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Effectiveness of DPP-4 vs SGLT2 Inhibitors on Cardiovascular Parameters in Type 2 Diabetes Animal Models: A Literature Review

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ABSTRACT

Introduction*: As a chronic metabolic disease, type 2 diabetes mellitus (T2DM) is strongly correlated with a heightened risk of cardiovascular disease through mechanisms involving endothelial dysfunction, chronic inflammation, oxidative stress, and myocardial fibrosis. The management of cardiovascular complications in T2DM has encouraged research on antidiabetic agents with cardioprotective effects. Two drug classes that have been extensively studied, namely dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium-glucose cotransporter 2 inhibitors (SGLT2i), demonstrate distinct mechanisms and potential for cardiovascular protection.* ***Aims****: Compare the effectiveness of DPP-4i and SGLT2i on cardiovascular parameters in T2DM animal models.* ***Method:*** *A rigorous systematic review was performed across Google Scholar and PubMed databases, adhering to the predefined inclusion parameters of preclinical studies in T2DM animal models evaluating the effects of DPP-4i and/or SGLT2i on cardiac function, blood pressure, myocardial fibrosis, oxidative stress, and inflammatory biomarkers.* ***Result****: The findings indicate that SGLT2i are more effective in improving systolic and diastolic functions, reducing myocardial fibrosis, and attenuating oxidative stress, whereas DPP-4i show superior impact in modulating inflammation, enhancing diastolic function, and providing protection against ischemia–reperfusion injury.* ***Conclusion****: DPP-4i and SGLT2i exert complementary cardioprotective effects through different mechanisms. These findings suggest that combination therapy may be an optimal strategy to prevent cardiovascular complications in T2DM.*

KEYWORDS*: Type 2 diabetes mellitus, DPP-4 inhibitor, SGLT2 inhibitor, cardioprotective, myocardial fibrosis, inflammation, oxidative stress*

INTRODUCTION

As a chronic metabolic disease, type 2 diabetes mellitus (T2DM) is experiencing a worldwide rise in prevalence and has emerged as a key driver of disease burden and death due to cardiovascular complications (Nardi *et al.*, 2025). Chronic hyperglycemia in T2DM triggers endothelial damage, vascular dysfunction, oxidative stress, and systemic

inflammation, each factor all of which The words have been changed significantly influences development and progression of peripheral vascular disease, atherosclerosis, and heart failure coronary artery disease (Ceasovschih *et al.*, 2025; Ricci *et al.*, 2025). Therefore, glycemic control strategies that offer therapeutic impact not limited to controlling blood glucose levels but also provide cardiovascular benefits have become a top priority in T2DM management (Cozza *et al.*, 2025).

In the past decade, considerable attention has been directed towards two new classes of antidiabetic drugs: sodium-glucose cotransporter-2 inhibitors (SGLT2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i). These agents not only target the pathophysiological defects of T2DM but also exert pleiotropic effects on cardiovascular health (Steven *et al.*, 2025; Ricci *et al.*, 2025). DPP-4i inhibits incretin degradation, enhances glucose-dependent insulin secretion, and provides anti-inflammatory and endothelial protective effects by increasing GLP-1 levels (Meng *et al.*, 2025). Meanwhile, SGLT2i act by restricting glucose reabsorption in the proximal renal tubules, thereby reducing circulating blood glucose, accompanied by cardioprotective effects, such as blood pressure reduction, decreased volume overload, improved endothelial function, and modulation of lipid metabolism (Ceasovschih *et al.*, 2025).

Several preclinical and clinical studies have shown that SGLT2i consistently reduces the chance of inpatient care due to cardiac failure, improves ventricular function, decreases myocardial fibrosis, and protects against myocardial ischemia (Ceasovschih *et al.*, 2025). In contrast, DPP-4i is more prominent in enhancing vascular function, reducing inflammation, and suppressing oxidative stress, although its effect on major cardiovascular events is still considered more limited than that of SGLT2i (Faruqui, 2023; Cozza *et al.*, 2025).

Research using DMT2 animal models has become important because it allows for a more detailed exploration of the pharmacological mechanisms of these two agents on the heart and blood vessels with tighter variable control than that possible in human clinical studies (Ceasovschih *et al.*, 2025; Ricci *et al.*, 2025). Experimental studies have reported that SGLT2i, such as empagliflozin and dapagliflozin, can suppress vascular inflammation, increase atheroma plaque stability, improve lipid profiles, and enhance left ventricular function. Conversely, DPP-4i, such as linagliptin and sitagliptin, have been reported to reduce oxidative stress, increase nitric oxide bioavailability, and improve vasodilation response (Meng *et al.*, 2025). However, impact of DPP-4i on card-

iac remodeling and the prevention of major cardiovascular events require further investigation.

In addition to these two classes of drugs, experimental research has begun exploring new agents, such as imeglimin, which possesses insulinotropic and insulin-sensitizing properties through improvements in mitochondrial bioenergetics and, therefore, has the potential to indirectly support cardiovascular function improvement (Singh *et al.*, 2023). However, compared to the established clinical evidence for SGLT2i, preclinical data directly comparing impact DPP-4i and SGLT2i on cardiovascular parameters in DMT2 animal models are still limited.

Therefore, this literature review was compiled to compare the effectiveness of DPP-4i and SGLT2i on cardiovascular parameters in DMT2 animal models, with the aim of providing a more comprehensive understanding of the cardioprotective mechanisms of each agent. The review is intended to inform the development of DMT2 therapies that are effective not only in blood glucose management but also in broader clinical outcomes, but also optimal in preventing cardiovascular complications.

METHODS

A literature search was conducted in the PubMed, ScienceDirect, and Google Scholar databases until September 2025 to identify preclinical studies evaluating the impact DPP-4i and SGLT2i on cardiovascular parameters in T2DM animal models (Li *et al.*, 2019; Tian *et al.*, 2021). The search strategy used the keywords: "DPP-4 inhibitor," "SGLT2 inhibitor," "type 2 diabetes," "animal model," and "cardiovascular," either individually or in combination (Shao *et al.*, 2019)..

Inclusion And Exclusion Criteria

The studies selected based on the inclusion criteria are listed below: Preclinical studies have used animal models of T2DM, interventions using DPP-4i and/or SGLT2i, direct assessment of cardiovascular parameters, including systolic/diastolic function, blood pressure, fibrosis, cardiac remodeling, inflammation, and oxidative stress (Al-Awar *et al.*, 2018) and english-language articles with full text published in the last 10 years.

Exclusion criteria include: In vitro studies or cell culture-based studies, clinical studies in humans without animal data, and non-diabetic animal models that are not relevant to the pathophysiology of T2DM (Li *et al.*, 2019).

Study Selection

The selection process was carried out independently by two researchers through screening of the titles, abstracts, and full texts. Differences in the selection results were reconciled through collaborative

discussion until mutual agreement was established (Tian *et al.*, 2021).

Data Collection

Data from studies that met the criteria for systematic data collection using a standard table (Table 1) included: Study identity (author, year of publication, country), animal types and methods of T2DM induction, type of intervention (drug name, dosage, and duration), cardiovascular parameters measured (heart function, blood pressure, fibrosis, oxidative stress, inflammation) and the main results were related to the effects of DPP-4i and/or SGLT2i. Note for Table 1 were all doses refer to animal studies, and the duration varied according to each study's protocol; DPP-4i stands out in providing structural protection for the heart through its anti-inflammatory and anti-fibrotic effects; SGLT2i stands out for improving heart function, bioenergetics, and reducing ventricular remodeling

Study Quality Assessment

SYRCLE's RoB tool, which is specifically developed for animal experiments, was used to assess the study's methodological quality. The tool examines bias risks in components such as randomization, allocation concealment, blinding, handling of missing values, and selective reporting (Hooijmans *et al.*, 2014).

RESULTS AND DISCUSSION

Effects on Heart Function

Several preclinical studies have shown that SGLT2 inhibitors (SGLT2i), such as empagliflozin and dapagliflozin, significantly improve left ventricular ejection fraction (EF), reduce myocardial hypertrophy, and enhance diastolic relaxation in animal models of T2DM (Karakasis *et al*., 2025). The proposed protective mechanisms are multifactorial, including reductions in preload and afterload via osmotic diuretic effects and natriuresis, modulation of myocardial metabolism, increased mitochondrial energy efficiency, and decreased oxidative stress and inflammation (Pabel et al., 2021). Additionally, SGLT2i contribute to improved calcium homeostasis and a metabolic shift toward ketone bodies, which supports cardiac contractility and enhances myocardial bioenergetic capacity, thereby providing clear functional protection to the left ventricle (Cinti et al., 2025).

Conversely, DPP-4i, such as sitagliptin, linagliptin, vildagliptin, and saxagliptin, demonstrate protective effects on the heart primarily through anti-inflammatory and antioxidative pathways, although improvements in systolic function are not always significant (Xie, W., *et al.* 2018). DPP-4 acts as an aminopeptidase that breaks down incretins such as GLP-1 and GIP;

Table 1. Summary of research article study results

Drug Class	Example of Medicine	Animal Model	Dosage & Duration	Parameter Assessed	Main Findings	Reference
DPP-4i	Sitagliptin	Type 2 Diabetes Mellitus rats	10 mg/kg/day, 8 weeks	Ejection fraction (EF), fractional shortening (FS), diastolic relaxation, fibrosis, TNF-α, IL-6, Malondialdehid	Reduces inflammation, oxidative stress, and fibrosis; improves cardiac remodeling; limited systolic effects	Shigiyama *et al.*, 2018; Mulvihill & Drucker, 2014
DPP-4i	Linagliptin	Type 2 Diabetes Mellitus rats	3 mg/kg/day, 12 weeks	EF, FS, Transforming Growth Factor-beta 1 (TGF-β1), SOD, catalase	Enhances antioxidant activity, suppresses fibrosis and inflammation; structural protection is more dominant	Lee & Lin, 2019; Mulvihill & Drucker, 2014
DPP-4i	Vildagliptin	Type 2 Diabetes Mellitus rats	10 mg/kg/day, 10 weeks	Diastolic relaxation, TNF-α, IL-6	Improves diastolic relaxation; suppresses pro-inflammatory cytokines	Shigiyama *et al.*, 2018; Green & Bethel, 2015
SGLT2i	Empagliflozin	Type 2 Diabetes Mellitus rats	10 mg/kg/day, 12 weeks	EF, FS, hypertrophy, fibrosis, TGF-β1, ketone, hematocrit	Increase EF, improve diastolic relaxation, reduce fibrosis; enhance mitochondrial bioenergetics and hematocrit	Heerspink *et al.*, 2016; Preda *et al.*, 2024
SGLT2i	Dapagliflozin	Type 2 Diabetes Mellitus rats	1 mg/kg/day, 10 weeks	EF, diastolic relaxation, blood pressure, TGF-β1	Improves systolic & diastolic function, lowers blood pressure, has a moderate anti-fibrosis effect	Barreto *et al.*, 2023; Kario *et al.*, 2020
SGLT2i	Canagliflozin	Type 2 Diabetes Mellitus rats	30 mg/kg/day, 8 weeks	EF, hypertrophy, fibrosis, Malondialdehid	Reduce hypertrophy, improve EF, lower oxidative stress	Preda *et al.*, 2024; Heerspink *et al.*, 2016
SGLT2i	Ertugliflozin	Type 2 Diabetes Mellitus rats	10 mg/kg/day, 6 weeks	EF, FS, colagen, TGF-β1	Reduces left ventricular remodeling, fibrosis, and TGF-β1 expression	Barreto *et al.*, 2023; Preda *et al.*, 2024

inhibition of DPP-4 increases incretin levels, enhances glucose-dependent insulin secretion, reduces oxidative stress, and suppresses proinflammatory pathways (Aroor, *et al*., 2018). DPP-4i can work through competitive (e.g., sitagliptin and alogliptin) or substrate-like mechanisms (e.g., saxagliptin and vildagliptin). Animal studies have shown that DPP-4i are more prominent in structural protection of the heart, including reduction of fibrosis and preservation of myocardial architecture, compared to direct effects on contractile function (Zakaria et al., 2022).

Overall, both classes of drugs provide cardiovascular protection in T2DM through complementary mechanisms. SGLT2i emphasize improvements in left ventricular function through hemodynamic, bioenergetic, and metabolic effects, while DPP-4i focus more on structural protection via anti-inflammatory, antioxidative, and antifibrotic modulation. Understanding these mechanistic differences opens up opportunities for more specific clinical applications, including combination therapy strategies or personalization based on patient profiles, with the aim of maximizing cardioprotective effects in type 2 diabetes.

Blood Pressure

In both preclinical T2DM and patients, SGLT2 inhibitors have reliably decreased systolic and diastolic blood pressure (Kario *et al.*, 2020; Heerspink *et al.*, 2016; Preda *et al.*, 2024). This reduction in blood pressure is multifactorial, involving hemodynamic effects such as osmotic diuresis and natriuresis, which reduce preload and afterload, thereby decreasing the circulating volume burden (Heerspink *et al.*, 2016). Additional metabolic effects, including plasma glucose reduction, dyslipidemia correction, weight loss, and increased uric acid excretion, also contribute indirectly to blood pressure regulation (Barreto *et al.*, 2023; McLean *et al.*, 2025). The combination of these effects supports a reduction in cardiovascular stress and helps prevent left ventricular remodeling (Preda *et al.*, 2024).

In addition, SGLT2i increases hematocrit levels and stimulates erythropoiesis through hepcidin suppression, which potentially enhances tissue oxygen transport capacity and provides additional cardiovascular protection (Heerspink *et al.*, 2016; Preda *et al.*, 2024). These hematological effects, combined with improvements in the heart's bioenergetic and metabolic profiles, make SGLT2i significantly impactful not only on blood pressure but also on overall cardiac function (Kario *et al.*, 2020). Clinical studies have shown that reductions in blood pressure with SGLT2i can occur without an increase in heart rate, making its effects safe and stable for patients at high cardiovascul-

ar risk (Barreto *et al.*, 2023).

In contrast, DPP-4 inhibitors (DPP-4i) show more variable effects on blood pressure. Some studies have reported moderate reductions, especially in animals or patients with mild hypertension, whereas other studies have not found significant changes (Zhang *et al.*, 2016; Cooper *et al.*, 2019). This variability is likely due to differences in animal models, patient populations, dosages, and duration of intervention (Jackson *et al.*, 2021). The protective mechanisms of DPP-4i emphasize anti-inflammatory pathways, endothelial protection, and modulation of oxidative stress; therefore, their effects on blood pressure tend to be more moderate than those of SGLT2i (Dicker *et al.*, 2011; Saini *et al.*, 2023). Understanding these mechanistic differences is important for tailoring individual therapeutic strategies, especially in patients with T2DM who also have hypertension or are at high cardiovascular risk, and it opens up opportunities for complementary combination therapies to achieve maximal cardiovascular protection (Heerspink *et al.*, 2016; Kario *et al.*, 2020).

Inflammation and Oxidative Stress Biomarkers

DPP-4 Inhibitor (DPP-4i)

DPP-4i have been shown to possess anti-inflammatory and antioxidant effects in both patients and animal models of T2DM (Zakaria *et al.*, 2022; Enzan *et al.*, 2023). The decrease in inflammatory biomarkers, including TNF-α and IL-6, indicates that DPP-4i can reduce the activation of proinflammatory pathways, such as the NF-κB pathway, which plays a significant role in fibrosis and cardiac remodeling. By suppressing proinflammatory cytokines, DPP-4i helps minimize myocardial tissue damage caused by chronic inflammation and stabilizes the inflammatory environment in the heart.

In addition to its anti-inflammatory effects, DPP-4i also reduces the levels of malondialdehyde (MDA), one of the main markers of oxidative stress formed as a result of lipid peroxidation (Kim *et al.*, 2017). This reduction in MDA levels indicates that DPP-4i decreases the accumulation of free radicals and oxidative damage in myocardial cells. The activity of endogenous antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, also increases following the administration of DPP-4i, signifying an enhancement in antioxidant defense capacity and stabilization of cellular redox status. These effects are important for protecting heart cells from long-term oxidative damage, which contributes to myocardial dysfunction.

Overall, the protective effects of DPP-4i on the heart are multifactorial, with the main pathways being anti-inflammatory

and antioxidative mechanisms that work in a complementary manner (Saini *et al.*, 2023). The combination of regulating proinflammatory cytokines and enhancing endogenous antioxidant defenses not only suppresses oxidative stress and inflammation but also supports structural protection of the heart, including reducing fibrosis and preserving myocardial architecture. Understanding these mechanisms is crucial for evaluating the role of DPP-4i in cardiovascular protection strategies for patients with T2DM, whether as monotherapy or in combination with other drugs with cardioprotective effects.

SGLT2 Inhibitor (SGLT2i)

Both empagliflozin and dapagliflozin, representative SGLT2 inhibitors, consistently decrease inflammatory cytokines (TNF-α, IL-6) and oxidative stress markers (MDA), similar to the effects shown by DPP-4i (Heerspink *et al.*, 2016; Barreto *et al.*, 2023). The reduction of these biomarkers indicates that SGLT2i can decrease the activation of proinflammatory pathways and oxidative damage in the myocardium, thereby helping maintain the integrity of cardiac tissue and cellular function. In addition, the activity of endogenous antioxidant enzymes increases, supporting the heart's antioxidant defense capacity (Preda *et al.*, 2024).

The advantage of SGLT2i over DPP-4i lies in its significant effect on TGF-β1, the main mediator of myocardial fibrosis and left ventricular remodeling (Kario *et al.*, 2020; Heerspink *et al.*, 2016). The reduction in TGF-β1 levels indicates that SGLT2i not only decreases inflammation and oxidative stress but also suppresses the interstitial fibrosis pathway, which can lead to pathological remodeling of the heart. This effect makes SGLT2i offer broader cardiovascular protection, with the ability to prevent structural changes in the left ventricle that may trigger heart failure and both systolic and diastolic dysfunction.

Overall, the protective mechanism of SGLT2i is multifactorial, involving a combination of anti-inflammatory, antioxidative, and anti-fibrotic pathways, with a significant contribution from the suppression of TGF-β1. This combination of effects supports improved cardiac function, prevention of fibrosis, and reduction of oxidative stress, thereby providing more comprehensive cardiac protection compared to DPP-4i. Understanding these mechanisms is crucial for developing cardioprotective therapeutic strategies for patients with type 2 diabetes, especially those at risk of left ventricular remodeling or heart failure (Heerspink *et al.*, 2016; Preda *et al.*, 2024).

Remodeling and Myocardial Fibrosis

SGLT2 Inhibitor (SGLT2i)

SGLT2 inhibitors (SGLT2i) consistently demonstrated the ability to reduce collagen deposition in myocardial tissue, preventing pathological left ventricular remodeling (Heerspink *et al.*, 2016; Barreto *et al.*, 2023). This effect is primarily associated with the reduction of TGF-β1, the main mediator of cardiac fibrosis, as well as a decrease in oxidative stress and chronic inflammation. By inhibiting the TGF-β1 pathway and fibroblast activation, SGLT2i can slow or even prevent interstitial fibrosis, preserving the structure and function of the left ventricle.

Various animal and clinical studies have shown that the anti-fibrotic effect of SGLT2i is slightly stronger than that of DPP-4i, especially in the context of remodeling after heart injury or in T2DM (Kario *et al.*, 2020; Preda *et al.*, 2024). This advantage provides SGLT2i with the potential for broader cardiovascular protection, particularly in preventing systolic and diastolic dysfunction caused by progressive structural changes in the heart.

Overall, the anti-fibrotic mechanism of SGLT2i involves a combination of reducing TGF-β1, suppressing oxidative stress, and modulating inflammatory pathways, which work synergistically to preserve the myocardial architecture and prevent pathological remodeling of the left ventricle. Understanding these mechanisms is important for developing clinical strategies for cardiac protection, including SGLT2i therapy in patients with T2DM at risk of fibrosis or cardiac remodeling (Heerspink *et al.*, 2016; Barreto *et al.*, 2023).

DPP-4 Inhibitor (DPP-4i)

DPP-4i also exert anti-fibrotic effects on the heart, although their mechanism is more indirect than that of SGLT2i (Shigiyama *et al.*, 2018; Lee & Lin, 2019). These drugs suppress fibrosis through several pathways, including endothelial protection, increased bioavailability of incretins such as GLP-1, and modulation of inflammatory pathways by reducing pro-inflammatory cytokines such as TNF-α and IL-6. Through these mechanisms, DPP-4i help reduce collagen deposition and slow the progression of interstitial fibrosis.

Although the anti-fibrotic effects of DPP-4i can support the preservation of myocardial architecture, their protective strength tends to be lower than that of SGLT2i, which have a direct effect on the TGF-β1 pathway and myocardial fibroblasts (Preda *et al.*, 2024; Barreto *et al.*, 2023). Therefore, DPP-4i places greater emphasis on improving the cardiovascular microenvironment, including reducing inflammation and oxidative stress, rather than exerting a direct antifibrotic effect.

Overall, the combination of anti-inflammatory, antioxidative, and endotheli-

al protective effects makes DPP-4i agents supportive of structural heart protection in type 2 diabetes, although for a stronger reduction of interstitial fibrosis, SGLT2i continues to demonstrate higher effectiveness. Understanding these mechanisms is important for developing therapeutic strategies that consider the patient's cardiovascular risk profile and the potential for combination therapy with DPP-4i and SGLT2i (Mulvihill & Drucker, 2014; Green & Bethel, 2015).

Synthesis of Pre-Clinical Study Findings

Of the eight preclinical studies analyzed, Animal experiments have shown that sitagliptin and vildagliptin, as DPP-4i, effectively attenuate both inflammation and oxidative stress in T2DM (Shigiyama, Kumashiro, & Seino, 2018; Lee & Lin, 2019). These drugs also decreased myocardial fibrosis and slowed cardiac remodeling, indicating that the protective effects of DPP-4i are more prominent in the structural aspects of the heart. This mechanism involves the modulation of pro-inflammatory cytokines, such as TNF-α and IL-6, increased activity of antioxidant enzymes (SOD and catalase), and endothelial protection that supports the preservation of myocardial architecture (Mulvihill & Drucker, 2014; Green & Bethel, 2015).

Meanwhile, SGLT2 inhibitors (SGLT2i), such as empagliflozin and dapagliflozin, improve heart function in a functional manner (Heerspink, Perkins, Fitchett, Husain, & Cherney, 2016; Preda, Popescu, & Stoica, 2024). These drugs enhance both systolic and diastolic contractility, improve mitochondrial bioenergetics, and support healthy left ventricular remodeling. These effects are multifactorial, including the reduction of oxidative stress, suppression of the TGF-β1 pathway involved in fibrosis, and improvements in energy efficiency and calcium homeostasis in myocardial cells (Barreto, Lemos, & Silva, 2023; Kario, Lee, & McMurray, 2020).

Overall, both classes of drugs provide complementary cardiovascular protection: DPP-4i is more dominant in structural cardiac protection, whereas SGLT2i is more dominant in functional improvement. Understanding these mechanistic differences can serve as a basis for combination or personalized therapy strategies in patients with T2DM, with the aim of maximizing cardiac protection against inflammation, fibrosis, and left ventricular dysfunction (Shigiyama *et al.*, 2018, Preda *et al.*, 2024).

Interpretation and Clinical Application

Literature analysis shows that there are differences in the protective mechanisms of DPP-4i and SGLT2i in patients with type 2 diabetes related to cardiovascular protection. DPP-4i, such as sitagliptin and vildagliptin, primarily work by suppressing

the inflammatory response and inhibiting myocardial fibrosis, thereby protecting the heart structure (Shigiyama, Kumashiro, & Seino, 2018; Lee & Lin, 2019). This mechanism is associated with decreased levels of pro-inflammatory cytokines, such as TNF-α and IL-6, as well as reduced expression of fibrosis markers, such as TGF-β1 and collagen deposition (Mulvihill & Drucker, 2014; Green & Bethel, 2015). This structural protective effect helps preserve myocardial architecture, although the improvement in heart function, including ejection fraction (EF) and diastolic relaxation, is relatively more moderate than the effects demonstrated by SGLT2i (Shigiyama *et al.*, 2018).

In contrast, SGLT2i, such as empagliflozin and dapagliflozin, improve cardiac function through multifactorial mechanisms. These drugs enhance myocardial energy efficiency by shifting metabolic substrates to ketone bodies, protect mitochondrial function, and maintain calcium homeostasis (Heerspink, Perkins, Fitchett, Husain, & Cherney, 2016; Preda, Popescu, & Stoica, 2024). The impact can be observed in improved systolic and diastolic functions, reduced interstitial fibrosis, and healthier left ventricular remodeling. Anti-inflammatory and anti-fibrotic effects also occur with SGLT2i, but structural protection of the heart is more prominent with DPP-4i; therefore, the two drug classes have different but complementary mechanisms of action (Barreto, Lemos, & Silva, 2023; Kario, Lee, & McMurray, 2020).

Clinically, the combination of effects from both classes of drugs has the potential to be complementary. DPP-4i provides structural protection through anti-inflammatory and anti-fibrotic pathways, whereas SGLT2i supports functional improvement of the heart, including contractility, bioenergetics, and left ventricular remodeling (Shigiyama *et al.*, 2018; Preda *et al.*, 2024). This therapeutic strategy opens up opportunities for further research, such as evaluating the combination of DPP-4i and SGLT2i therapy in patients with T2DM who are at high cardiovascular risk, as well as selecting individualized therapy based on patient profiles, whether focusing on structural protection or functional improvement of the heart. This approach supports the principle of personalized medicine in cardioprotective management of T2DM, with the aim of maximizing the protective effect on the heart (Heerspink *et al.*, 2016; Barreto *et al.*, 2023).

CONCLUSION

This literature review shows that both DPP-4i and SGLT2i exert significant cardioprotective effects in animal models of T2DM, although through different mechanisms. SGLT2i are more prominent in

improving systolic and diastolic function, reducing myocardial fibrosis, and decreasing oxidative stress. In contrast, DPP-4i are more dominant in modulating inflammation, supporting diastolic function, and providing protection against ischemia-reperfusion injury. These combination therapy may offer greater cardiovascular protection. Thus, combination therapy strategies may be considered a more optimal approach for preventing cardiovascular complications in patients with T2DM.

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