]. Consistently, DM significantly increased the cardiovascular mortality, all-cause mortality, hospitalization rate and prognosis of patients with HFpEF [30, 36, 37]. Another study found a higher proportion of females than males with diabetic HFpEF, which further implied the increased risk of death in women [38]. Collectively, there is a positive correlation between DM and HFpEF-associated morbidity and mortality.

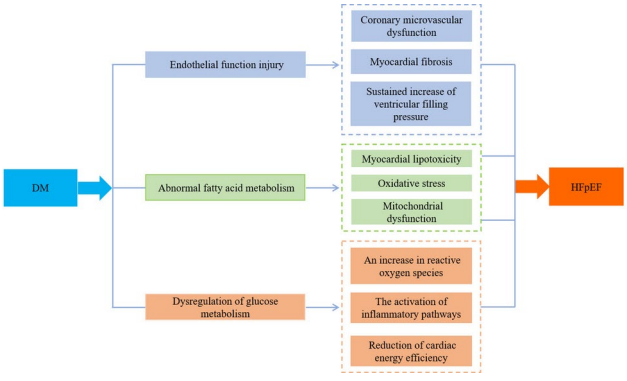


Fig. 1 The pathophysiology of DM with HFpEF. DM patients are accompanied with endothelial function injury, abnormal fatty acid metabolism and dysregulation of glucose metabolism. Among them, endothelial function injury leads to coronary microvascular dysfunction, myocardial fibrosis and sustained increase of ventricular filling pressure; abnormal fatty acid metabolism contributes to myocardial lipotoxicity, oxidative stress, and mitochondrial dysfunction; dysregulation of glucose metabolism results in an increase in reactive oxygen species (ROS), the activation of inflammatory pathways and reduction of cardiac energy efficiency, which ultimately prompts the development of HFpEF

The pathological changes of diabetic HFpEF were reported to be involved in many factors, such as endothelial function injury, abnormal fatty acid metabolism, oxidative stress, etc. [39–42] (Fig. 1). An investigational trial revealed that exosome microRNAs, miR-30d-5p and miR-126a-5p, and SIRT6 expression, were significantly reduced in diabetic HFpEF patients compared to non-diabetic patients [39, 40]. The pathological mechanism might be the dysregulation of glucose metabolism, which triggered the accumulation of epicardial adipose tissue (EAT) and free fatty acids in heart, leading to myocardial lipotoxicity, oxidative stress, and mitochondrial dysfunction [41]. Another study supported that the stress of hyperglycemia induced the accumulation of advanced glycation end (AGE) products, which led to an increase in reactive oxygen species, the activation of inflammatory pathways and reduction of cardiac energy efficiency [42]. Endothelial cell apoptosis induced by hyperglycemia also led to coronary microvascular dysfunction, myocardial fibrosis and sustained increase of ventricular filling pressure [43, 44].

The role of novel antidiabetic drugs in diabetic HFpEF

Emerging studies indicated that the novel antidiabetic drugs, including SGLT2i, GLP-1 RA and DPP4i, provided the cardiovascular benefits in diabetic HFpEF patients [45–49]. Notably, there were also several clinical trials that supported this point (Table 1).

Table 1 Clinical trial of novel antidiabetic drugs in HFpEF population

Intervention	Population	Median follow–up	Primary outcomes	Outcomes in diabetic HFpEF	References
Dapagliflozin	324 HFpEF patients (included 181 diabetic HFpEF patients)	12 weeks	Mean 12-weeks change in KCCQ-CSS and 6MWTD was 5.8 points (95% CI 2.3–9.2; $p=0.001$) and 20 m (95% CI 5.6–34.7; $p=0.007$), respectively	Mean 12-weeks change in KCCQ-CSS was 7.3 points (95% CI 2.3–12.3, $p=0.22$)	[53]
Dapagliflozin	52 T2DM patients with HF	6 months	E/e′ decreased from 9.3 to 8.5 in T2DM patients with stable HF ($p=0.02$)	Relative changes in E/e′ in diabetic HFpEF patients with dyslipidemia were significantly larger ($p=0.014$)	[66]
Dapagliflozin	37 diabetic HFpEF patients, 7 diabetic HFrEF patients and 9 diabetic HFmrEF patients	6 months	Global longitudinal strain showed significant improvement from 15.5 ± 3.5% to 16.9 ± 4.1% ($p<0.01$)	Global longitudinal strain was more significant from 17.0 ± 1.9% to 18.7 ± 2.0% ($p<0.001$)	[67]
Semaglutide	616 obesity-related HFpEF patients with T2DM	52 weeks	Mean 52-weeks change in KCCQ-CSS and body weight was 13.7 points (95% CI 4.1–10.4; $p<0.001$) and 9.8% (95% CI − 7.6 to − 5.2; $p<0.001$), respectively	Mean 52-weeks change in KCCQ-CSS and body weight was 13.7 points (95% CI 4.1–10.4; $p<0.001$) and 9.8% (95% CI − 7.6 to − 5.2; $p<0.001$), respectively	[85]
Exenatide	516 T2DM HFpEF patients, 574 T2DM HFmrEF patients, 303 T2DM HFrEF patients	3.2 years	Reduced all-cause death (95% CI 0.77–0.97, $p=0.031$) and composite outcome of all-cause death or HHF (95% CI 0.80–0.99, $p=0.015$), respectively	The incidence of HHF was reduced by 5.2%	[89]
Semaglutide	491 obesity-related HFpEF patients with T2DM	52 weeks	Improved adverse cardiac remodeling	Improved adverse cardiac remodeling	[90]

HFpEF heart failure with preserved ejection fraction; *HFmrEF* heart failure with midrange ejection fraction; *HFrEF* heart failure with reduced ejection fraction; *KCCQ-CSS* Kansas city cardiomyopathy questionnaire clinical summary score; *6MWTD* 6-min walk test distance; *E/e′* ratio of the mitral inflow E to the mitral e′ annular velocity; *T2DM* type 2 diabetes mellitus; *HF* heart failure; *PBO* placebo; *HHF* hospitalization for heart failure; *LA* left atrium

The role of SGLT2i in diabetic HFpEF

SGLT2i, a class of the most recent anti-hyperglycemic drugs, have demonstrated beneficial effects on cardiovascular outcomes and played an important role in DM patients with HFpEF (Table 2). The ESC and the American Diabetes Association issued a statement in which they recommend the use of SGLT2i in patients with T2DM and LVEF > 40% (HFmrEF and HFpEF) to improve life quality by reducing the risk of heart failure hospitalization (HHF) and cardiovascular death (CVD) [50]. A recent systematic review and meta-analysis also showed that SGLT2i led to a decreased risk of cardiovascular hospitalization [51]. Meanwhile, there were abundant clinical trial results corresponding to this recommendation of SGLT2i. For instance, dapagliflozin had improved the symptoms, physical function limitation and exercise function of HFpEF patients, and had shown good tolerance [52, 53]. Nassif et al. showed that the incidence of all adverse events of dapagliflozin was slightly higher than that of the placebo [53]. On the other hand, no cases of diabetic ketoacidosis, severe hypoglycemia or lower limb amputation occurred during the trial period. The reason for the cardiovascular benefit may be that SGLT2i not only have a significant impact on circulating biomarker levels of in diabetic patients with HFpEF, but also ameliorate the deterioration of cardiac function [54, 55].

There is growing evidence that normal biomarker levels are important for maintaining normal cardiac function in diabetic HFpEF patients. To date, SGLT2i has been shown to attenuate biomarker levels of cardiac hypertrophy and vasodilation [56]. For example, a recent meta-analysis of two randomized controlled trials showed that SGLT2i significantly reduced N-terminal B-type ANP (NT-proBNP) levels compared with placebo [57, 58], although Ueda et al. demonstrated that canagliflozin did not significantly reduce plasma levels of BNP, with insufficient sample size [59]. Furthermore, a prospective multicentre study indicated that SGLT2i ameliorated albuminuria and reduced carotid intima-media thickness (CIMT), a marker of myocardial damage in T2DM patients [60]. In the model of diabetic cardiomyopathy mice, Du et al. underscored that canagliflozin could reduce the level of both markers of cardiac injury, lactate dehydrogenase and cardiac troponin I, as well as alleviate the damage of cardiac function [61]. Similarly, dapagliflozin and/or liraglutide also had a significant improvement of biochemical indices, including pro-inflammatory mediators (NF-κB and tumor necrosis factor-α (TNF-α)), and apoptotic effectors (caspase-3), and cardiac function in diabetes-induced cardiomyopathy rats [62]. A recent study reported that dapagliflozin significantly downregulated the key markers of myocardial fibrosis, nitro-oxidative stress, pro-inflammatory cytokines, myocardial hypertrophy, fibrosis, and reduced apoptosis, ultimately retarding the development of HFpEF in diabetic rats [63].

Table 2 The role of SGLT2i in diabetic HFpEF

SGLT2i	Subjects	Follow-up period	Main findings	References
Dapagliflozin	324 HFpEF patients (included 181 diabetic HFpEF patients)	12 weeks	Improved patient-reported symptoms, physical limitations and exercise function and was well tolerated	[53]
Dapagliflozin, ertugliflozin, sotagliflozin, canagliflozin, luseogliflozin, empagliflozin and ipragliflozin	10,845 HFpEF patients	NA	Reduced the risk of a composite of HHF and CVD	[57]
Canagliflozin	82 HFpEF patients with T2DM	24 weeks	Significantly reduced body weight, but did not reduce plasma BNP concentrations	[59]
Canagliflozin, dapagliflozin and empagliflozin	1,150 patients with T2DM	2 years	Reduced CIMT and albuminuria	[60]
Canagliflozin	Diabetic cardiomyopathy mice	6 weeks	Reduced the levels of lactate dehydrogenase and cardiac troponin I, as well as alleviate the damage of cardiac function	[61]
Dapagliflozin	Diabetes-induced cardiomyopathy rats	8 weeks	Improved the biochemical indices of cardiac function	[62]
Dapagliflozin	HFpEF in diabetic rats	12 weeks	Mitigated nitro-oxidative stress, pro-inflammatory cytokines, myocardial hypertrophy, fibrosis, and reduced apoptosis	[63]
SGLT2i	3,428 patients with HFpEF and T2DM	NA	Significantly improved LVEF and functional capacity, and reduced myocardial fibrosis	[64]
Dapagliflozin	53 T2DM patients with stable HF	6 months	Improved LV diastolic function	[66]
Dapagliflozin	53 T2DM patients with stable HF (included 37 diabetic HFpEF patients)	6 months	Improved LV longitudinal myocardial function	[67]
Canagliflozin	233 patients with chronic HF and T2DM (include 166 diabetic HFpEF patients)	24 weeks	Maintained optimal intravascular volume with the reduction of extravascular volume plasma volume	[68]
Empagliflozin	74 patients with chronic HF (included 17 DM patients)	3 months	Caused a decrease in the stiffness of the aorta and the proximal branches, and reduced the afterload of the LV	[70]
Empagliflozin	180 participants with HFpEF	6 months	Reduced myocardial extracellular volume and LV mass	[71]
Canagliflozin, dapagliflozin, empagliflozin and or ertugliflozin	250 patients with HFpEF and T2DM	295 days	Reduced incidence of HHF and acute kidney injury	[72]
Sotagliflozin	10,584 patients with DM and chronic kidney disease	16 months	Resulted in a lower risk of the rate of deaths from cardiovascular causes and HHF	[73]
Empagliflozin	5988 patients with class II–IV HF (included 2938 DM patients and 4005 HFpEF patients)	26.2 months	Reduced the combined risk of CVD or HHF	[74, 75]
Empagliflozin	530 patients hospitalized for acute de novo or decompensated HF (included 236 DM patients)	90 days	Decreased the risk of CVD or first HF acute	[77]
Dapagliflozin	17,160 patients with T2DM (included 808 diabetic HFpEF patients	4.2 years	Reduced HHF in patients with and without HFrEF	[78]
Dapagliflozin	6263 patients with HFmrEF or HFpEF (included 2806 DM patients)	32 weeks	Reduced the risk of CVD or worsening HF events	[79, 80]

SGLT2i sodium glucose cotransporter 2 inhibitors; *HFpEF* heart failure with preserved ejection fraction; *HFmrEF* heart failure with midrange ejection fraction; *NA* not available; *CVD* cardiovascular death; *HF* heart failure; *T2DM* type 2 diabetes mellitus; *BNP* B-type natriuretic peptide; *CIMT* carotid intima-media thickness; *LV* left ventricular; *HHF* hospitalization for heart failure; *HFrEF* HF with reduced ejection fraction; *HFmrEF* HF with mildly reduced ejection fraction

In addition to the impact on circulating biomarker levels of in patients with diabetic HFpEF, SGLT2i was associated with early improvements in cardiac structure and function in the diabetic HFpEF patients [64, 65]. Dapagliflozin had been reported to improve LV diastolic function by reducing the ratio of mitral inflow E/e′ and improving longitudinal strain [66, 67]. Further studies showed that canagliflozin contributed to the cardiorenal benefits by the maintenance of optimal intravascular volume with the reduction of extravascular volume plasma volume in patients with chronic HF and T2DM [68]. Besides, other studies showed that empagliflozin decreased cardiac burden and reversed adverse cardiac remodeling [69, 70]. Chai et al. performed a prospective clinical study including 180 participants with HFpEF and demonstrated that empagliflozin attenuated LV mass

index, improved myocardial fibrosis and ameliorated LV remodeling [65, 71].

Recently, several large clinical trials also supported the cardiovascular benefits of SGLT2i in diabetic HFpEF patients. For instance, a retrospective study revealed that SGLT2i reduced incidence of HHF and acute kidney injury [72]. In the analysis of the SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with T2DM and Moderate Renal Impairment Who Are at Cardiovascular Risk) trial, there was a significant risk reduction in total number of hospitalizations and emergency visits for HF patients with sotagliflozin treatment [73]. Additionally, this trial also reported that compared with placebo, sotagliflozin was more frequently associated with diarrhea, genital candidiasis, hypovolemia and diabetic ketoacidosis. Intriguingly, a first-of-its-kind SGLT2i trial and secondary analysis in patients with HFmrEF and HFpEF showed a 29% reduction in patients' risk of HHF [74, 75], although this effect was diminished in patients with EF ≥ 65%. The reason may be that patients is far more likely to have atrial arrhythmias or other common disorders in this subgroup (EF ≥ 65%) [76]. Furthermore, the EMPULSE (empagliflozin in patients hospitalized with acute heart failure who have been stabilized) trial showed that empagliflozin decreased the risk of CVD or first events HF regardless of LVEF [77]. However, in terms of safety, the incidence of volume depletion with empagliflozin was slightly higher than that with placebo. In addition, a double-blind trial examining the cardiovascular efficacy and safety of ertugliflozin in patients with T2DM stratified by ejection fraction, showing that dapagliflozin diminished HHF in patients with or without HFrEF [78]. In DELIVER trail and secondary analysis, dapagliflozin not only reduced the risk of CVD or worsening HF events, but also consistently enhanced overall health and New York Heart Association functional ratings in HFpEF patients [79, 80]. Collectively, the available evidence suggests that treatment with SGLT2i could ameliorate clinical outcomes in patients with DM and HFpEF.

The role of GLP-1 RA in diabetic HFpEF

There is growing evidence of great concern supporting the protective effect of GLP-1 RA on the heart in diabetic HFpEF patients (Table 3). Patel et al. conducted a retrospective cohort study and found that there was a significantly lower risk of HHF in patients with T2DM, overweight/obesity, and HFpEF receiving GLP-1 RA plus SGLT2i therapy compared with the SGLT2i-only therapy, suggesting a potential incremental benefit of GLP-1 RA

Table 3 The role of GLP-1 RA in diabetic HFpEF

GLP-1 RA	Subjects	Follow-up period	Main findings	References
GLP-1 RA	14,088 patients with T2DM, overweight/obesity, and HFpEF	12 months	Associated with a significantly lower risk of HHF	[81]
Semaglutide	1145 participants with obesity-related HFpEF (included 616 diabetic HFpEF patients)	52 weeks	Improved HF-related symptoms, physical limitations and reduced NT-proBNP levels	[82, 83]
Semaglutide	1146 participants with obesity-related HFpEF (included 636 diabetic HFpEF patients)	52 weeks	Reduced C-reactive protein levels and improved symptoms, physical limitations, and exercise function	[84]
Semaglutide	616 T2DM patients with obesity-related HFpEF	52 weeks	Contributed to larger reductions in HF-related symptoms and physical limitations	[85]
Liraglutide	95 T2DM patients	6 months	Reduced EAT levels	[87]
Semaglutide	20 subjects with T2DM and obesity	12 weeks	Significantly decreased EAT thickness	[88]
Exenatide	14,752 T2DM patients with or without HF (included 516 diabetic HFpEF patients)	3.2 years	Lowered the incidence of the composite outcome of all-cause death or HHF	[89]
Semaglutide	491 patients with obesity-related HFpEF (included 422 diabetic HFpEF patients)	52 weeks	Ameliorated adverse cardiac remodeling	[90]
Semaglutide	3743 participants with a history of HFpEF (included 941 diabetic HFpEF patients)	NA	Decreased the risk of the combined endpoint of CVD or HF, as well as the worsening HF events	[91]
Liraglutide	HFpEF mice model	12 weeks	Attenuated the cardiometabolic dysregulation and improved cardiac function	[92]
Liraglutide	HFpEF mice model	4 weeks	Markedly improved diastolic function, cardiomyocyte hypertrophy and myocardial fibrosis	[93]
Semaglutide	HFpEF mice model	4 weeks	Improved the cardiometabolic profile, cardiac function and structure	[94]
Liraglutide	30 T2DM patients with coronary artery disease	24 weeks	Did not improve any diastolic function parameters	[95]
SGLT2i and GLP-1RA	336,334 patients with T2DM and without cardiovascular disease (included 17,451 patients with T2DM and HF)	4 years	Prevented HF	[96]

GLP-1RA glucagon-like peptide-1 receptor agonists; *HFpEF* heart failure with preserved ejection fraction; *T2DM* type 2 diabetes mellitus; *HF* heart failure; *NT-proBNP* N-terminal B-type ANP; *EAT* epicardial adipose tissue; *HHF* hospitalization for heart failure; *NA* not available

[81]. However, it should be emphasized that the combination therapy group demonstrated a significantly higher incidence of diabetic retinopathy compared to monotherapy, necessitating careful risk-benefit evaluation in clinical decision-making. In pooled analyses of the STEP-HFpEF (Semaglutide Treatment Effect in People with obesity and HFpEF) and STEP-HFpEF-DM trials, GLP-1 RA had consistent beneficial effects on HF-related symptoms, exercise function, and inflammatory markers in patients receiving diuretics with obesity-related HFpEF [82]. It is generally accepted that NT-proBNP levels are biochemical markers of the extent of cardiac damage and predictors of adverse outcomes. A secondary analysis of the STEP-HFpEF and STEP-HFpEF DM trials involving 1145 obese T2DM-associated HFpEF patients showed that semaglutide reduced NT-proBNP levels and improved health status after 52 weeks [83]. Furthermore, another secondary analysis of the STEP-HFpEF and STEP-HFpEF DM trials showed that semaglutide reduced C-reactive protein levels and improved symptoms, physical limitations, and exercise function in HFpEF obese patients [84]. Recently, Kosiborod et al. also reported that semaglutide contributed to larger reductions in HF-related symptoms, physical limitations and weight loss among patients with obesity-related HFpEF and T2DM [85]. However, the occurrence of treatment discontinuation due to serious adverse events was 1.8% higher in the semaglutide group.

A previous study identified that there was significantly higher EAT level and severe myocardial damage in HFpEF patients with atrial fibrillation and/or T2DM [86]. In a randomized trial of 95 T2DM patients with body mass index (BMI) ≥ 27 kg/m^2, liraglutide reduced EAT levels by 29% and 36% after 3 months and 6 months, respectively, in patients receiving liraglutide plus metformin compared with those receiving metformin monotherapy [87]. During the study period, no serious adverse events occurred, but the incidence of expected mild gastrointestinal side effects was slightly higher in the liraglutide group. Likewise, Lacobellis and colleagues demonstrated that weekly administration of semaglutide or duraglutide resulted in a rapid reduction in EAT thickness, by 20% within 12 weeks [88]. In the EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial, Fudim et al. found that once-a-week medication of exenatide had lowered the incidence of the composite outcome of all-cause death or HHF in patients without baseline HF [89]. The echocardiography substudy of the STEP-HFpEF indicated that semaglutide ameliorated adverse cardiac remodeling among patients with obesity-related HFpEF [90]. More recently, a pooled analysis of four randomized, placebo-controlled trials showed that semaglutide decreased the risk of the combined endpoint of CVD or HF, as well as the risk of worsening HF events in patients with HFpEF [91]. Overall, these results suggested that GLP-1 RA were beneficial to the cardioprotection of people with diabetic HFpEF.

On the other hand, GLP-1 RA have protective effects on experimental HFpEF murine. In HFpEF female rats aged 18 to 22 months, liraglutide reduced myocardial hypertrophy and the attenuation of atrial weight, as well as improved myocardial fibrosis, which contributed to the reduction of cardiometabolic dysregulation [92]. Analogously, treatment with liraglutide markedly improved diastolic function, cardiomyocyte hypertrophy and myocardial fibrosis in a mouse model of HFpEF [93]. Recently, in a mouse model of diabetic HFpEF, Withaar et al. found that semaglutide improved the cardiometabolic profile, cardiac function and structure [94]. Moreover, they also found that semaglutide could significantly up-regulate the activities of antioxidant enzymes and alleviate the cardiac damage caused by oxidative stress in HFpEF mice [94]. Nevertheless, Kumarathurai et al. found that liraglutide did not improve diastolic function parameters in patients with T2DM and coronary artery disease [95]. The reason for this might be that the study did not use diastolic function parameters for power calculation and did not assess carry-over effects.

Apart from monotherapy, the combination regimens have shown great potential in the treatment of diabetic HFpEF. For instance, a meta-analysis demonstrated that SGLT2i/GLP-1 RA combination therapy lowered the incidence of HF and major adverse cardiac and cerebrovascular events more effectively than either agent alone [96]. The potential additive benefits of SGLT2i/GLP-1 RA combination therapy might be attributed to their distinct mechanisms of action. For example, the potential adverse effect of GLP-1 RA in promoting adipose tissue inflammation could be attenuated by SGLT2i [97]. Therefore, SGLT2i/GLP-1 RA combination therapy negated adverse effect and increased additive benefits. However, more large-scale trials are needed to clarify the safety and efficacy of the combined treatment approaches in patients with HFpEF.

The role of DPP4i in diabetic HFpEF

Unlike GLP-1 RA and SGLT2i, DPP4i, a relatively new class of anti-diabetic drugs, have aroused controversy due to inconsistency about their cardiovascular effects in diabetic HFpEF (Table 4). A number of randomized controlled trials have generated conflicting data [98, 99]. For example, sitagliptin decreased LV passive stiffness and ameliorated global LV performance in a model of T2DM-induced LV dysfunction mouse [100]. A retrospective cohort study found that sitagliptin and linagliptin significantly lowered HF risk compared with sulfonylurea monotherapy in patients with or without pre-existing cardiovascular disease [98]. Analogously, a

Table 4 The role of DPP4i in diabetic HFpEF

DPP4i	Subjects	Follow-up period	Main findings	References
Sitagliptin and linagliptin	761,349 T2DM patients	435.1 days	Statistically lowered risk for HHF	[98]
Saxagliptin	16,492 patients with T2DM and a history of cardiovascular events	2.1 years	Increased the rate of HHF, but did not increase or decrease the rate of ischemic events	[99]
Sitagliptin	T2DM-induced LV dysfunction mouse	8 weeks	Decreased LV passive stiffness and ameliorated global LV performance	[100]
Sitagliptin, vildagliptin, alogliptin, saxagliptin, linagliptin and anagliptin	6,023 patients with HF and DM	NA	Attenuated all-cause mortality in female HF patients and HFpEF patients	[101]
Sitagliptin, vildagliptin, teneligliptin, alogliptin, linagliptin and anagliptin	797 patients with DM and HF (included 17 diabetic HFpEF)	423 days	Improved cardiovascular outcomes in DM patients with HFpEF	[102]
Saxagliptin	74,737 participants with HF	NA	Significantly increased risk of HF	[103]

DPP4i dipeptidyl peptidase 4 inhibitors; *HFpEF* heart failure with preserved ejection fraction; *T2DM* type 2 diabetes mellitus; *HHF* hospitalization for heart failure; *HF* heart failure; *NA* not available; *LV* left ventricular; *DM* diabetes mellitus

pooled analysis of trials demonstrated that DPP4i might attenuate all-cause mortality in HF patients in the subgroups of women and HFpEF [101]. Several studies disclosed that DPP4i was associated with a lower incidence of the composition of CVD and HHF in HFpEF cohort [14, 102].

Conversely, in SAVOR-TIMI 53 (saxagliptin assessment of vascular outcomes recorded in patients with DM thrombolysis in myocardial infarction) trail, Scirica et al. found that there were more HHF patients in the saxagliptin group than in the placebo group, and saxagliptin did not increase the occurrence of ischemic events in patients with HF [99]. At the same time, they also reported that the number of patients with one episode of hypoglycemia in the saxagliptin group was 1.9% higher than that in the placebo group. A previous meta-analysis of randomized clinical trials suggested a differential effect of each DPP4i on the risk of HF [103]. It found that saxagliptin significantly increased the risk of HF by 21%, especially in patients at high risk for cardiovascular, while no signal was detected for other DPP4i. The possible explanation of these inconsistent results was that the use of DPP4i might not have been long enough to reverse the effects of cardiovascular events. Another potential explanation for the differential effect could be discrepancy in the study population. More importantly, the use of saxagliptin may have a substance-specific effect on HF risk [103]. Future clinical studies with large samples and long-term follow-up are warranted to further investigate the role of DPP4i in diabetic HFpEF patients.

Overall, although the cardiovascular implications of DPP4i remain complex and somewhat contentious, emerging evidence points toward their potential benefits, particularly in diabetic HFpEF patients.

Relevant mechanisms of novel antidiabetic drugs in diabetic HFpEF

As mentioned above, novel hypoglycemic agents, SGLT2i, GLP-1 RA and DPP4i, have shown favorable cardiovascular benefits in patients with diabetic HFpEF. However, their underlying mechanisms in diabetic HFpEF remain complex and still elusive. It is imperative to broaden the understanding of their potential mechanisms. In recent years, several main relevant mechanisms of the novel antidiabetic drugs in preclinical model of diabetic HFpEF were investigated (Table 5).

Inflammation, oxidative stress and lipotoxicity

A previous study suggested that dapagliflozin significantly prevented the development of HFpEF in diabetic rats. Further mechanism experiments revealed that dapagliflozin mitigated pro-inflammatory cytokines, nitro-oxidative stress, and fibrosis, as well as reduced apoptosis, and restored autophagy via activating adenosine monophosphate kinase (AMPK) and mTOR pathway [63]. Also, Kolijin et al. revealed that empagliflozin improved cardiomyocyte stiffness and diastolic dysfunction by reducing inflammation, oxidative stress and protein kinase GIα (PKGIα) oxidation and polymerization in human and murine HFpEF [104]. In addition, dapagliflozin attenuated the progression of diabetic cardiomyopathy by activating AMPK, mTOR and NOD-like receptor 3 (NLRP3) inflammasome in T2DM mice [105]. Moreover, in addition to alleviating hyperglycemia and hyperlipidemia, sitagliptin also ameliorated inflammation and oxidative stress by down-regulating JAK/STAT signaling pathway in diabetic rats, conferring evidence for the therapy of diabetic cardiomyopathy [106]. A recent study underscored that dapagliflozin and/or liraglutide attenuated cardiac tissue injury via reducing key elements of oxidative stress, inflammation and apoptosis in diabetes-induced cardiomyopathy rats [62]. Though in vivo and in vitro experiment, Li et al. indicated that empagliflozin partially exerted anti-oxidative stress and anti-apoptotic effects on cardiomyocytes under high glucose conditions by activating AMPK/PGC-1α and

Table 5 Preclinical model of the novel antidiabetic drugs in diabetic HFpEF

Preclinical model	Antidiabetic drugs	Results	Relevant mechanism	References
DCM mice	Canagliflozin	Attenuated myocardial injury and inhibited diabetic myocardial tissues fibrosis and oxidative stress	Inhibited ferroptosis by balancing cardiac iron homeostasis and promoting the system Xc^-/GSH/GPX4 axis	[61]
DCM rats	Dapagliflozin and liraglutide	Attenuated diabetes-induced cardiac tissue injury	Markedly decreased the expression of pro-inflammatory cytokine mRNA levels	[62]
DCM rats	Dapagliflozin	Downregulated the key markers of myocardial fibrosis, nitro-oxidative stress, pro-inflammatory cytokines, myocardial hypertrophy, fibrosis, and reduced apoptosis	Restoring autophagy through AMPK activating and mTOR pathway repressing	[63]
HFpEF mice	Liraglutide and empagliflozin	Markedly improved diastolic function, cardiomyocyte hypertrophy, myocardial fibrosis and exercise tolerance	Up-regulated the phosphorylation of ERK1/2 and down-regulated the phosphorylation of PKCα through Erbb4 signaling pathway	[93]
HFpEF mice	Semaglutide	Improved the cardiometabolic profile and cardiac function and structure	By improving left ventricular cytoskeleton function and endothelial function and restored protective immune responses in visceral adipose tissue	[94]
HFpEF mice	Empagliflozin	Improved cardiomyocyte stiffness, reduced myocardial oxidative stress and pro-inflammatory cytokines	Reduced pro-inflammatory-oxidative pathways and PKGIα oxidation	[104]
DCM mice	Dapagliflozin	Reduced LV internal diameter, myocardial fibrosis, myocardial BNP, Caspase-1 mRNA levels and activation of NLRP3 inflammasome	Activated the AMPK-mTOR pathway and increased the level of RICTOR	[105]
DCM rats	Sitagliptin	Alleviated hyperglycemia, hyperlipidemia, heart-to-body weight ratio oxidative stress and inflammation	Through down-regulating the JAK/STAT signaling pathway	[106]
DCM mice	Empagliflozin	Enhanced the diastolic and systolic functions of the heart, attenuated diabetic-induced mitochondrial injury, oxidative stress and cardiomyocyte apoptosis	Activated AMPK/PGC-1α and suppressed the RhoA/ROCK pathway	[107]
DCM mice	Semaglutide	Alleviated glucose metabolism disorders and improved cardiac insufficiency, oxidative stress and apoptosis	Activated Sirt1/AMPK pathway and restorated Cx43 expression	[108]
Type 2 diabetic HF model	Canagliflozin	Ameliorated heart functions and inflammatory responses	Bound to the mTOR and then inhibited the mTOR/HIF-1α pathway	[109]
DCM mice	Exendin-4	Attenuated cardiac remodeling, improved cardiac function, oxidative stress, inflammation, and apoptosis	Inhibited the ROCK/PPARα pathway	[110]
HFpEF rats	Canagliflozin	Improved cardiac remodeling markers and enhanced diastolic function	Restored balance in multiple metabolic pathways, particularly affecting β-alanine metabolism, pyrimidine metabolism, and the citrate cycle	[115]
HFpEF rats	Dapagliflozin	Mainly improved cardiomyocyte hypertrophy, apoptosis, inflammation, oxidative stress, and fibrosis	Inhibited myocardial fatty acid uptake and energy pathway activation	[116]
DCM rats	Liraglutide	Alleviated diabetic myocardium injury	By promoting AMPK-dependent autophagy	[117]
DCM rats	Dapagliflozin	Attenuated cardiac dysfunction, myocardial fibrosis and EndMT	Through suppressing fibroblast activation and EndMT via AMPKα-mediated inhibition of TGF-β/Smad signalling	[120]

DCM diabetic cardiomyopathy; *AMPK* AMP-activated protein kinase; *mTOR* mammalian target of rapamycin; *LV* left ventricular; *PKGIα* protein kinase GIα; *NLRP3* NLR family pyrin domain containing 3; *JAK/STAT* janus kinase/signal transducer and activator of transcription; *EndMT* endothelial to mesenchymal transition; *TGF-β* transforming growth factor-β

suppressing other RhoA/ Rho-associated protein kinase (ROCK) pathway in diabetes-induced cardiomyopathy mice [107]. Analogously, semaglutide protected diabetic cardiomyopathy mice against oxidative stress and apoptosis, and thereby improved cardiac dysfunction by activating Sirt1/AMPK pathway and restoring of Cx43 expression [108].

In addition to inflammation and oxidative stress, lipotoxicity also played a vital role in diabetic HFpEF. Sun et al. indicated that canagliflozin could attenuate lipotoxicity and inflammatory injury in cardiomyocytes and protected diabetic mouse hearts via inhibiting the mTOR/hypoxia-inducible factor-1α (HIF-1α) pathway [109]. Likewise, exendin-4 ameliorated lipotoxicity and protected cardiac function by suppressing the ROCK/peroxisome proliferator activated receptorsα (PPARα) pathway in diabetic cardiomyopathy [110]. Besides, evogliptin, was also reported to improve cardiac function through reducing lipotoxicity and mitochondrial injury, thereby preventing diabetic cardiomyopathy [111]. All these results highlight the underlying mechanisms of

novel antidiabetic drugs in diabetic HFpEF in modulating inflammation, oxidative stress and lipotoxicity (Fig. 2).

Autophagy and mitochondrial dysfunction

Autophagy plays a crucial role in maintaining cardiac homeostasis and promoting cardiac protection by preserving mitochondrial function [112, 113]. Empagliflozin activated SIRT3-mediated autophagic signaling pathways via AMPK/Beclin1 and autophagosome membrane elongation, which induced the formation of myocardial autophagosomes and reduced cardiac pathological remodeling, ultimately alleviating damage to the cardiac structure [114]. Canagliflozin ameliorated myocardial remodeling in HFpEF rats by optimizing cardiac energy metabolism, enhancing mitochondrial function, and consequently reducing myocardial hypertrophy and fibrosis, with simultaneous improvement of diastolic function [115]. Dapagliflozin alleviated cardiac diastolic and systolic dysfunction in the advanced progression of HFpEF by attenuating cardiac metabolic dysregulation through inhibiting myocardial fatty acid uptake and energy pathway activation [116]. Similarly, Zhang et al. provided evidence that liraglutide alleviated diabetic myocardium injury by promoting AMPK-dependent autophagy in the vivo and in the vitro models [117]. Moreover, sitagliptin attenuated diabetes-induced cardiac injury by reducing nitroxidative stress and promoting autophagy [118]. Recently, Xie et al. investigated that dulaglutide prevented diabetic HF and myocardial metabolic remodeling by impeding mitochondria fragmentation [119]. In short, these findings underscored that increased autophagy and improved mitochondrial dysfunction was involved in the cardioprotective effects of novel antidiabetic drugs (Fig. 3).

In addition to the above related mechanisms, several other relevant mechanisms were also considered. Du et al. suggested that canagliflozin inhibited ferroptosis by balancing cardiac iron homeostasis and activating Xc^{-}/GSH/GPX4 axis in diabetic cardiomyopathy [61]. Another interesting study implied that dapagliflozin mitigated myocardial fibrosis and diabetic cardiomyopathy by suppressing fibroblast activation and endothelial-to-mesenchymal transition via AMPKα-mediated inhibition of TGF-β/Smad signaling [120].

Conclusion and future perspectives

It is unequivocal that the risk and burden of HFpEF is increasing due to aging of population, the global epidemic of obesity and T2DM. Current evidence supports that the novel antidiabetic drugs exert cardioprotective effects and reduce the comorbidity in DM patients with HFpEF.

In spite of increasing overall prevalence of conditions that contributed to the pathophysiology of HFpEF, there was considerable international variation in the prevalence of HFpEF and its contributing factors. It should also be pointed out that the combination of the new hypoglycemic drugs and other drugs alleviated the clinical symptoms of patients, causing the NT-proBNP value to return to normal, thereby providing additional cardiovascular

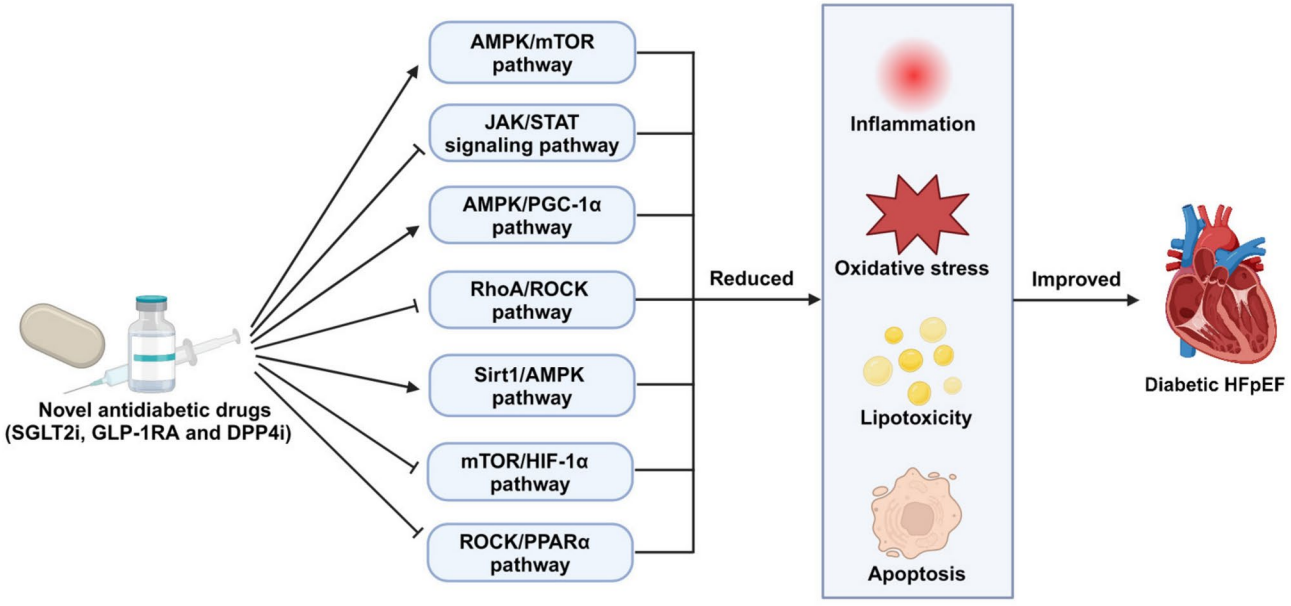


Fig. 2 The mechanisms of novel antidiabetic drugs in diabetic HFpEF via inflammation, oxidative stress and lipotoxicity. Novel antidiabetic drugs could reduce inflammation, oxidative stress, apoptosis and lipotoxicity, by activating several signaling pathways, including AMPK/mTOR, AMPK/PGC-1α, Sirt1/AMPK, or by inhibiting certain signaling pathways, such as JAK/STAT, RhoA/ROCK, mTOR/HIF-1α and ROCK/PPARα pathway, ultimately improving diabetic HFpEF

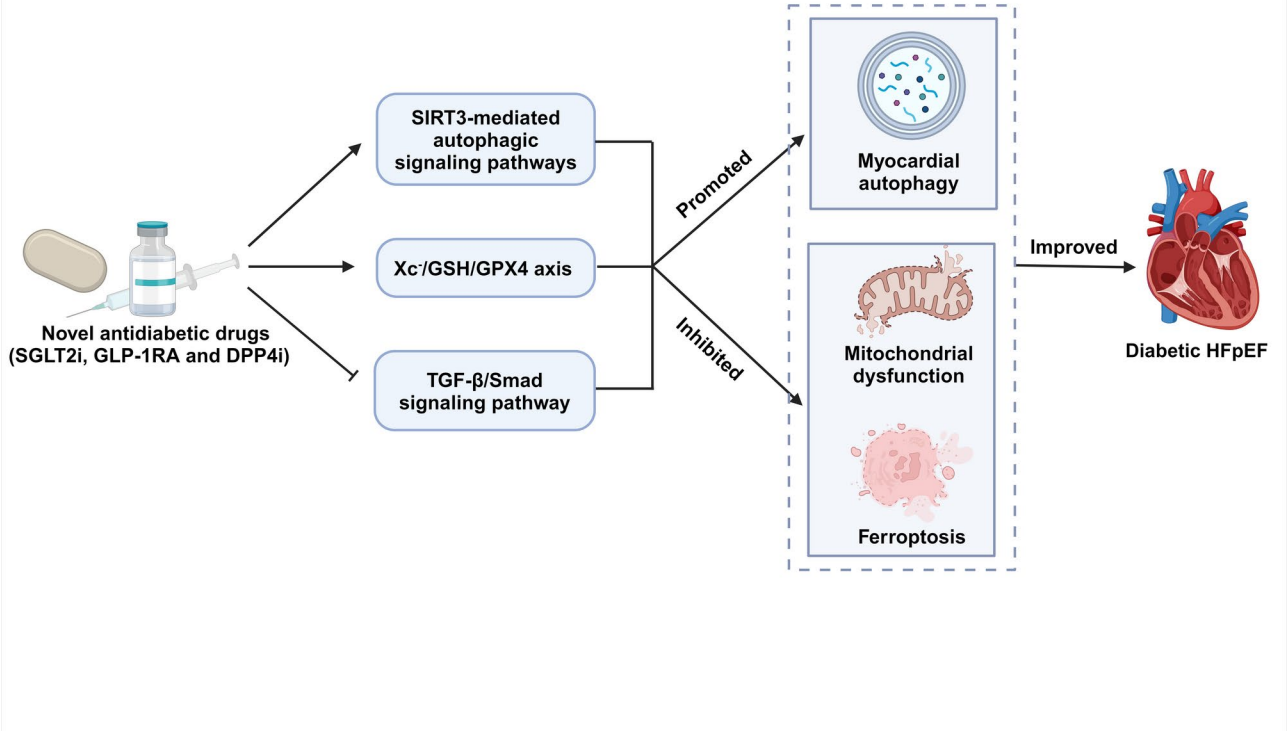


Fig. 3 The relevant mechanisms of the novel antidiabetic drugs in diabetic HFpEF through mitochondrial dysfunction, autophagy and ferroptosis. Novel antidiabetic drugs mitigated mitochondrial dysfunction and ferroptosis, as well as promoted autophagy by activating Xc^-/GSH/GPX4 axis and SIRT3-mediated autophagic pathway, or by inhibiting TGF-β/Smad pathway, ultimately improving diabetic HFpEF

event protection for HFpEF, without new safety signals found [121, 122]. The possible mechanism might be the interference of those drugs with sodium retention and cardiac inflammation, microvascular sparseness and fibrosis [123].

Naturally, the mechanisms in which the novel antidiabetic drugs were involved in diabetic HFpEF were multifactorial. Moreover, several novel antidiabetic drugs, such as DPP4i and SGLT2i, remained complex and somewhat contentious in providing the cardiovascular benefits in diabetic HFpEF. For example, the pooled analysis of EMPEROR-Reduced and EMPEROR-Preserved trial demonstrated that the use of empagliflozin in patients with LVEF ≥ 65% was also controversial [124]. The Food and Drugs Administration of the United States has pointed out that it is not recommended to use SGLT2i for patients with eGFR < 45 mL/min/1.73 m^2. One possible cause for such controversy might be the substance-specific effects of saxagliptin, which could be attributed to off-target side effects of DPP4 enzyme, resulting in unexpected alterations of other bioactive substrates in the body. Another explanation could be the differences in the study population and the distinct baseline characteristics of potential diseases. Therefore, larger and longer durations of randomized controlled trials, along with well-designed mechanistic studies, are needed to comprehensively unlock the exact roles and mechanisms of novel antidiabetic drugs in diabetic HFpEF in the future.

Abbreviations

DM	Diabetes mellitus
HF	Heart failure
EF	Ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
HFnEF	Heart failure with normal ejection fraction
SGLT2i	Sodium glucose cotransporter 2 inhibitors
GLP-1 RA	Glucagon-like peptide-1 receptor agonists
DPP4i	Dipeptidyl peptidase 4 inhibitors
LV	Left ventricular
ANP	Abnormal natriuretic peptide
EAT	Epicardial adipose tissue
AGE	Advanced glycation end
LVEF	Left ventricular ejection fraction
HHF	Heart failure hospitalization
CVD	Cardiovascular death
NT-proBNP	N-terminal B-type ANP
CIMT	Carotid intima-media thickness
TNF-α	Tumor necrosis factor-α
AMPK	Adenosine monophosphate kinase
NLRP3	NOD-like receptor 3
ROCK	Rho-associated protein kinase
PPARα	Peroxisome proliferator activated receptors α

Acknowledgements
Not applicable.

Author contributions
XLD and XMZ wrote the manuscript draft and designed the figures. BS revised the manuscript. All authors approved the final version of the manuscript.

Funding
The study was supported by National Natural Science Foundation of China (No. 82104307), Natural Science Foundation of Hunan Province (No. 2024JJ4080), Scientific Research Project of Human Provincial Health Commission (No. B202313016776), Talent Project established by Chinese Pharmaceutical Association Hospital Pharmacy Department (No.CPA-Z05-ZC-2024-003) and Scientific Research Launch Project for new employees of the Second Xiangya Hospital of Central South University.

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

Declarations

Ethical approval
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pharmacy, The Second Xiangya Hospital, Central South University, No. 139, People's Middle Street, Changsha 410011, China
[2]National Clinical Research Center for Metabolic Diseases, The Second Xiangya Hospital, Central South University, Changsha 410011, China
[3]Department of Clinical Chinese Pharmacy, School of Chinese Materia Medica, Beijing University of Chinese Medicine, Beijing 102488, China

Received: 22 January 2025 / Accepted: 19 April 2025
Published online: 28 April 2025

References

1. Gregory GA, et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol. 2022;10(10):741–60.
2. Taylor SI, Yazdi ZS, Beitelshees AL. Pharmacological treatment of hyperglycemia in type 2 diabetes. J Clin Invest. 2021;131(2):e142243.
3. Paulus WJ, Dal Canto E. Distinct myocardial targets for diabetes therapy in heart failure with preserved or reduced ejection fraction. JACC Heart Fail. 2018;6(1):1–7.
4. Karwi QG, et al. Concurrent diabetes and heart failure: interplay and novel therapeutic approaches. Cardiovasc Res. 2022;118(3):686–715.
5. Lam CSP, Solomon SD. Classification of heart failure according to ejection fraction: JACC review topic of the week. J Am Coll Cardiol. 2021;77(25):3217–25.
6. Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: a review. JAMA. 2023;329(10):827–38.
7. McHugh K, et al. Heart failure with preserved ejection fraction and diabetes: JACC state-of-the-art review. J Am Coll Cardiol. 2019;73(5):602–11.
8. 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(4):263–71.
9. Lindman BR, et al. Cardiovascular phenotype in HFpEF patients with or without diabetes: a RELAX trial ancillary study. J Am Coll Cardiol. 2014;64(6):541–9.
10. Franssen C, et al. Myocardial microvascular inflammatory endothelial activation in heart failure with preserved ejection fraction. JACC Heart Fail. 2016;4(4):312–24.
11. Hsu CN, et al. Anti-diabetic therapy and heart failure: recent advances in clinical evidence and molecular mechanism. Life (Basel). 2023;13(4):1024.
12. Solomon SD, et al. Baseline characteristics of patients with HF with mildly reduced and preserved ejection fraction: DELIVER trial. JACC Heart Fail. 2022;10(3):184–97.
13. Temporelli PL. Role of glucagon-like peptide-1 agonists in obesity and heart failure with preserved ejection fraction. Eur Heart J Suppl. 2024;26(Suppl 1):i127–30.
14. Enzan N, et al. Beneficial effects of dipeptidyl peptidase-4 inhibitors on heart failure with preserved ejection fraction and diabetes. JACC Asia. 2023;3(1):93–104.
15. Fan L, et al. Optimal management of blood glucose, blood pressure and atrial fibrillation to reduce the risk of heart failure with preserved ejection fraction. Intern Med J. 2022;52(2):301–9.
16. Morbach C, Störk S. Heart failure with preserved ejection fraction (HFpEF): diagnosis and treatment. Herz. 2023;48(2):159–68.
17. Borlaug BA, et al. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. Cardiovasc Res. 2023;118(18):3434–50.
18. Bistola V, et al. Hospitalized advanced heart failure with preserved vs reduced left ventricular ejection fraction: a global perspective. JACC Heart Fail. 2025;13(2):229–47.
19. Shiga T, et al. Clinical characteristics of hospitalized heart failure patients with preserved, mid-range, and reduced ejection fractions in Japan. ESC Heart Fail. 2019;6(3):475–86.
20. Gerber Y, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med. 2015;175(6):996–1004.
21. Tsao CW, et al. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. JACC Heart Fail. 2018;6(8):678–85.
22. Tromp J, et al. Heart failure with preserved ejection fraction in the young. Circulation. 2018;138(24):2763–73.
23. Ceia F, et al. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. Eur J Heart Fail. 2002;4(4):531–9.
24. Chioncel O, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC heart failure long-term registry. Eur J Heart Fail. 2017;19(12):1574–85.
25. Kittleson MM, et al. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American college of cardiology solution set oversight committee. J Am Coll Cardiol. 2023;81(18):1835–78.
26. Pop-Busui R, et al. Heart failure: an underappreciated complication of diabetes. A consensus report of the American diabetes association. Diabetes Care. 2022;45(7):1670–90.
27. Berezin AA, Fushtey IM, Berezin AE. Discriminative utility of apelin-to-NT-pro-brain natriuretic peptide ratio for heart failure with preserved ejection fraction among type 2 diabetes mellitus patients. J Cardiovasc Dev Dis. 2022;9(1):23.
28. Kristensen SL, et al. Prevalence of prediabetes and undiagnosed diabetes in patients with HFpEF and HFrEF and associated clinical outcomes. Cardiovasc Drugs Ther. 2017;31(5–6):545–9.
29. Lejeune S, et al. Diabetic phenotype and prognosis of patients with heart failure and preserved ejection fraction in a real life cohort. Cardiovasc Diabetol. 2021;20(1):48.
30. Arévalo-Lorido JC, et al. Comorbidities and their implications in patients with and without type 2 diabetes mellitus and heart failure with preserved ejection fraction. Findings from the rica registry. Int J Clin Pract. 2021;75(1):e13661.
31. Kristensen SL, et al. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-preserve trial (Irbesartan in heart failure with preserved ejection fraction). Circulation. 2017;135(8):724–35.
32. Peng KL, et al. Cardiac structural and functional features in patients with type 2 diabetes mellitus and heart failure with preserved ejection fraction: a study based on propensity score matching. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2023;45(2):264–72.
33. Yang W, et al. Long-term outcomes prediction in diabetic heart failure with preserved ejection fraction by cardiac MRI. Eur Radiol. 2024;34(9):5678–90.

34. Cimino G, et al. Obesity, heart failure with preserved ejection fraction, and the role of glucagon-like peptide-1 receptor agonists. ESC Heart Fail. 2024;11(2):649–61.
35. Zhang X, et al. WATCH-DM risk score predicts the prognosis of diabetic phenotype patients with heart failure and preserved ejection fraction. Int J Cardiol. 2023;385:34–40.
36. Yap J, et al. Association of diabetes mellitus on cardiac remodeling, quality of life, and clinical outcomes in heart failure with reduced and preserved ejection fraction. J Am Heart Assoc. 2019;8(17):e013114.
37. Kong MG, et al. Impact of diabetes mellitus on mortality in patients with acute heart failure: a prospective cohort study. Cardiovasc Diabetol. 2020;19(1):49.
38. Palau P, et al. Differential prognostic impact of type 2 diabetes mellitus in women and men with heart failure with preserved ejection fraction. Rev Esp Cardiol (Engl Ed). 2020;73(6):463–70.
39. Huang JP, et al. Exosomal microRNAs miR-30d-5p and miR-126a-5p are associated with heart failure with preserved ejection fraction in STZ-induced type 1 diabetic rats. Int J Mol Sci. 2022;23(14):7514.
40. Wu X, et al. SIRT6 mitigates heart failure with preserved ejection fraction in diabetes. Circ Res. 2022;131(11):926–43.
41. Shi YJ, Dong GJ, Guo M. Targeting epicardial adipose tissue: a potential therapeutic strategy for heart failure with preserved ejection fraction with type 2 diabetes mellitus. World J Diabetes. 2023;14(6):724–40.
42. Park JJ. Epidemiology, pathophysiology, diagnosis and treatment of heart failure in diabetes. Diabetes Metab J. 2021;45(2):146–57.
43. Wang Y, et al. Endothelial-cell-mediated mechanism of coronary microvascular dysfunction leading to heart failure with preserved ejection fraction. Heart Fail Rev. 2023;28(1):169–78.
44. Sinha A, Rahman H, Perera D. Coronary microvascular dysfunction and heart failure with preserved ejection fraction: what are the mechanistic links? Curr Opin Cardiol. 2023;38(6):521–6.
45. Khunti K. SGLT2 inhibitors in people with and without T2DM. Nat Rev Endocrinol. 2021;17(2):75–6.
46. Cannon CP, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med. 2020;383(15):1425–35.
47. Lincoff AM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389(24):2221–32.
48. Sattar N, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol. 2021;9(10):653–62.
49. Xie Y, et al. Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of major adverse cardiovascular events: emulation of a randomised target trial using electronic health records. Lancet Diabetes Endocrinol. 2023;11(9):644–56.
50. Mondal S, et al. Sodium glucose cotransporter-2 inhibitors and heart disease: current perspectives. World J Cardiol. 2024;16(5):240–59.
51. Hamid AK, et al. Empagliflozin and other SGLT2 inhibitors in patients with heart failure and preserved ejection fraction: a systematic review and meta-analysis. Ther Adv Cardiovasc Dis. 2024;18:17539447241289068.
52. Treewaree S, et al. Is it time for class I recommendation for sodium-glucose cotransporter-2 inhibitors in heart failure with mildly reduced or preserved ejection fraction?: an updated systematic review and meta-analysis. Front Cardiovasc Med. 2023;10:1046194.
53. Nassif ME, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. 2021;27(11):1954–60.
54. Scheen AJ. Counteracting heart failure with diabetes drugs: a review into the pharmacokinetic and pharmacodynamic properties. Expert Opin Drug Metab Toxicol. 2022;18(6):381–93.
55. Aguiar-Neves I, Santos-Ferreira D, Fontes-Carvalho R. SGLT2 inhibition in heart failure with preserved ejection fraction-the new frontier. Rev Cardiovasc Med. 2023;24(1):1.
56. Deng J, et al. Potential clinical biomarkers and perspectives in diabetic cardiomyopathy. Diabetol Metab Syndr. 2023;15(1):35.
57. Fukuta H, Hagiwara H, Kamiya T. Sodium-glucose cotransporter 2 inhibitors in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. Int J Cardiol Heart Vasc. 2022;42:101103.
58. Wahinya M, Khan Z. Sodium-glucose cotransporter-2 (SGLT2) inhibitor therapy for the primary and secondary prevention of heart failure in patients with and without type 2 diabetes mellitus: a systematic review. Cureus. 2023;15(4):e37388.
59. Ueda T, et al. Effect of the sodium-glucose cotransporter 2 inhibitor canagliflozin for heart failure with preserved ejection fraction in patients with type 2 diabetes. Circ Rep. 2021;3(8):440–8.
60. Longo M, et al. Two years with GIOIA 'Effects of gliflozins and gliptins on markers of cardiovascular damage in type 2 diabetes': a prospective, multicentre, quasi-experimental study on sodium-glucose cotransporter 2 and dipeptidyl peptidase-4 inhibitors in diabetes clinical practice. Diabetes Obes Metab. 2024;26(4):1492–501.
61. Du S, et al. Canagliflozin mitigates ferroptosis and improves myocardial oxidative stress in mice with diabetic cardiomyopathy. Front Endocrinol (Lausanne). 2022;13:1011669.
62. El-Shafey M, et al. Role of dapagliflozin and liraglutide on diabetes-induced cardiomyopathy in rats: implication of oxidative stress, inflammation, and apoptosis. Front Endocrinol (Lausanne). 2022;13:862394.
63. Feng B, et al. Therapeutic effects on the development of heart failure with preserved ejection fraction by the sodium-glucose cotransporter 2 inhibitor dapagliflozin in type 2 diabetes. Diabetol Metab Syndr. 2023;15(1):141.
64. Albulushi A, et al. Comparative effects of glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors on heart failure with preserved ejection fraction in diabetic patients: a meta-analysis. Cardiovasc Diabetol. 2024;23(1):324.
65. Tadic M, et al. New antidiabetic therapy and HFpEF: light at the end of tunnel? Heart Fail Rev. 2022;27(4):1137–46.
66. Soga F, et al. Impact of dapagliflozin on the left ventricular diastolic function in diabetic patients with heart failure complicating cardiovascular risk factors. Intern Med. 2021; 60(15): 2367-74.
67. Tanaka H, et al. Positive effect of dapagliflozin on left ventricular longitudinal function for type 2 diabetic mellitus patients with chronic heart failure. Cardiovasc Diabetol. 2020;19(1):6.
68. Fujiki S, et al. Body fluid regulation via chronic inhibition of sodium-glucose cotransporter-2 in patients with heart failure: a post hoc analysis of the CANDLE trial. Clin Res Cardiol. 2023;112(1):87–97.
69. Ostrominski JW, et al. Dapagliflozin and New York heart association functional class in heart failure with mildly reduced or preserved ejection fraction: the DELIVER trial. Eur J Heart Fail. 2022;24(10):1892–901.
70. Kolwelter J, et al. Effects of the sodium-glucose cotransporter 2 inhibitor empagliflozin on vascular function in patients with chronic heart failure. ESC Heart Fail. 2021;8(6):5327–37.
71. Chai K, et al. Effects of empagliflozin on cardiac structure, function and biomarkers in patients with heart failure with preserved ejection fraction: study protocol for a randomised, placebo-controlled prospective trial. BMJ Open. 2023;13(8):e070766.
72. Li W, et al. Sodium-glucose cotransporter-2 inhibitor use is associated with a reduced risk of heart failure hospitalization in patients with heart failure with preserved ejection fraction and type 2 diabetes mellitus: a real-world study on a diverse urban population. Drugs Real World Outcomes. 2022;9(1):53–62.
73. Bhatt DL, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med. 2021;384(2):129–39.
74. Anker SD, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385(16):1451–61.
75. Butler J, et al. Safety and efficacy of empagliflozin and diuretic use in patients with heart failure and preserved ejection fraction: a post hoc analysis of the EMPEROR-preserved trial. JAMA Cardiol. 2023;8(7):640–9.
76. Butler J, et al. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. Eur Heart J. 2022;43(5):416–26.
77. Tromp J, et al. Treatment effects of empagliflozin in hospitalized heart failure patients across the range of left ventricular ejection fraction-results from the EMPULSE trial. Eur J Heart Fail. 2024;26(4):963–70.
78. Kato ET, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation. 2019;139(22):2528–36.
79. Ostrominski JW, et al. Dapagliflozin and New York heart association functional class in heart failure with mildly reduced or preserved ejection fraction: the DELIVER trial. Eur J Heart Fail. 2022;24(10):1892–901.
80. Solomon SD, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387(12):1089–98.
81. Patel R, et al. GLP-1 receptor agonists among patients with overweight or obesity, diabetes, and HFpEF on SGLT2 inhibitors. JACC Heart Fail. 2024;12:1814–26.
82. Shah SJ, et al. Semaglutide and diuretic use in obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF-DM trials. Eur Heart J. 2024;45(35):3254–69.

83. Petrie MC, et al. Semaglutide and NT-proBNP in obesity-related HFpEF: insights from the STEP-HFpEF program. J Am Coll Cardiol. 2024;84(1):27–40.
84. Kosiborod MN, et al. Design and baseline characteristics of STEP-HFpEF program evaluating semaglutide in patients with obesity HFpEF phenotype. JACC Heart Fail. 2023;11(8 Pt 1):1000–10.
85. Kosiborod MN, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. N Engl J Med. 2024:390(15):1394-407.
86. van Woerden G, et al. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. Eur J Heart Fail. 2018;20(11):1559–66.
87. Iacobellis G, et al. Liraglutide causes large and rapid epicardial fat reduction. Obesity (Silver Spring). 2017;25(2):311–6.
88. Iacobellis G, Villasante Fricke AC. Effects of semaglutide versus dulaglutide on epicardial fat thickness in subjects with type 2 diabetes and obesity. J Endocr Soc. 2020;4(4):bvz042.
89. Fudim M, et al. Effect of once-weekly exenatide in patients with type 2 diabetes mellitus with and without heart failure and heart failure-related outcomes: insights from the EXSCEL trial. Circulation. 2019;140(20):1613–22.
90. Solomon SD, et al. Effect of semaglutide on cardiac structure and function in patients with obesity-related heart failure. J Am Coll Cardiol. 2024:84(17):1587-602.
91. 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(10456):949–61.
92. Withaar C, et al. The effects of liraglutide and dapagliflozin on cardiac function and structure in a multi-hit mouse model of heart failure with preserved ejection fraction. Cardiovasc Res. 2021;117(9):2108–24.
93. Ni XY, et al. Empagliflozin and liraglutide ameliorate HFpEF in mice via augmenting the Erbb4 signaling pathway. Acta Pharmacol Sin. 2024;45(8):1604–17.
94. 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(10):1298–314.
95. Kumarathurai P, et al. Effects of liraglutide on diastolic function parameters in patients with type 2 diabetes and coronary artery disease: a randomized crossover study. Cardiovasc Diabetol. 2021;20(1):12.
96. Wright AK, et al. Primary prevention of cardiovascular and heart failure events with SGLT2 inhibitors, GLP-1 receptor agonists, and their combination in type 2 diabetes. Diabetes Care. 2022;45(4):909–18.
97. Volpe, M, et al. Cardiometabolic phenotype of heart failure with preserved ejection fraction as a target of sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide receptor agonists. Cardiovasc Res. 2021;117(9):1992-4.
98. Kim YG, et al. Dipeptidyl peptidase-4 inhibitors and risk of heart failure in patients with type 2 diabetes mellitus: a population-based cohort study. Circ Heart Fail. 2017;10(9):e003957.
99. Scirica BM, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317–26.
100. Hamdani N, et al. Left ventricular diastolic dysfunction and myocardial stiffness in diabetic mice is attenuated by inhibition of dipeptidyl peptidase 4. Cardiovasc Res. 2014;104(3):423–31.
101. Li J, Liu Y, Hao P. Re-evaluation of dipeptidyl peptidase-4 inhibitors in patients with heart failure and diabetes mellitus. Diabetes Res Clin Pract. 2023;202:110798.
102. Yamamoto M, et al. Effect of dipeptidyl peptidase-4 inhibitors on cardiovascular outcome and cardiac function in patients with diabetes and heart failure-insights from the ibaraki cardiac assessment study-heart failure (ICAS-HF) registry. Circ J. 2017;81(11):1662–9.
103. Kongwatcharapong J, et al. Effect of dipeptidyl peptidase-4 inhibitors on heart failure: a meta-analysis of randomized clinical trials. Int J Cardiol. 2016;211:88–95.
104. Kolijn D, et al. Empagliflozin improves endothelial and cardiomyocyte function in human heart failure with preserved ejection fraction via reduced pro-inflammatory-oxidative pathways and protein kinase Gα oxidation. Cardiovasc Res. 2021;117(2):495–507.
105. Chen H, et al. Dapagliflozin and ticagrelor have additive effects on the attenuation of the activation of the NLRP3 inflammasome and the progression of diabetic cardiomyopathy: an AMPK-mTOR interplay. Cardiovasc Drugs Ther. 2020;34(4):443–61.
106. Al-Rasheed NM, et al. Sitagliptin attenuates cardiomyopathy by modulating the JAK/STAT signaling pathway in experimental diabetic rats. Drug Des Devel Ther. 2016;10:2095–107.
107. Li N, et al. Empagliflozin ameliorates diabetic cardiomyopathy probably via activating AMPK/PGC-1α and inhibiting the RhoA/ROCK pathway. World J Diabetes. 2023;14(12):1862–76.
108. Yan M, et al. Semaglutide attenuates pathological electrophysiological remodeling in diabetic cardiomyopathy via restoring Cx43 expression. Endocrine. 2024;84(3):969–79.
109. Sun P, et al. Canagliflozin attenuates lipotoxicity in cardiomyocytes and protects diabetic mouse hearts by inhibiting the mTOR/HIF-1α pathway. iScience. 2021;24(6):102521.
110. Wu L, et al. Glucagon-like peptide-1 ameliorates cardiac lipotoxicity in diabetic cardiomyopathy via the PPARα pathway. Aging Cell. 2018;17(4):e12763.
111. Pham TK, et al. Evogliptin, a DPP-4 inhibitor, prevents diabetic cardiomyopathy by alleviating cardiac lipotoxicity in db/db mice. Exp Mol Med. 2023;55(4):767–78.
112. Rabinovich-Nikitin I, et al. Mitochondrial autophagy and cell survival is regulated by the circadian Clock gene in cardiac myocytes during ischemic stress. Autophagy. 2021;17(11):3794–812.
113. Shirakabe A, et al. Drp1-dependent mitochondrial autophagy plays a protective role against pressure overload-induced mitochondrial dysfunction and heart failure. Circulation. 2016;133(13):1249–63.
114. Luo Y, et al. Empagliflozin alleviates obesity-related cardiac dysfunction via the activation of SIRT3-mediated autophagosome formation. Lipids Health Dis. 2024;23(1):308.
115. Zhang G, et al. Metabolomic Analysis of the effects of canagliflozin on hfpef rats and its underlying mechanism. Endocr Metab Immune Disord Drug Targets. 2025.
116. Zhang X, et al. Dapagliflozin attenuates heart failure with preserved ejection fraction remodeling and dysfunction by elevating β-hydroxybutyrate-activated citrate synthase. J Cardiovasc Pharmacol. 2023;82(5):375–88.
117. 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.
118. Zhou Y, et al. Sitagliptin protects cardiac function by reducing nitroxidative stress and promoting autophagy in zucker diabetic fatty (ZDF) rats. Cardiovasc Drugs Ther. 2018;32(6):541–52.
119. Xie S, et al. Long-term activation of glucagon-like peptide-1 receptor by dulaglutide prevents diabetic heart failure and metabolic remodeling in type 2 diabetes. J Am Heart Assoc. 2022;11(19):e026728.
120. Tian J, et al. Dapagliflozin alleviates cardiac fibrosis through suppressing EndMT and fibroblast activation via AMPKα/TGF-β/Smad signalling in type 2 diabetic rats. J Cell Mol Med. 2021;25(16):7642–59.
121. Vaduganathan M, et al. Effects of the nonsteroidal MRA finerenone with and without concomitant SGLT2 inhibitor use in heart failure. Circulation. 2025;151(2):149–58.
122. Miric D, Juric Paic M, Borovac JA. Bradycardia-induced heart failure with preserved ejection fraction successfully treated with empagliflozin and theophylline: a case report. Eur Heart J Case Rep. 2024;8(9):ytae481.
123. Packer M, Kitzman DW. Obesity-related heart failure with a preserved ejection fraction: the mechanistic rationale for combining inhibitors of aldosterone, neprilysin, and sodium-glucose cotransporter-2. JACC Heart Fail. 2018;6(8):633–9.
124. Maltês S, et al. Dapagliflozin in a real-world chronic heart failure population: how many are actually eligible? Cardiology. 2021;146(2):201–6.

Publisher's note