

# A study on the beneficial evidence and mechanism of the therapeutic effect of dapagliflozin on heart failure

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**Abstract:** Heart failure (HF) is the final manifestation of various cardiovascular (CV) diseases, which has caused a huge health burden. Although great progress has been made in the treatment strategy, it still cannot solve the dilemma of HF treatment. As a sodium glucose transporter 2 inhibitor, dapagliflozin is a hypoglycemic drug. However, recent research has found that it can play a crucial role in preventing HF, regardless of whether patients have diabetes or not. There are many mechanisms involved, so this review focuses on elucidating the beneficial evidence and mechanism of dapagliflozin in treating HF, in order to provide new insights into the treatment of HF.

**Keywords:** Dapagliflozin, Heart failure, Clinical trial, Cardioprotective effects

## Introduction

The increasing burden of heart failure (HF) becomes a serious health problem facing society today. Currently, about 50 million people worldwide suffer from HF, which is a common cause of hospitalizations of people over 65 [1]. Dapagliflozin is an inhibitor of sodium-glucose transporter 2 (SGLT2). SGLT2, a sodium-dependent glucose transport protein, exists in the proximal renal tubule and is involved in approximately 90% of glucose reabsorption from urine [2]. Most of the remaining glucose is transported and absorbed by SGLT1 at the distal end of the proximal renal tubule. It has been discovered to significantly improve CV and HF hospitalization outcomes in previous cardiovascular outcome trials (CVOTs). These CVOTs include the DECLARE-TIMI and DAPA-HF studies, showing significant benefits of dapagliflozin in HF patients, particularly those with heart failure with reduced ejection

fraction (HFrEF). Moreover, dapagliflozin can reduce CV endpoints in patients with HFrEF without type 2 diabetes mellitus (T2DM) dependence. Ongoing DELIVER studies are assessing the use of dapagliflozin among patients with heart failure with preserved ejection fraction (HFpEF), which can have a huge impact on the treatment and have considerable economic consequences. Therefore, we summarize the latest research on dapagliflozin, review the clinical trials, and analyse the direct and indirect protective effects of dapagliflozin on the heart as well as the mechanisms in this article.

## Clinical trial

The DECLARE-TIMI 58 trial is a Phase III clinical trial designed to assess the safety and efficacy of dapagliflozin in CV diseases at 882 sites in 33 countries. It randomly as-

Received: Apr.18,2022; Revised: May 13,2022; Accepted: Jun.8,2022; Published: Jun.13,2022

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DOI: <https://doi.org/10.55976/cds.1202216617-23>

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signed 17160 T2DM patients who had atherosclerotic CV diseases (n = 6974) or multiple risk factors (n = 10186) to receive dapagliflozin or placebo treatment. Dapagliflozin lowered the risks of major adverse cardiac events (MACE), HF hospitalization and CV mortality in patients with T2DM and prior myocardial infarction [3]. In the DAPA-HF trial, a total of 4744 patients with HF (New York Heart Association class II, III or IV) with an ejection fraction of 40% or less were randomized to take dapagliflozin (10 mg/day) or placebo, in addition to the recommended treatment. Patients with HFrEF who took dapagliflozin were less likely to cause worsening HF or CV death, regardless of diabetes [4]. Besides, the influence of dapagliflozin on the primary and other outcomes was not affected by baseline BMI [5]. In a combined analysis of data from the DAPA-CKD and DAPA-HF trials, therapy with dapagliflozin lowered the incidence of T2DM in patients with chronic kidney disease and HF, but had no significant effect on levels of HbA1c [6]. These results fully indicate that the function of dapagliflozin in HF is independent of human basal metabolism. In addition, the mean event-free survival of 65-year-old individuals was calculated based on the primary composite end-point event, and it was 6.2 years in the placebo group and 8.3 years in the dapagliflozin group, with an increase of 2.1 years in event-free survival. When taking any causes of death into account, the average extrapolated life expectancy for 65-year-old individuals was 9.1 years in the placebo group and 10.8 years in the dapagliflozin group. Dapagliflozin has consistent benefits in both event-free and overall survival [7]. In the DAPA-HF trial, the Kansas City Cardiomyopathy Questionnaire (KCCQ) was utilized to study the effect of dapagliflozin on various health outcomes after 8 months, proving that dapagliflozin improves the health status of patients [8]. Dapagliflozin also retards the deterioration of HF in outpatients [9]. Dapagliflozin decreases the risk of HF progression and improves clinical outcomes in both inpatients and outpatients.

HFrEF and HFpEF differ greatly in treatment and prognosis due to their different pathophysiological mechanisms. Current research has proved the impact of dapagliflozin on HFrEF, but the function of dapagliflozin in HFpEF remains unclear. In DECLARE-TIMI 58, it was discovered that dapagliflozin cut down the number of hospitalizations for HF in both HFrEF and non-HFrEF patients, but it only reduced all-cause mortality in HFrEF patients [10]. The DELIVER trial, a multicenter, randomized, double-blind trial, was used to assess the effect and safety of dapagliflozin on the basis of conventional treatment of HF with preserved and mildly reduced ejection fraction patients [11]. The study ended in June 2021, and we look forward to the results. Another randomized trial about patients with HFpEF (NCT03030235) focused on whether dapagliflozin reduces the primary endpoint of the KCCQ Clinical Summary Score (KCCQ-CS). A total of 324 patients were randomly treated with dapagliflozin or placebo. Dapagliflozin therapy for 12 weeks signifi-

cantly improves patients' reported physical limitations, symptoms, and exercise level, and is well tolerated in chronic HFpEF [12]. Dapagliflozin may also have some benefits in HFpEF.

N-terminal pro-B type natriuretic peptide (NT-proBNP) is generally considered to be a diagnostic and prognostic indicator of HF; besides, the therapeutic effect of dapagliflozin is also associated with NT-proBNP. NT-proBNP was decreased by 300 pg/mL after 8 months of treatment with dapagliflozin compared with placebo in HFrEF patients. Furthermore, dapagliflozin lowers the risk of worsening HF and death and alleviates symptoms in DAPA-HF [13]. The DEFINE-HF was a multicenter, randomized controlled trial in which 263 patients were randomly assigned to receive dapagliflozin (10 mg) or placebo daily for 12 weeks, reflecting that dapagliflozin do not influence the mean NT-proBNP value, but increase the proportion of patients who showed clinically significant improvements in HF-related health status or natriuretic peptides [14]. Compared with traditional drugs, the effect and safety of dapagliflozin on HF are also assured. The efficacy and safety of dapagliflozin are consistent with those of diuretics in the DAPA-HF trial [15]. The efficacy and safety of dapagliflozin are consistent in patients with and without sacubitril/valsartan in the DAPA-HF trial, suggesting that concomitant use of the two agents can further reduce morbidity and mortality in patients with HFrEF [16]. Furthermore, dapagliflozin lowers the risk of worsening HF and death, which is not associated with the background treatment of HF [17]. There is no significant difference in tolerability or safety events between dapagliflozin and placebo in older adults even when drug metabolism slows down [18]. In addition, the safety and tolerability of dapagliflozin are independent of sex [19]. Patients with HF often have multiple complications involving various systemic diseases. One in eight HFrEF patients had chronic obstructive pulmonary disease (COPD) in the DAPA-HF trial. However, the benefits of dapagliflozin for all pre-defined outcomes are consistent in patients with and without COPD [20]. Other systemic diseases cannot affect the efficacy of dapagliflozin, and CV diseases other than HF are not likely to benefit from dapagliflozin. In HFrEF patients with and without atrial fibrillation, dapagliflozin decreases the risk of worsening HF and CV mortality, but cannot reduce the risk of new atrial fibrillation [21]. The net benefit of dapagliflozin is not only reflected on the improved symptoms, but also on significant savings for the vast number of people with the disease. McEwan et al. found that the lifetime cost of treating major adverse CV events with dapagliflozin in patients with T2DM was reduced by £2552 [22]. In a study that extrapolated data from the US healthcare system, the addition of dapagliflozin to guideline-directed medical therapy (GDMT) was shown to be beneficial in terms of long-term cost-benefit ratios, possibly in both diabetic and non-diabetic populations [23].

## Indirect protective effect of dapagliflozin on the heart

SGLT2i is shown to improve patients' metabolic status, such as plasma glucose, body weight, blood pressure (BP) and lipid status. The improvement of these risk factors is modest, but the cumulative impact of improvement in traditional risk factors for CV disease may have produced CV-benefited effects. SGLT2i can reduce blood glucose levels; however, hypoglycaemia events of non-diabetic patients in the DAPA-HF trial are very rare [4]. The reason is that when the glucose load after filtration is below 80 g/d, the proximal renal tubule maintains its glucose reabsorption ability through the function of SGLT1 [24]. From this, dapagliflozin can maintain blood glucose of HF patients in a certain range, to avoid high and low blood glucose harmful to the heart muscle. It is well known that body weight is one of the causes of CV disease, and weight control can reduce its incidence. SGLT2i usually leads to a weight loss of 2 to 3 kg 24 to 52 weeks after the start of treatment [25]. Six-month dapagliflozin treatment is also proved to decrease systemic TNF- $\alpha$  plasma levels and reduce epicardial fat; moreover, TNF- $\alpha$  discharged from epicardial fat causes myocardial dysfunction through paracrine and vascular interactions [26]. Dapagliflozin induces pancreatic alpha cells to secrete glucagon and decreases insulin secretion, resulting in a transfer of energy utilization from free fatty acids and glucose to ketone bodies [27]. Ketone bodies are easily absorbed by cardiac tissue, decreasing oxygen demand and improving heart and kidney functions.

SGLT2 inhibitors exert advantageous vascular effects by dilating arteries and improving endothelial function, combined with increased natriuretic and osmotic diuretic effects, which can explain lower systemic blood pressure (BP) and reduced afterload. SGLT2i reduces BP regardless of baseline BP in patients with T2DM, and patients with higher BP may achieve a greater BP reduction [28]. In addition, SGLT2i can restore physiological BP decline during sleep and change circadian rhythm of BP from non-arytenoid to arytenoid, which reduces CV risk. Decreased plasma volume and BP are not relevant to increased heart rate, indicating no secondary sympathetic activation [29]. Dapagliflozin has been shown to reduce sodium concentrations of the skin, which are associated with left ventricular mass and BP [30, 31]. In the DAPA CKD trial, dapagliflozin significantly reduces the incidence of deterioration of renal function and death from renal failure compared with placebo [32]. In addition, it was found that in the DARE-19 trial dapagliflozin is well tolerated and cannot increase the risk of acute kidney injury in participants with eGFR below or above 60 mL/min per 1.73 m [33]. This may be the reason why dapagliflozin reduces renal-related secondary hypertension. Diuretic and natriuretic effects lead to a reduction in plasma volume, and sodium content is the crux to prevent fluid overload

and exacerbation of HF leading to hospitalization. Lytvyn et al. found that the natriuretic and osmotic diuretic functions of dapagliflozin can reduce the blood volume of patients and the anterior and posterior loads, thus improving the subendocardial blood flow of patients with HF and reducing the heart volume, which is conducive to ventricular remodeling [34]. However, dapagliflozin decreases volume load not merely by reducing intravascular volume but also by reducing interstitial fluid volume, which can even exceed diuretic-mediated intravascular volume contraction [35]. Moreover, SGLT2 inhibitors cannot cause electrolyte abnormalities or hyperuricemia compared with classical diuretics.

The relationship between heart and kidney functions is so complex, because one organ dysfunction often leads to dysfunction in the other, and dapagliflozin is beneficial to both the heart and the kidney. Blocking renal SGLT2 receptors increases urinary sodium excretion and decreases volume, which in turn reduces levels of atrial natriuretic peptides, leading to the constriction of afferent renal arterioles. At the same time, macula densa can monitor the increase of sodium concentration in renal tubules, which activates tubuloglomerular feedback by inducing adenosine-mediated constriction of afferent arterioles and then inhibits renin unleashed from juxtaglomerular cells, resulting in the vasodilation of efferent arterioles [36]. These effects ultimately lead to renal protective outcomes, and preservation of renal function is especially important in HF patients to avert volume overload and diuretic resistance.

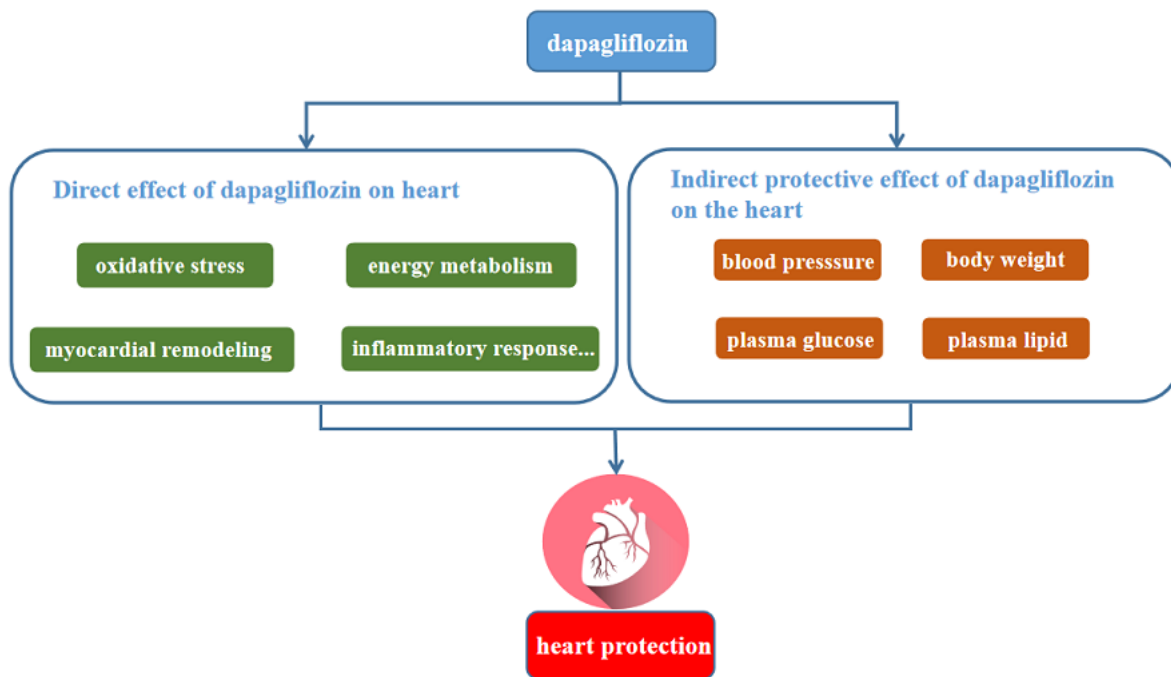
## Direct effect of dapagliflozin on the heart

Animal studies have shown that SGLT2i ameliorates the harmful effects of myocardial injury through a variety of mechanisms, including improving oxidative stress and cardiac energy metabolism, reducing sympathetic nerve activity, and inhibiting autophagy and cardiac remodeling. Diabetic cardiomyopathy is the main cause of HF in diabetic patients, and effective treatment is limited. Because the damage of diabetes to cardiac function is mainly due to the high blood glucose concentration, which produces glucolipid toxicity to myocardial cells, thus leading to early diastolic dysfunction of the heart and calcium circulation disorder in myocardial cells. Koutroumpakis et al. found that dapagliflozin restricts the supply of glucose to cardiomyocytes, improving cardiac function by restoring metabolic homeostasis [37]. In type 2 diabetic rats, dapagliflozin was shown to prevent diabetic cardiomyopathy and myocardial fibrosis by inhibiting fibroblast activation and EndMT via AMPK $\alpha$ -mediated TGF- $\beta$ /Smad signaling [38]. Dapagliflozin combined with ticagrelor can inhibit the progression of diabetic cardiomyopathy and block NLRP3 inflammasome activation and myocardial fibrosis

in BTBR mice [39]. Compared with using rosuvastatin or dapagliflozin alone, the combination of the above-mentioned two drugs significantly enhances cardiac protective effect. Furthermore, they have a potential cardioprotective effect on ischemia/reperfusion injury by activating the PI3K/Akt/mTOR axis [40]. Dapagliflozin has a cardioprotective effect on diabetic mice. It reduces the activity of oxygen radicals and membrane channels associated with calcium transport, thereby reducing myocardial fibrosis and inflammation and improving systolic function. In HF, especially in diabetic cardiomyopathy, the upregulation of sodium-hydrogen exchanger 1 is associated with the increase of the cardiomyocyte cytoplasmic sodium-calcium level [41]. Dapagliflozin blocks the activation of NHE 1 in cardiomyocytes through an unknown mechanism, leading to the downregulation in cytoplasmic sodium levels, followed by an increase in mitochondrial calcium levels, enhancing mitochondrial metabolic efficiency and thereby improving cardiac contractility and overall cardiac function [42]. These findings suggest that dapagliflozin can improve metabolic disorders and myocardial remodeling in diabetic cardiomyopathy. Dapagliflozin exerts direct protective effects on cardiomyocyte injury caused by saturated fatty acids through negatively regulating the MAPK/AP-1 signal pathway in an NHE1-dependent manner [43]. This research suggests that dapagliflozin also has potential clinical application in the prevention of obesity-related cardiac dysfunction.

Dapagliflozin regulates TGF- $\beta$ 1/Smad signaling in a non-glucose-dependent manner and improves Ang II-induced cardiac remodeling [44]. Dapagliflozin improves myocardial systolic function, and inhibits myocardial fibrosis and apoptosis in TAC mice [45]. By activating SIRT1 in Ang II-treated cardiomyocytes, dapagliflozin blocks the development of HF in vivo by inhibiting the perk-eIF2  $\alpha$ -CHOP axis of endoplasmic reticulum (ER) stress response [46]. Dapagliflozin mediates M2 polarization through a RONS-dependent STAT3-mediated pathway, reducing fibroblast infiltration during post-infarction remodeling [47]. In an HFpEF pig model induced by hypertension and hyperlipidemia, 9-week treatment with dapagliflozin reduces hypertension and reverses left ventricular remodeling by inhibiting aortic sympathetic tone, suppressing inflammatory response and activating the NO-GMP-PKG pathway [48]. Dapagliflozin has a cardiac protective effect, suggesting that dapagliflozin can be used as a new therapy to prevent cardiac remodeling in non-diabetic patients. Although the combined effect of SGLT1i and SGLT2i exceeds that of SGLT2i alone, dual SGLT1/2 inhibitors, compared with dapagliflozin, worsens cardiac dysfunction after myocardial infarction in rats by ligation of the anterior descending branch of the left coronary artery [49].

In summary, SGLT2i is beneficial for patients with T2DM and CV diseases, but the complicated mechanisms by which they exert CV- and renal-protective effects are



**Figure 1.** Mechanisms for the benefit of dapagliflozin on heart protection.



being investigated. Dapagliflozin significantly improves HF's clinical outcomes and reduces HF-related hospitalizations and CV-related deaths through its unique mechanism, regardless of diabetes (Figure 1). Dapagliflozin also provides more benefits with fewer side effects than conventional HF drugs. Further research is required to elucidate the optimal timing of taking dapagliflozin, screen candidates who benefit most, and explain the mechanisms underlying the cardioprotective effects of SGLT2 inhibitors.

## Author Contribution

Selection of theme: QW; Writing-Original draft: QX; Writing-review & editing: QY; Approval of the final manuscript: QW; Supervision: QW.

## Funding

This work was supported by grants from the National Natural Science Foundation of China (Nos. 8217020393 and 81700353).

## Disclosure

All authors declare that there is no conflict of interest to disclose.

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