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Cardio-Renal Protective Effects of Dapagliflozin in Type 2 Diabetic Patients: A Systematic Review.

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ABSTRACT

Sodium-glucose co-transporter 2 (SGLT2) inhibitors increase urine glucose excretion in non-insulin-dependent patients, which lowers plasma glucose and hemoglobin A1c (HbA1c) in patients with type 2 diabetes mellitus. Numerous cardiovascular outcome studies have shown that the positive effects of these drugs go beyond glycemic management. In patients with type 2 diabetes who are at high cardiovascular risk, sodium-glucose co-transporter 2 (SGLT2) inhibitors reduce the progression of chronic kidney disease (CKD). We searched the electronic databases of PubMed, ScienceDirect, Google Scholar, and Cochrane Library for studies discussing the renal and cardio-protective effects of dapagliflozin. Terms related to Dapagliflozin, SGLT2 inhibitors, CV outcomes, renal outcomes, and RCTs were included in the search terms. Our review showed that dapagliflozin improves glycemic control without variation, it is safe and well-tolerated in the general population including older patients and those with high-risk CV factors or preexisting CV disease. Dapagliflozin has shown reduced blood glycemic fluctuations without an increase in hypoglycemic episodes in patients newly diagnosed with T2DM on continuous glucose monitoring devices. Dapagliflozin use was associated with reduced CVD and renal mortality compared with the use of other glucose-lowering drugs. Dapagliflozin reduces oxidative stress and may delay atherosclerosis. Recent findings indicate that SGLT2 inhibitors may also reduce atrial natriuretic peptide levels. This systematic review showed that Dapagliflozin improved cardiovascular (CV) and renal outcomes, particularly by lowering the risks of heart failure and kidney failure in diabetics with high CV risk.

Keywords: Dapagliflozin**,** SGLT2 inhibitors, Rena, Cardioprotective, Diabetic

1. 1. Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors were initially developed and approved as glucose-lowering drugs with the specific mechanism of producing glycosuria in people with type 2 diabetes [1]. In extensive clinical trials involving type 2 diabetes patients, sodium-glucose cotransporter 2 (SGLT2) inhibitors reduced glycated hemoglobin levels and positively impacted renal and cardiovascular outcomes [2] [3].

The amount of glucose filtered by the glomerulus determines how well SGLT2 inhibitors lower blood glucose levels. As a result, compared to patients with maintained renal function, the effectiveness of increasing urine glucose excretion and lowering hemoglobin A1c (HbA1c) is reduced in patients with a lowered eGFR [4]. It has been advised against using SGLT2 inhibitors in patients with compromised renal function due to this diminished capacity to enhance glucose management. It is unknown, though, if eGFR also influences how SGLT2 inhibition affects other renal and cardiovascular risk factors [5].

The oral glucose-lowering medication dapagliflozin is a member of a new class. Dapagliflozin has been demonstrated to enhance glycemic management by reducing renal glucose reabsorption in the kidneys and increasing urine glucose excretion. It inhibits sodium-glucose cotransporter 2 (SGLT2) [6].

Dapagliflozin has also been demonstrated to reduce body weight, blood pressure, uric acid, and albuminuria, all of which are linked to elevated renal and cardiovascular risk in people with type 2 diabetes [6] [7].

The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial evaluated the effects of dapagliflozin on cardiovascular and renal outcomes in a broad population of patients who had or were at risk for atherosclerotic cardiovascular disease[8].

Recent major randomized clinical trials (RCTs) have shown that SGLT2 inhibitors improved cardiovascular (CV) and renal outcomes, most notably lowering the risks of heart failure and kidney failure in individuals with diabetes who had a high CV risk[9].

Characteristics of Dapagliflozin

Dapagliflozin is quickly absorbed and has a 78% bioavailability. Due to its 12.9 h half-life, it can be administered once a day. There are no known significant drug-drug interactions for dapagliflozin. UGT1A9 is mainly responsible for metabolizing dapagliflozin, with cytochrome P450 playing a minor role. Dapagliflozin has been tested in combination with glimepiride, metformin, pioglitazone, and sitagliptin. Its metabolism does not impact these antihyperglycemic medications, and there are no known pharmacokinetic (PK) changes associated with their combination [10].

Dapagliflozin competitively, reversibly, and highly selectively inhibits SGLT2. Type 2

SGLT2s are expressed in the kidney and on the epithelial lining of the S1 segment of the proximal convoluted tubule. Physiologically, these transporters are responsible for approximately 90% of renal glucose absorption, Dapagliflozin is dosed starting at 5 mg orally in the morning and can be titrated up to 10 mg orally in the morning if clinically indicated [11].

In a study conducted by Kaku and colleagues, Japanese patients with type 2 diabetes who were either treatment-naive or had little to no prior treatment history were assessed for the safety and efficacy of dapagliflozin monotherapy. In this double-blind, randomized clinical trial, participants were randomly assigned to receive a placebo or dapagliflozin at doses of 1 mg, 2.5 mg, 5 mg, or 10 mg daily. Within six weeks of enrolment, patients who were taking T2DM medication received a six-week washout phase followed by a four-week placebo run-in period. All other patients underwent the 4-week placebo run-in period but were not included in the washout. After 12 weeks, all dapagliflozin doses significantly lowered HbA1c levels as compared to placebo; the changes ranged from 5 mmol/mol (-0.49%) to

9 mmol/mol (-0.80%), p0.0001. FPG reductions were similar; FPG in the dapagliflozin groups ranged from 15.61 3.43 mg/dl in the 1 mg group to 31.94 3.57 mg/dl in the 10 mg group (all p0.0001 compared with placebo), while FPG in the placebo group increased by

11.17 3.43 mg/dl [12].

2. 2. Methods: Systemic review approach

1. 2.1 Search strategy and selection criteria:

This research was carried out as a systematic review. We extracted the published articles from databases like PubMed, Google Scholar, ScienceDirect, and Cochrane. The searches covered journals, clinical trials, reviews, and other similar items written in English as shown in Table 1. Search syntax.

86 articles were found and examined for content, title, and abstract based on inclusion and exclusion criteria.

Finally,20 articles were included in this study. The algorithm for the selection and filtering of articles is represented in Figure 1. The final selected articles were analyzed in detail to assess the most current and relevant information about Dapagliflozin and its protective effects on the renal and cardiovascular systems according to Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA).

Table 1: Search syntax

Database	Search syntax	N
ScienceDirect	"Dapagliflozin, Cardioprotective effects, renoprotective effects of Dapagliflozin	32
PubMed	Sodium-Glucose Transporter 2 Inhibitors/administration, and dosage	24
Cochrane	"Sodium-Glucose Transporter 2 Inhibitors/adverse effects and SGLT2 inhibitors	6
Google Scholar	Dapagliflozin, renoprotective, Cardioprotective effects, SGLT2 inhibitors	24

No	Authors/year	Purpose of Study	Type of Study	Sample size & duration	Summary of Results

Figure 1. Flow chart of the selection of studies based on PRISMA.

2. 2.2. Inclusion and exclusion criteria

We included peer-reviewed randomized controlled trials (RCTs) and reviews of studies that met the following criteria were included: (1). Relevant to dapagliflozin and their effects as renal and cardioprotective, (2). All articles are in the English Language (3). Published in the past 10 years, focusing on the adult and geriatric population (> 18 years). (4). The articles should include one member of SGLT2 inhibitor drugs like empagliflozin, dapagliflozin, and canagliflozin or other members of this group. We excluded articles published in other languages, books, case series, case reports, unpublished literature, duplicate articles, the pediatric population, and animal studies.

3. 3. Results:

86 articles were selected from four databases, and extraction of the articles according to inclusion and exclusion criteria was done as shown in table 1. The articles were selected for the systematic review after reviewing the full texts, excluding duplicated articles, animal studies, and other excluding criteria.

Table 2 displays ultimately twenty articles that were more relevant to this systemic review. This table displays the characteristics of studies from the last seven years on the cardio-renal protective effect of dapagliflozin.

Table (2) Characteristics of Studies from the last seven years on the cardio-renal protective effects of dapagliflozin

1	**(Petrykiv et al., 2017)** [13]	Estimate the Impact of Dapagliflozin on Cardiovascular Risk Factors at Various Renal Function Levels	Review Article	**4,404** Patients. For **24 weeks**	dapagliflozin consistently reduced BP, body weight, and albuminuria, regardless of baseline renal function. These findings support hard outcome trials in patients with diabetic kidney disease
2	**Petrie *et al.*, 2020)** [14]	To evaluate the effects of dapagliflozin in patients with HF with and without diabetes.	Randomized Trials	**4744** patients For **29-months**	dapagliflozin compared with placebo, when added to recommended therapy, significantly reduced the risk of worsening heart failure or cardiovascular death independently of diabetes status.
3	**Phrommintikul *et al.*, 2019)** [15]	Examine the effects of dapagliflozin and vildagliptin on the cardiometabolic system in T2DM patients with CAD.	Randomized Trials	**49** Patients For **6 months**	Dapagliflozin showed greater improvements in cardiovascular outcomes than vildagliptin.
4	**Mosenzon et al., 2019)** [9]	Study the Effects of dapagliflozin on the development and progression of kidney disease in patients with type 2 diabetes	Randomized Trials	**17 160** participants For **4-years**	dapagliflozin prevented and reduced the progression of kidney disease when compared to placebo. in this large and diverse population of patients with type 2 diabetes with and without established atherosclerotic cardiovascular disease, most of whom had preserved renal function.
5	**Heerspink et al., 2020)** [16]	Examine how dapagliflozin affects renal and cardiovascular events in people with and without diabetes who have chronic kidney disease.	Randomized, double-blind, controlled trial	**4300** Patients For **8-months**	Improvement in renal function and decreased mortality in CKD patients, regardless of DM status
6	**Lim et al., 2022** [17]	to compare the clinical outcomes between dapagliflozin, empagliflozin, and dipeptidyl peptidase-4 inhibitors (DPP4i) in patients with type 2 DM	Retrospective study	**3684** Patients For **55-months**	Compared to those who used DPP4 inhibitors, those who used SGLT2 inhibitors had a considerably lower risk of atherosclerotic cardiovascular disease, hospitalization for HF, and renal events.
7	**Heerspink et al., 2021)** [18]	The objective of this study is to evaluate the effect of dapagliflozin on the rate of change in the estimated glomerular filtration rate (eGFR)	Randomized controlled trial	**7020** Patients For **104-weeks**	In comparison to placebo, dapagliflozin dramatically delayed the long-term decline in eGFR in patients with chronic renal disease.
8	**Cahn *et al.*, 2021)** [19]	To assess the cardiorenal outcomes with dapagliflozin versus placebo in the DECLARE-TIMI 58 study	Clinical Trial	**14 068** patients, For **4 years**	Dapagliflozin reduced the composite of CVD/HHF (HR [95% CI] 0.83 [0.73, 0.95]) regardless of baseline GLA Dapagliflozin had consistent advantages regardless of baseline metformin use and largely consistent impacts on cardiorenal

					outcomes, regardless of baseline
9	**Tsai et al., 2022** [20]	to evaluate sodium-glucose cotransporter-2 (SGLT2) inhibitors' effectiveness and safety in the cardiovascular and renal systems in people without diabetes.	A Systemic Review.	**8927** participants For **2.4-years**	demonstrated that dapagliflozin medication had extra cardiorenal advantages in people without diabetes who had already received standard care for heart failure or CKD.
10	**Jongs et al., 2021)** [21]	Estimate the Impact of Dapagliflozin on Cardiovascular Risk Factors at Various Renal Function Levels	Double-blind, placebo-controlled, randomized trial	**4304** participants For **35-moths**	Dapagliflozin significantly decreased albuminuria, with a larger relative reduction in patients with type 2 diabetes.
11	**Memon, Rahat A., et al,. 2022** [14]	To evaluate the effects of dapagliflozin in patients with HF with and without diabetes	Meta-Analysis.	**25715** patients	Results have shown that the risks of developing stroke, heart failure, myocardial infarction, and cardiac-related death are not different in the two groups. It is suggested that SGLT2 inhibitors can reduce the risk of cardiovascular diseases but the current study did not identify any significant difference in the effectiveness of dapagliflozin and empagliflozin. In the future, more prospective studies need to be carried out to identify which of these two drugs are more effective in preventing cardiovascular outcomes in patients with type 2 diabetes.
12	**Gopal Palandurkar et al., 2022**] [22]	this study aimed to compare the subsequent cardiovascular risk, including HF, myocardial infarction (MI) ,angina pectoris (AP), stroke, and atrial fibrillation (AF), between individual SGLT2 inhibitors.	**Retrospective cohort study**	**25,315** patients between January **2005 and April 2021**	The risks for subsequent development of HF, MI, AP, stroke, and AF were comparable between individual SGLT2 inhibitors.
13	**Gopal Palandurkar et al., 2022**] [15]	To compare DAPA-HF patients to participants in contemporary heart failure (HF) registries and other recent HF trials, and compare individuals with diabetes, pre-diabetes, and a normal glycated hemoglobin (HbA1c) in DAPA-HF.	A randomized, double-blind, controlled trial	**4744** Patients For **21 months**	In summary, DAPA-HF has enrolled patients with and without diabetes who has persisting symptoms, a reduced LVEF, and an elevated NT-proBNP level, who are similar to those enrolled in contemporary HFrEF registries and randomized in other recent HFrEF trials.

14	**Zachary L. Cox, et al, 2020)** [9]	to assess the efficacy and safety of initiating dapagliflozin within the first 24- hours of hospitalization in patients with AHF compared to usual care	Randomized Trials	**240** participants For **5 days**	Initiation of dapagliflozin early in the course of an AHF hospitalization among patients with diabetes may facilitate both decongestion and optimization of chronic HF medical therapies. The DICTATE-AHF trial will evaluate the safety and efficacy of in-hospital initiation of dapagliflozin in patients with diabetes admitted with AHF.
15	[**J.J.V. McMurray et al. 2019**] [23]	To evaluate the efficacy of Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction	Randomized controlled trial	**2373** participants **18.2 months**	the risk of worsening heart failure or death from cardiovascular causes were lower among those who received dapagliflozin than among those who received a placebo, regardless of the presence or absence of diabetes
16	**Paola Fioretto MD et al, 2018** [24]	This study assessed the efficacy and safety of dapagliflozin 10 mg vs placebo in patients with type 2 diabetes (T2D) and moderate renal impairment	Randomized Trials	**361** participants **For 24weeks**	The findings of this study support the positive benefit/risk profile of dapagliflozin for the treatment of patients with T2D and CKD 3A.
17	[**J.J.V. McMurray et al, 2019** [25]	To evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF)	Randomized, double-blind, trial	**4744** patients **For 16 months**	DAPA-HF demonstrated the efficacy and safety of the SGLT2 inhibitor dapagliflozin, added to conventional therapy, in a broad spectrum of patients with heart failure and reduced ejection fraction
18	**Dharam J. Kumbhani, et al, 2020** [26]	The goal of the trial was to assess the safety and efficacy of dapagliflozin in patients with left ventricular ejection fraction (LVEF) >40%, irrespective of diabetes status.	Clinical trials	**6263** patients **for 2.3 years**	Dapagliflozin resulted in a lower risk of worsening HF or CV death vs. placebo among patients with LVEF>40%
19	**Batyushin M.M. 2021** [27]	The article presents the main results of a randomized, double-blind, parallel, placebo-controlled trial of DAPA-CKD.	Systemic review	**4304** patients	dapagliflozin demonstrated the ability, in comparison with placebo, to reduce the primary composite point and several secondary composite points in patients with both diabetic and non-diabetic CKD.
20	**Pardeep S. Jhund et al, 2022** [28]	To assess if the sodium-glucose cotransporter 2 inhibitor dapagliflozin reduces the risk of a range of morbidity and mortality outcomes in patients with heart failure regardless of	Systemic review	**11007** patients for **22 months**	in patients with HF, gliflozin led to significant reductions in the risk of death from CV causes and any cause, as well as MACE, irrespective of LVEF. There was a larger reduction in total hospital admissions for HF than in death, which was also consistent across the range of

		ejection fraction			ejection fraction, are likely to benefit from treatment with an SGLT2 inhibitor

4. 4. Discussion:

Dapagliflozin is an antihyperglycemic drug that shows significant promise in managing blood glucose levels, but it also has potential therapeutic effects that address comorbidities commonly found in patients with type 2 diabetes. This drug is part of the SGLT2 inhibitors class and is relatively new, but its effects on HbA1c, CV safety profile, and versatility as both monotherapy and combination therapy have made it a powerful option [13]

Dapagliflozin was found to significantly reduce the risk of heart failure and cardiovascular death, with a hazard ratio of 0.78 and a 95% confidence interval of 0.52-0.87 ($p = 0.02$), as well as composite renal outcomes, with a hazard ratio of 0.60 and a 95% confidence interval of 0.47-0.77 ($p < 0.001$) in patients with type 2 diabetes, as reported by Neal et al. (2017). In the DECLARE-TIMI 58 trial, dapagliflozin demonstrated a lower rate of cardiovascular death and hospitalization for heart failure compared to placebo in patients with type 2 diabetes and established atherosclerotic cardiovascular disease (40%) or at high risk for atherosclerotic cardiovascular disease (60%), with a hazard ratio of 0.83 and a 95% confidence interval of 0.73-0.95 ($p = 0.005$) [8].

In a meta-analysis, the use of SGLT2 inhibitors was linked to a lower risk of major adverse cardiovascular events, HHF, and unfavorable kidney outcomes, regardless of the baseline ASCVD status [14].

Additionally, people without a history of cardiovascular disease, HF, or CKD have benefited from using SGLT2i. Dapagliflozin therapy was linked to a 28% lower risk for HF in diabetic patients without cardiovascular disease in the EMPRISE East Asia research [14]. In diabetic patients without a history of heart disease, SGLT2i usage reduced the risk of HF by 36%, and in diabetic patients with a GFR below 60 mL/min/1.73 m2, it reduced the risk of HHF by 30%–40% and the risk of poor renal outcomes by 40%–50%. The advantages of SGLT2i for primary prevention in people with type 2 diabetes who don't have obvious ASCVD, HF, or CKD are supported by these studies[15].

The benefits of dapagliflozin observed in clinical trials can be explained by multiple mechanisms, beyond the glucose-lowering effect: improvement in ventricular loading condition by natriuresis and osmotic diuresis, improvement in cardiac metabolism, reduced myocardial necrosis and fibrosis, in comparison to patients receiving the placebo, dapagliflozin exhibited beneficial or neutral effects on all specific kinds of CV events. In addition, compared to controls, it seems to be advantageous in those who are hospitalized for heart failure [16].

1. 4.1. Cardioprotective effects of Dapagliflozin

The primary mechanisms underpinning the cardioprotective effects of dapagliflozin include its capacity to increase natriuresis because of the suppression of Na+-glucose reabsorption in the proximal renal tubules, the concomitant osmotic diuresis, and the improvement of diuretic efficacy [17].

as seen in figure 2. Additionally, a small number of diabetic patients treated with dapagliflozin and empagliflozin demonstrated improvements in diastolic function and a decrease in left ventricular mass, which can be partially related to a drop in preload, neutral RAAS, and reduced sympathetic outflow [17], [18].

2. 4.2. Reno-protective effects of Dapagliflozin

The renoprotective effects of dapagliflozin in prediabetes are mediated by a decrease in obesity-induced kidney inflammation, oxidative stress, fibrosis, apoptosis, and lipid accumulation [19]. The vasoprotective effects of dapagliflozin may be due to its impact on hematological parameters by improving the transport of bone marrow-derived hemopoietic cells to the site of vascular damage as shown in Figure 2. [17] [20].

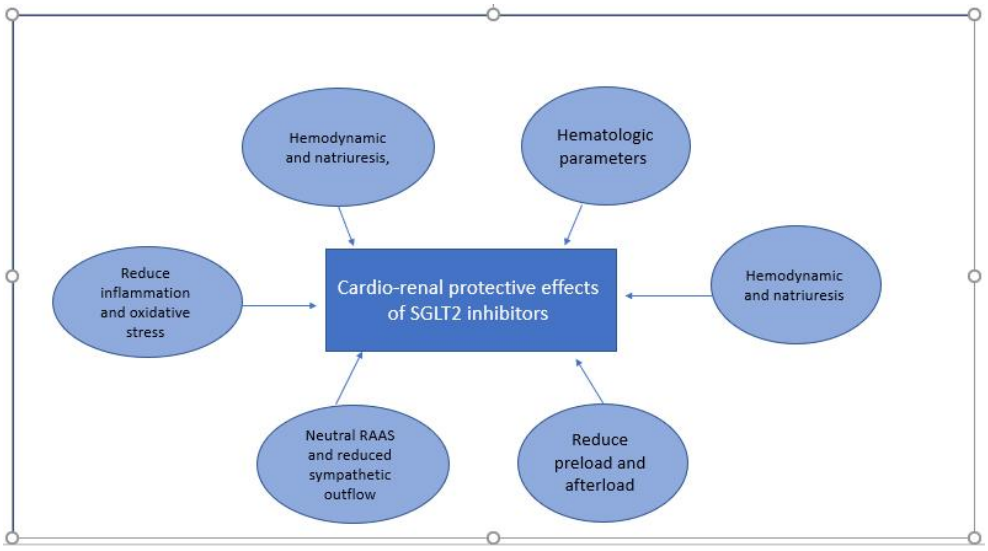

Figure 2: Cardio-renal protective mechanisms of Dapagliflozin in diabetic patients

Moreover, the current assessment of the 20 articles shows consistent cardiovascular, renal, and metabolic benefits with dapagliflozin compared to placebo, regardless of the type or number of GLAs used at baseline. Cardiorenal outcomes did not differ irrespective of baseline use of metformin. CVD/HHF was more prominently reduced with dapagliflozin versus placebo in the small subset of patients who used GLP-1 RAs at baseline compared with those who did not, yet the magnitude of CVD/HHF reduction with dapagliflozin was similar when comparing those using versus those not using GLP-1 RAs at any time during the study. Adverse renal outcomes were less frequent with dapagliflozin versus placebo regardless of baseline GLA; moreover, new onset albuminuria was less frequent with dapagliflozin consistently across all of the subgroups assessed [20].

Multiple studies in our review evaluating the cardiometabolic advantages of combining SGLT-2 inhibitors and GLP-1 RAs have shown greater improvement in cardiometabolic variables when therapy is intensified with one class in addition to the other [29].

Our study further explains the long-term renal outcomes of combining SGLT-2 inhibitors—a class with established robust renal benefits—with incretin-based therapies, which have also shown some favorable renal outcomes. DPP-4 inhibitors have been shown to reduce albuminuria in most (but not all) studies. (Mosenzon et al.,2017). Compared to placebo, dapagliflozin caused a larger decrease in HbA1c, weight, and systolic blood pressure. According to previously published findings, these changes were mostly unaffected by baseline GLA, demonstrating the favorable metabolic benefit of including dapagliflozin in any currently used glucose-lowering strategy [30].

Based on evidence, Dapagliflozin has a potent antihyperglycemic effect and can reduce inflammation, oxidative stress, and apoptosis, which may contribute to its nephroprotective effects. It also reduces albuminuria, indicating its potential in managing diabetic nephropathy. Glucose-lowering medications with positive cardiovascular effects are crucial for improving the long-term outcomes of diabetes patients. In particular, Dapagliflozin and canagliflozin, two SGLT2 inhibitors, have been shown to improve cardiovascular outcomes in patients. with established cardiovascular disease compared to a placebo [31].

Empagliflozin, canagliflozin, and dapagliflozin all significantly decreased the risk of HF in patients with pre-existing cardiovascular disease or at high risk for developing it. In contrast, compared to placebo, DPP-4 inhibitors like sitagliptin, alogliptin, or saxagliptin showed no effect on cardiovascular outcomes in patients with a high risk of cardiovascular disease [2].

The results of the current review showed that dapagliflozin lowers systolic blood pressure (SBP) and body weight. Vildagliptin, in contrast, was observed to increase body weight over a 6-month follow-up period while not affecting blood pressure. This study's findings regarding dapagliflozin's effects on blood pressure are consistent with earlier studies that showed a significant drop in blood pressure without any changes to heart rate [32].

5. Conclusion:

Through the results of this review, we found that dapagliflozin has a clear protective effect on the renal and cardiovascular system, especially with diabetic patients who suffer from kidney and heart problems. dapagliflozin significantly decreased the risk of HF in patients with pre-existing cardiovascular disease or at high risk for developing it.

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