HHS Public Access

Author manuscript

*Expert Opin Investig Drugs*. Author manuscript; available in PMC 2024 October 13.

Published in final edited form as:

*Expert Opin Investig Drugs*. 2023 ; 32(9): 839–847. doi:10.1080/13543784.2023.2263354.

# SGLT2 Inhibitors: An Evidence-Based Update on Cardiovascular Implications

**Imma Forzano**[1], **Scott Wilson**[2], **Angela Lombardi**[2], **Stanislovas S. Jankauskas**[2], **Urna Kansakar**[2], **Pasquale Mone**[2], **Fahimeh Varzideh**[2], **Gaetano Santulli**[1,2,*]

[1]University of Naples "Federico II"

[2]Department of Medicine, Albert Einstein College of Medicine, New York City, NY, USA.

## Abstract

**Introduction—**Sodium Glucose co-Transporter 2 (SGLT2) inhibitors (also known as "gliflozins") represent a cornerstone to treat diabetes mellitus. Moreover, recent randomized clinical trials have demonstrated important cardioprotective effects of gliflozins, independent of the presence of diabetes. Herein, we summarize the recent therapeutic progress in the cardiovascular field obtained with SGLT2 inhibitors.

**Area covered—**This review critically examines the rationale and results of recent clinical studies examining the effects of SGLT2 inhibitors on cardiovascular outcomes, along with a brief overview of the main ongoing trials that have been designed in order to answer the many unanswered questions in the field of gliflozins and cardiovascular disease.

**Expert opinion—**The favorable results of several clinical trials have broadened the therapeutic scenario for SGLT2 inhibitors, opening, at the same time, new challenges. Additionally, recent preclinical findings have evidenced off-target effects of SGLT2 inhibitors.

### Keywords

Canagliflozin; Dapagliflozin; Empagliflozin; Ertugliflozin; Heart failure; HFpEF; SGLT2i

## 1. Introduction

Sodium Glucose co-Transporter 2 (SGLT2) is a co-transporter that leads to glucose and sodium ($Na^+$) reabsorption in the kidney. SGLT2 inhibitors (which are also known as "gliflozins") are oral antidiabetic drugs that act interfering with this process, reducing glycemia. These drugs have rapidly become a main pillar to treat type 2 diabetes mellitus (T2DM) [1–3].

In 2013, the Food and Drug Administration (FDA) of the United States approved canagliflozin as the first SGLT2 inhibitor as antihyperglycemic agent for patients with T2DM, followed by empagliflozin and dapagliflozin in 2014, and ertugliflozin in 2017 [4].

[*]**Corresponding author:** Gaetano Santulli, Albert Einstein College of Medicine, 1300 Morris Park Avenue, New York City, NY, gaetano.santulli@einsteinmed.edu.

Before the FDA approval of canagliflozin, numerous concerns about the cardiovascular safety of antidiabetic agents had been raised. A classic example is given by rosiglitazone; a thiazolidinedione that in 2007 was found to be associated with an increased risk of myocardial infarction and death from cardiovascular causes [5]. These findings led the FDA to issue a recommendation requiring sponsors of antidiabetic agents to “demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk” [6]. As a result, several significant trials testing cardiovascular outcomes have been conducted to assess new antidiabetic agents, including SGLT2 inhibitors.

## 2. Cardioprotective effects of SGLT2 inhibitors: from preclinical studies to clinical trials

Various preclinical studies have shown a potentially favorable impact on the heart of SGLT2 inhibitors (Table 1). For instance, empagliflozin was shown to prevent the worsening of cardiac function in an experimental model of heart failure (HF) induced by pressure overload [7] and to decrease lipid peroxidation [8], interstitial fibrosis [9], aortic stiffness, renal resistivity index, and kidney injury [10] in mice. Equally important, cardiomyocytes obtained from non-diabetic mice exposed to the cardiotoxic drug doxorubicin, when treated with empagliflozin display an ameliorated contractility [11], indicating that this SGLT2 inhibitor markedly reduces the cardiotoxic effects of doxorubicin, independently of glycemic control [12]. Similarly, dapagliflozin decreases infarct size, post-infarction myofibroblast infiltration, and risk of arrhythmias in rats [13,14].

Moving to the clinical scenario, in 2015 Zinman and colleagues sought to determine the cardiovascular safety of empagliflozin in a cohort of patients with T2DM and high cardiovascular risk in the EMPA-REG OUTCOME (*Cardiovascular Outcome Event Trial in T2DM Patients*) trial: 7020 patients with T2DM at high risk for cardiovascular events were randomly assigned to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group vs. the placebo group. The primary endpoint occurred in 490 of 4687 patients (10.5%) in the treatment group and in 282 of 2333 patients (12.1%) in the placebo group (HR in the empagliflozin group: 0.86; CI: 95.02%, 0.74 to 0.99; P=0.04). The key secondary endpoint was the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke plus hospitalization for unstable angina. No significant difference between groups in this secondary endpoint (P=0.08) occurred; similarly, there were no significant differences in the rates of myocardial infarction or stroke between groups. However, in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for HF (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction) [15,16].

To specifically explore the effects of SGLT2 inhibitors on HF, several randomized controlled trials have been completed. The DECLARE (*Dapagliflozin Effect on Cardiovascular Events*)-TIMI 58 trial evaluated the cardiovascular outcomes of Dapagliflozin vs. placebo

over a period of up to 5 years, across 33 countries and in more than 17000 adults with T2D with multiple cardiovascular risk factors or established cardiovascular disease [17]. Dapagliflozin met the primary safety endpoint of non-inferiority for major adverse cardiovascular events (MACE) and achieved a statistically-significant reduction in the composite endpoint of hospitalization for HF or cardiovascular death [17]. In the SOLOIST-WHF (*Effect of Sotagliflozin on Cardiovascular Events in Participants With Type 2 Diabetes Post Worsening HF*) trial, the SGLT2 inhibitor Sotagliflozin, initiated in-hospital or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes, hospitalizations and urgent need of medical attention in patients with diabetes and recent worsening HF, compared to placebo [18].

Of note, in other trials, participants did not have to meet a diagnosis of diabetes to be enrolled. These include the DAPA-HF (*Dapagliflozin and Prevention of Adverse Outcomes in HF*) [19], the EMPEROR-Reduced (*Empagliflozin Outcome Trial in Patients With Chronic HF With Reduced Ejection Fraction*) [20], and the EMPEROR-Preserved (*Empagliflozin Outcome Trial in Patients with Chronic HF with Preserved Ejection Fraction, HFpEF*) trials [21]. Remarkably, in these studies, 40–60% of patients did not have T2DM [22]. In line with the other clinical studies conducted exclusively in diabetic patients, these trials reported a significant decrease in cardiovascular death or hospitalization for HF using SGLT2 inhibitors vs. standard of care plus placebo. Besides, this effect was significant within groups of patients both with and without T2DM. Other cardiovascular benefits of SGLT2 inhibitors substantiated by these trials include a decreased incidence of atrial/ventricular arrhythmia and anemia [23,24]. The first effect could be attributed to the modulation to oxidative stress and altered cardiac energy metabolism [25–27], whilst the second one might be due to increased erythropoiesis [28].

The DAPA-HF trial evaluated the impact of dapagliflozin compared to placebo as add-on recommended therapy on the incidence of worsening HF or cardiovascular death in patients with HFrEF (HF with Reduced Ejection Fraction). The primary outcome was a composite of cardiovascular death or episodes of worsening HF. In 4744 patients with EF ≤40%, moderately elevated levels of N-terminal pro B-type natriuretic peptide, and an estimated glomerular filtration rate ≥30 mL/min/1.73 $m^2$, dapagliflozin was shown to reduce the risk of worsening HF or death from cardiovascular causes compared to placebo, regardless of the presence of diabetes [29–33]. Another gliflozin, ertugliflozin, was tested by randomizing 8246 patients with T2DM and atherosclerotic cardiovascular disease, establishing as primary outcome a composite of MACE. In the ertugliflozin group, MACE occurred in 653 out of 5493 patients (11.9%) vs. 327 out of 2745 patients (11.9%) in the placebo group (HR 0.97; CI 95.6%, 0.85 to 1.11; P<0.001) demonstrating the non-inferiority of ertugliflozin. Death from cardiovascular causes or hospitalization for HF occurred in 444 of 5499 patients (8.1%) in the ertugliflozin group and in 250 of 2747 patients (9.1%) in the placebo group (HR 0.88; CI 95.8%, 0.75 to 1.03; P = 0.11). The HR for death from cardiovascular causes and HR for death from renal causes, renal replacement therapy, or doubling of the serum creatinine level were 0.92 (CI 95.8%, 0.77 to 1.11) and 0.81 (CI 95.8%, 0.63 to 1.04), respectively [34–36].

The results of the EMPEROR-Reduced trial were published in 2021, showing that empagliflozin decreases the risk of inpatient and outpatient worsening HF events in patients with HFrEF. The authors analyzed data from 3730 subjects randomized to receive empagliflozin or placebo in addition to recommended treatments for HF. Empagliflozin reduced the total number of hospitalizations for HF that required intensive care (HR, 0.67; CI 95%, 0.50–0.90; P=0.008) or that required a vasopressor or positive inotropic drug or mechanical or surgical intervention (HR, 0.64; CI 95%, 0.47–0.87; P=0.005). Patients assigned to empagliflozin had a greater likelihood (20–40%) of improvement in New York Heart Association (NYHA) functional class and were less likely to experience worsening of their NYHA class [37,38]. When evaluating patients with volume overload, data from this trial confirmed that the diuretic effect of SGLT2 inhibitors does not have a dominant role in their physiological changes and clinical benefits [39]. In most of the above-mentioned trial, the main adverse effects of gliflozins were infections of the genito-urinary tract and volume depletion, without an increased risk of hypoglycemia [40–44].

A wide range of clinical conditions where gliflozins could exert their beneficial effect on the cardiovascular system are being currently evaluated. Especially thrilling is the interest of the scientific community in gliflozins to treat HFpEF, a clinical syndrome for which there is not a universally accepted therapy, lacking evidence for a specific disease-modifying medication [45–49]. This aspect represents a critical unmet need and according to available evidence in the quest to find a valid therapeutic regimen for HFpEF, it would seem that gliflozins could respond to this need.

To evaluate the effects of SGLT2 inhibition in HFpEF, in the EMPEROR-Preserved trial, 5988 patients with HFpEF (NYHA class II-IV) were randomized to receive empagliflozin or placebo in addition to usual therapy. Notably, in this trial, not having diabetes was not considered an exclusion criterion. The primary outcome, a composite of cardiovascular death or hospitalization for HF, occurred in 13.8% of patients receiving empagliflozin vs. 17.1% of subjects in the placebo group (HR, 0.79; CI 95%, 0.69 to 0.90; P<0.001). Furthermore, the total number of hospitalizations for HF was lower in the empagliflozin group than in the placebo group (HR, 0.73; CI 95%, 0.61 to 0.88; P<0.001). Strikingly, these results were consistent regardless of the presence of diabetes [21,50–52]. Other pieces of evidence support the use of SGLT2 inhibitors in HFpEF [53,54]: SGLT2 inhibitors have been indeed shown to improve the quality of life in patients with HFpEF [55–57], and significant favorable effects of empagliflozin on cognitive and physical impairment have been reported in subjects with diabetes and HFpEF [58]. Neuroprotective effects of empagliflozin have been recently demonstrated also in zebrafish, through mechanisms that include ketogenesis and autophagy [59]. A new microRNA signature functionally involved in the regulation of endothelial function was shown to be significantly regulated in frail patients with HFpEF and diabetes, and the treatment with empagliflozin was demonstrated to attenuate endothelial dysfunction and rescue the modifications of the microRNA signature [60], thereby identifying in these microRNAs novel reliable biomarkers of disease and response to therapy.

The EMPA-TROPISM (*Are the "Cardiac Benefits" of Empagliflozin Independent of Its Hypoglycemic Activity?*) trial demonstrated that empagliflozin can improve adiposity,

interstitial myocardial fibrosis, aortic stiffness, and inflammatory markers in non-diabetic patients with HFrEF, providing new insights on the potential mechanisms of action of SGLT2 inhibitors [61]. Intriguingly, a recent meta-analysis of 60 randomized trials has investigated the effects of SGLT2 inhibitors on cholesterol and triglycerides, concluding that SGLT2-inhibition significantly decreases circulating levels of triglycerides but increases total, LDL, and HDL cholesterol [62]. Collectively, these data suggest the possible application of these medications not only in HF but also in other clinical conditions. Thus, the cardioprotective effects of SGLT2 inhibitors are also being investigated in other settings; in fact, in a variety of preclinical studies gliflozins have been shown to reduce acute myocardial ischemia/reperfusion injury [63,64]. The main drug tested was dapagliflozin, which was shown to have the capacity of reducing the infarct size and the risk of arrhythmias and to improve EF in obese rats undergoing cardiac ischemic-reperfusion injury [13] and even to have a negative effect on myofibroblast infiltration and cardiac fibrosis after AMI [14]. Similarly, empagliflozin has been shown to improve myocardial function and reduce infarct size in mice [8]. In a recent meta-analysis, these results were confirmed to be independent of the presence of diabetes [65].

Acute decompensated HF is another enthralling setting in which SGLT2 inhibitors effects are being evaluated. In this sense, SGLT2 inhibitors have been shown to increase the urine output without worsening the renal function when started in-hospital in addition to standard diuretic therapy in patients admitted for acute decompensated HF [66–69]. In the EMPULSE (*Empagliflozin in Patients Hospitalized for Acute HF*) trial, 530 patients hospitalized for acute HF were randomized to receive empagliflozin or placebo; the primary outcome was a hierarchical composite of death from any cause, number of HF events, and time to first HF event, or a 5 point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom (used to independently measure the patients' perception of their health status). The empagliflozin group met the primary endpoint showing a greater clinical benefit than placebo group (stratified win ratio, 1.36; CI 95%, 1.09–1.68; P = 0.0054) [68,70,71].

To specifically assess the effects of gliflozins in acute cardiovascular conditions, the AMI PROTECT (*Cardioprotective Effect of SGLT2-Inhibitors in Diabetic Patients With Acute Myocardial Infarction*; NCT05261867) study has been designed, evaluating the use of SGLT2 inhibitors in patients with T2DM and acute myocardial infarction; the study has shown a lower risk of adverse cardiovascular outcomes during hospitalization, as well as long-term follow-up and a lower risk of new-onset arrhythmic events (particularly ventricular arrhythmias) during the hospitalization for myocardial infarction [57,72,73]. Additionally, a significantly reduced inflammatory response and smaller infarct size has been observed in diabetic patients treated with SGLT2 inhibitors compared to those receiving other oral anti-diabetic agents, independently of glucose-metabolic control [74]. Consistent with these findings, the investigators of the EMMY (*Impact of EMpagliflozin on Cardiac Function and Biomarkers of HF in Patients With Acute MYocardial Infarction*, NCT03087773) trial recently demonstrated that an early administration of empagliflozin (within 72h) after myocardial infarction is associated with a significantly greater NT-proBNP reduction over 26 weeks, mirrored by a significant improvement in echocardiographic functional and structural parameters [75].

The potential pleiotropic effects of SGLT2 inhibitors have been also evaluated in terms of antiarrhythmic actions, based on the concept that the prevention or attenuation of oxidative and inflammatory stress might have an influence on the reduction of pro-arrhythmic factors and on the development of a pro-arrhythmic substrate [76,77]. The EMBODY (*Effect of Empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with T2DM: Multi-center placebo-controlled Double-Blind Randomized*) trial was the first clinical study to assess the effect of empagliflozin on cardiac sympathetic and parasympathetic activity in patients with T2DM and myocardial infarction via ECG Holter monitoring, evidencing that the early administration of SGLT2 inhibitors in T2DM patients with myocardial infarction could be effective in improving cardiac nerve activity without major adverse events [78]. Similarly, a post-hoc analysis of the DAPA-HF trial pointed out that dapagliflozin, compared to placebo, significantly reduced the risk of any serious ventricular arrhythmia, cardiac arrest, or sudden death when added to conventional therapy in patients with HFrEF (HR 0.79; CI 95%, 0.63–0.99; P = 0.037) [79].

The effects of SGLT2 inhibitors are also being investigated on the incidence of atrial fibrillation (AF), an aspect particularly relevant if we consider that AF is more frequent in patients with HF and in patients with diabetes [80,81]. In preclinical assays conducted in a diabetic rat model, empagliflozin was shown to modify atrial remodeling, both structural and electrical, decreasing left atrial diameter and interstitial fibrosis, therefore reducing the incidence of AF [9]. In the clinical setting, dapagliflozin was shown to reduce epicardial fat volume in patients with T2DM [82], potentially suggesting a beneficial influence of the drug on the reduction of AF episodes, especially if we consider that an analysis from the Framingham Heart Study established that epicardial fat volume is directly associated with prevalent AF [26,83]. In the DECLARE-TIMI 58 trial, dapagliflozin was actually shown to decrease the incidence of reported episodes of AF/Atrial Flutter in high-risk patients with T2DM [84]. Furthermore, a pooled analysis of 31 trials totaling 75000 patients confirmed that SGLT2 inhibitors reduced the incidence and recurrence of AF [85]. However, it is not clearly known whether the effects of SGLT2 inhibitors on AF are an indirect consequence of the benefits on the HF phenotype and/or if there is an underlying direct action [86].

## 3. Ongoing clinical trials

Due to the extreme potentiality of gliflozins, various studies are about to be published or are currently ongoing with an estimated completion date within the next 2 years. These trials could potentially answer several points on the clinical applications of SGLT2 inhibitors that remain outstanding.

The main purpose of the EMPA-AF (*Empagliflozin and Atrial Fibrillation Treatment*; NCT04583813) trial is to evaluate the impact of empagliflozin, as compared with placebo, in patients with T2DM or overweight, HF and AF; DAPA-AF (*Use of Dapagliflozin to Reduce Burden of Atrial Fibrillation in Patients Undergoing Catheter Ablation of Symptomatic Atrial Fibrillation*; NCT04792190) will study the impact of treatment with dapagliflozin vs. placebo following catheter ablation of AF on the burden of AF during 6–12 months of follow-up; DAPA-MI (*Dapagliflozin Effects on Cardiometabolic Outcomes in Patients With an Acute Heart Attack*; NCT04564742) has been designed to investigate the effects of

dapagliflozin on cardiovascular events in patients with acute myocardial infarction; ERASE (*Ertugliflozin to Reduce Arrhythmic Burden in ICD/CRT patientS*; NCT04600921) has the aim to analyze the impact of ertugliflozin on the incidence of ventricular arrhythmias; the scope of the EMPACT-MI (*A Study to Test Whether Empagliflozin Can Lower the Risk of Heart Failure and Death in People Who Had a Heart Attack*; NCT04509674) study is to find out whether empagliflozin can reduce the rate of hospitalization for HF and the rate of cardiovascular death in patients with acute myocardial infarction. The results obtained from these trials, summarized in Table 2, could give additional information on the use and future applications of SGLT2 inhibitors in a wide range of clinical conditions.

## 4. Conclusions

SGLT2 inhibitors represent molecules with a very broad clinical potential, confirmed by numerous studies. Nevertheless, further data are needed to better clarify their precise mechanism of action and off-target effects (see the section below) as well as to assess their efficacy and safety in other clinical conditions. Many ongoing trials, discussed in detail in the section above, could potentially answer several points that remain outstanding.

## 5. Expert opinion

Gliflozins have rapidly become part of the keystone tools of HFrEF therapy thanks to the (initially unexpected) results obtained in numerous clinical trials. Among these findings, a substantial improvement of different cardiovascular outcomes emerged, suggesting their potential use even in other cardiovascular conditions. Promising results have already been reached for HFpEF, although more data are needed to assess their effective role in this type of HF.

The use of SGLT2 inhibitors in acute HF could represent another valuable application, considering their effects on urine output without worsening kidney function [87,88]. The cardioprotective actions of these medications have been confirmed even in terms of myocardial remodeling, showing a benefit both in acute myocardial ischemia/reperfusion injury and on the incidence of ventricular and atrial arrhythmias, albeit at the moment the exact mechanisms of action remain not fully clear. Many of the mechanisms proposed in the context of HF—including blood pressure reduction, altering parenchymal lipid-glucose metabolism, inhibition of $Na^+/H^+$ Exchanger 1 (NHE1), and decreasing pro-fibrotic/inflammatory molecules—have also been suggested to play a reno-protective role [64,89–91].

Owing to their antidiabetic properties and protective effects on the cardiovascular system, SGLT2 inhibitors have been recommended by the American Diabetic Association (ADA) in its 2023 "*Standards of Medical Care in Diabetes*" [1]. In particular, the ADA recommends SGLT2 inhibitors in patients with T2DM in presence of established (or high risk of) atherosclerotic cardiovascular disease, defined as coronary heart disease, cerebrovascular disease, or peripheral arterial disease of atherosclerotic origin [92]. Moreover, in the current update of the American Council of Cardiologists consensus practice guidelines, gliflozins are indicated as add-on therapy to Angiotensin Receptor Neprilysin Inhibitors (ARNI)/

Angiotensin Converting Enzyme Inhibitors (ACEI)/Angiotensin Receptor Blockers (ARB) and evidence-based Beta Blocker (BB) with diuretic agents, especially in patients belonging to New York Heart Association (NYHA) class II-IV and meeting GFR criteria [93]. In the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF, SGLT2 inhibitors dapagliflozin and empagliflozin are recommended in all patients affected by HFrEF already in treatment with ARNI/ACEI/ARB, beta blockers, and Mineralocorticoid Receptor Antagonists, to reduce cardiovascular death and worsening HF. Hence, unless contraindicated or not tolerated, SGLT2 inhibitors are suitable regardless of whether the patient has or not diabetes [46,94].

Another compelling aspect of the pharmacological properties of SGLT2 inhibitors relies on their off-target effects. Indeed, in 2023, a collaborative study between research groups from the Netherlands and Greece has generated a novel global SGLT2 knock-out mouse demonstrating that the beneficial cardiovascular effects of empagliflozin are independent of SGLT2 [95], at least in a model of cardiac ischemia/reperfusion injury. These findings clearly indicate off-target effects of empagliflozin. Several non-canonical mechanisms have been proposed to explain the beneficial cardiac effects of empagliflozin, including an inhibitory action on NHE1, thereby causing a reduction in intracellular $[Na^+]$ ($[Na^+]_i$) [96,97]. However, a recent paper from Coert Zuurbier's research group seems to disprove these theories [95]. Alternative mechanisms have been proposed to explain the beneficial effects of SGLT2 inhibitors, including modifications in the metabolic substrate preference and more efficient mitochondrial energy production, improved endothelial function, and enhanced ventricular loading secondary to an amelioration of renal fitness [98–100]. Further studies are therefore warranted to clarify the exact mechanisms underlying the beneficial cardiovascular effects of SGLT2 inhibitors.

## Funding

The authors' lab is currently supported in part by the National Institutes of Health (**NIH**): National Heart, Lung, and Blood Institute (**NHLBI**), National Institute of Diabetes and Digestive and Kidney Diseases (**NIDDK**), and National Center for Advancing Translational Sciences (**NCATS**).

### Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

## References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. ElSayed NA, Aleppo G, Aroda VR, et al. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. Diabetes Care. 2023 Jan 1;46(Suppl 1):S140–S157. [PubMed: 36507650] (•) Most updated guidelines for the treatment of diabetes published by the American Diabetes Association (ADA).
2. Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm - 2023 Update. Endocr Pract. 2023 May;29(5):305–340. [PubMed: 37150579]

3. Yuan S, Song C, He J, et al. Trends in Cardiovascular Risk Factors Control Among US Adults by Glycemic Statuses, 2007–2018. Eur J Prev Cardiol. 2023 Mar 17.
4. Teo YN, Ting AZH, Teo YH, et al. Effects of Sodium/Glucose Cotransporter 2 (SGLT2) Inhibitors and Combined SGLT1/2 Inhibitors on Cardiovascular, Metabolic, Renal, and Safety Outcomes in Patients with Diabetes: A Network Meta-Analysis of 111 Randomized Controlled Trials. Am J Cardiovasc Drugs. 2022 May;22(3):299–323. [PubMed: 35316484]
5. Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. New England Journal of Medicine. 2007;356(24):2457–2471. [PubMed: 17517853]
6. Hiatt WR, Kaul S, Smith RJ. The cardiovascular safety of diabetes drugs--insights from the rosiglitazone experience. N Engl J Med. 2013 Oct 3;369(14):1285–7. [PubMed: 23992603] (•) Paper highlighting the importance of cardiovascular safety when testing new drugs to treat diabetes.
7. Byrne NJ, Parajuli N, Levasseur JL, et al. Empagliflozin Prevents Worsening of Cardiac Function in an Experimental Model of Pressure Overload-Induced Heart Failure. JACC Basic Transl Sci. 2017 Aug;2(4):347–354. [PubMed: 30062155]
8. Andreadou I, Efentakis P, Balafas E, et al. Empagliflozin Limits Myocardial Infarction in Vivo and Cell Death in Vitro: Role of STAT3, Mitochondria, and Redox Aspects. Front Physiol. 2017;8:1077. [PubMed: 29311992]
9. Shao Q, Meng L, Lee S, et al. Empagliflozin, a sodium glucose co-transporter-2 inhibitor, alleviates atrial remodeling and improves mitochondrial function in high-fat diet/streptozotocin-induced diabetic rats. Cardiovasc Diabetol. 2019 Nov 28;18(1):165. [PubMed: 31779619]
10. Aroor AR, Das NA, Carpenter AJ, et al. Glycemic control by the SGLT2 inhibitor empagliflozin decreases aortic stiffness, renal resistivity index and kidney injury. Cardiovasc Diabetol. 2018 Jul 30;17(1):108. [PubMed: 30060748]
11. Quagliariello V, De Laurentiis M, Rea D, et al. The SGLT-2 inhibitor empagliflozin improves myocardial strain, reduces cardiac fibrosis and pro-inflammatory cytokines in non-diabetic mice treated with doxorubicin. Cardiovasc Diabetol. 2021 Jul 23;20(1):150. [PubMed: 34301253]
12. Sabatino J, De Rosa S, Tamme L, et al. Empagliflozin prevents doxorubicin-induced myocardial dysfunction. Cardiovasc Diabetol. 2020 May 15;19(1):66. [PubMed: 32414364] (•) Research paper demonstrating that empagliflozin prevents anthracycline-induced cardiomyopathy.
13. Lahnwong S, Palee S, Apaijai N, et al. Acute dapagliflozin administration exerts cardioprotective effects in rats with cardiac ischemia/reperfusion injury. Cardiovasc Diabetol. 2020 Jun 15;19(1):91. [PubMed: 32539724]
14. Lee TM, Chang NC, Lin SZ. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. Free Radic Biol Med. 2017 Mar;104:298–310. [PubMed: 28132924]
15. Zinman B, Inzucchi SE, Lachin JM, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). Cardiovasc Diabetol. 2014 Jun 19;13:102. [PubMed: 24943000]
16. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117–28. [PubMed: 26378978]
17. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347–357. [PubMed: 30415602]
18. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. New England Journal of Medicine. 2020;384(2):117–128. [PubMed: 33200892] (•) Clinical trial showing that in patients with diabetes and recent worsening HF, sotagliflozin therapy results in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for HF than placebo.
19. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. New England Journal of Medicine. 2019;381(21):1995–2008. [PubMed: 31535829] (••) Randomized clinical trial (DAPA-HF) demonstrating the beneficial effects of dapagliflozin in patients with HFrEF.
20. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. NEJM. 2020 Oct 8;383(15):1413–1424. [PubMed: 32865377] (••) Seminal trial

(EMPEROR-Reduced) showing the beneficial effects of empagliflozin on cardiovascular and renal outcomes in in HFrEF.

21. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. New England Journal of Medicine. 2021;385(16):1451–1461. [PubMed: 34449189] (••) Groundbreaking trial (EMPEROR-Preserved) showing the beneficial effects of empagliflozin in patients with HFpEF.
22. Braunwald E. Gliflozins in the Management of Cardiovascular Disease. New England Journal of Medicine. 2022;386(21):2024–2034. [PubMed: 35613023]
23. Murashima M, Tanaka T, Kasugai T, et al. Sodium-glucose cotransporter 2 inhibitors and anemia among diabetes patients in real clinical practice. J Diabetes Investig. 2022 Apr;13(4):638–646.
24. Fernandes GC, Fernandes A, Cardoso R, et al. Association of SGLT2 inhibitors with arrhythmias and sudden cardiac death in patients with type 2 diabetes or heart failure: A meta-analysis of 34 randomized controlled trials. Heart Rhythm. 2021 2021/07/01/;18(7):1098–1105. [PubMed: 33757845]
25. Gao J, Xue G, Zhan G, et al. Benefits of SGLT2 inhibitors in arrhythmias. Front Cardiovasc Med. 2022;9:1011429. [PubMed: 36337862]
26. Kolesnik E, Scherr D, Rohrer U, et al. SGLT2 Inhibitors and Their Antiarrhythmic Properties. Int J Mol Sci. 2022 Jan 31;23(3).
27. Huang K, Luo X, Liao B, et al. Insights into SGLT2 inhibitor treatment of diabetic cardiomyopathy: focus on the mechanisms. Cardiovasc Diabetol. 2023 Apr 13;22(1):86. [PubMed: 37055837]
28. Thiele K, Rau M, Hartmann NK, et al. Effects of empagliflozin on erythropoiesis in patients with type 2 diabetes: Data from a randomized, placebo-controlled study. Diabetes Obes Metab. 2021 Dec;23(12):2814–2818. [PubMed: 34378852]
29. McMurray JJV, DeMets DL, Inzucchi SE, et al. A trial 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). Eur J Heart Fail. 2019 May;21(5):665–675. [PubMed: 30895697]
30. McMurray JJV, DeMets DL, Inzucchi SE, et al. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. Eur J Heart Fail. 2019 Nov;21(11):1402–1411. [PubMed: 31309699]
31. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995–2008. [PubMed: 31535829]
32. Solomon SD, Jhund PS, Claggett BL, et al. Effect of Dapagliflozin in Patients With HFrEF Treated With Sacubitril/Valsartan: The DAPA-HF Trial. JACC Heart Fail. 2020 Oct;8(10):811–818. [PubMed: 32653447]
33. Iacoviello M, Marini M, Gori M, et al. DAPA-HF applicability: the point of view of a cardiology setting. Acta Cardiol. 2023 Aug 22:1–6.
34. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med. 2020 Oct 8;383(15):1425–1435. [PubMed: 32966714]
35. Cannon CP, McGuire DK, Pratley R, et al. Design and baseline characteristics of the eValuation of ERTugliflozin effIcacy and Safety CardioVascular outcomes trial (VERTIS-CV). Am Heart J. 2018 Dec;206:11–23. [PubMed: 30290289]
36. Cosentino F, Cannon CP, Cherney DZI, et al. Efficacy of Ertugliflozin on Heart Failure-Related Events in Patients With Type 2 Diabetes Mellitus and Established Atherosclerotic Cardiovascular Disease: Results of the VERTIS CV Trial. Circulation. 2020 Dec 8;142(23):2205–2215. [PubMed: 33026243]
37. Packer M, Anker SD, Butler J, et al. Effect of Empagliflozin on the Clinical Stability of Patients With Heart Failure and a Reduced Ejection Fraction: The EMPEROR-Reduced Trial. Circulation. 2021 Jan 26;143(4):326–336. [PubMed: 33081531]
38. Packer M, Butler J, Filippatos GS, et al. Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and

a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial. Eur J Heart Fail. 2019 Oct;21(10):1270–1278. [PubMed: 31584231]

39. Packer M, Anker SD, Butler J, et al. Empagliflozin in Patients With Heart Failure, Reduced Ejection Fraction, and Volume Overload: EMPEROR-Reduced Trial. J Am Coll Cardiol. 2021 Mar 23;77(11):1381–1392. [PubMed: 33736819]
40. Tager T, Atar D, Agewall S, et al. Comparative efficacy of sodium-glucose cotransporter-2 inhibitors (SGLT2i) for cardiovascular outcomes in type 2 diabetes: a systematic review and network meta-analysis of randomised controlled trials. Heart Fail Rev. 2021 Nov;26(6):1421–1435. [PubMed: 32314085]
41. Tromp J, Ouwerkerk W, van Veldhuisen DJ, et al. A Systematic Review and Network Meta-Analysis of Pharmacological Treatment of Heart Failure With Reduced Ejection Fraction. JACC Heart Fail. 2022 Feb;10(2):73–84. [PubMed: 34895860]
42. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393(10166):31–39. [PubMed: 30424892]
43. Requena-Ibanez JA, Santos-Gallego CG, Rodriguez-Cordero A, et al. Mechanistic Insights of Empagliflozin in Nondiabetic Patients With HFrEF: From the EMPA-TROPISM Study. JACC Heart Fail. 2021 Aug;9(8):578–589. [PubMed: 34325888]
44. Anker SD, Butler J, Filippatos G, et al. Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status: Results From the EMPEROR-Reduced Trial. Circulation. 2021 Jan 26;143(4):337–349. [PubMed: 33175585]
45. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2019 Oct 24;381(17):1609–1620. [PubMed: 31475794] (•) Clinical trial showing that sacubitril-valsartan does not result in a significantly lower rate of total hospitalizations for HF and death from cardiovascular causes among patients with HFpEF.
46. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599–3726. [PubMed: 34447992] (•) Most updated European guidelines for the diagnosis and treatment of acute and chronic HF.
47. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003 Sep 6;362(9386):759–66. [PubMed: 13678868]
48. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 May 3;145(18):e876–e894. [PubMed: 35363500]
49. Upadhya B, Kitzman DW. Heart failure with preserved ejection fraction: New approaches to diagnosis and management. Clin Cardiol. 2020 Feb;43(2):145–155. [PubMed: 31880340]
50. Anker SD, Butler J, Filippatos G, et al. Baseline characteristics of patients with heart failure with preserved ejection fraction in the EMPEROR-Preserved trial. Eur J Heart Fail. 2020 Dec;22(12):2383–2392. [PubMed: 33251670]
51. Anker SD, Butler J, Filippatos GS, et al. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. Eur J Heart Fail. 2019 Oct;21(10):1279–1287. [PubMed: 31523904]
52. Butler J, Siddiqi TJ, Filippatos G, et al. Early benefit with empagliflozin in heart failure with preserved ejection fraction: insights from the EMPEROR-Preserved trial. Eur J Heart Fail. 2022 Feb;24(2):245–248. [PubMed: 34989083]
53. Sandhu AT, Cohen DJ. Cost-effectiveness of Sodium-Glucose Cotransporter-2 Inhibitors for Patients With Heart Failure and Preserved Ejection Fraction-Living on the Edge. JAMA Cardiol. 2023 May 1;8(5):415–416. [PubMed: 36870043]
54. Kittleson MM, Panjrath GS, Amancherla K, 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 May 9;81(18):1835–1878. [PubMed: 37137593]

55. Requena-Ibanez JA, Santos-Gallego CG, Rodriguez-Cordero A, et al. Empagliflozin improves quality of life in nondiabetic HFrEF patients. Sub-analysis of the EMPATROPISM trial. Diabetes Metab Syndr. 2022 Feb;16(2):102417. [PubMed: 35121204]
56. Butler J, Filippatos G, Jamal Siddiqi T, et al. Empagliflozin, Health Status, and Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial. Circulation. 2022 Jan 18;145(3):184–193. [PubMed: 34779658]
57. Paolisso P, Bergamaschi L, Gragnano F, et al. Outcomes in diabetic patients treated with SGLT2-Inhibitors with acute myocardial infarction undergoing PCI: The SGLT2-I AMI PROTECT Registry. Pharmacol Res. 2023 Jan;187:106597. [PubMed: 36470546]
58. Mone P, Lombardi A, Gambardella J, et al. Empagliflozin Improves Cognitive Impairment in Frail Older Adults With Type 2 Diabetes and Heart Failure With Preserved Ejection Fraction. Diabetes Care. 2022 May 1;45(5):1247–1251. [PubMed: 35287171]
59. Unal I, Cansiz D, Beler M, et al. Sodium-dependent Glucose Co-Transporter-2 Inhibitor Empagliflozin Exerts Neuroprotective Effects in Rotenone-Induced Parkinson's Disease Model in Zebrafish; Mechanism Involving Ketogenesis and Autophagy. Brain Res. 2023 Aug 15:148536. [PubMed: 37591458]
60. Mone P, Lombardi A, Kansakar U, et al. Empagliflozin Improves the MicroRNA Signature of Endothelial Dysfunction in Patients with Heart Failure with Preserved Ejection Fraction and Diabetes. J Pharmacol Exp Ther. 2023 Jan;384(1):116–122. [PubMed: 36549862]
61. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, et al. Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction. J Am Coll Cardiol. 2021 Jan 26;77(3):243–255. [PubMed: 33197559]
62. Bechmann LE, Emanuelsson F, Nordestgaard BG, et al. SGLT2-inhibition increases total, LDL, and HDL cholesterol and lowers triglycerides: Meta-analyses of 60 randomized trials, overall and by dose, ethnicity, and drug type. Atherosclerosis. 2023 Aug 9:117236. [PubMed: 37582673]
63. Tanajak P, Sa-Nguanmoo P, Sivasinprasasn S, et al. Cardioprotection of dapagliflozin and vildagliptin in rats with cardiac ischemia-reperfusion injury. J Endocrinol. 2018 Feb;236(2):69–84. [PubMed: 29142025]
64. Hu Z, Ju F, Du L, et al. Empagliflozin protects the heart against ischemia/reperfusion-induced sudden cardiac death. Cardiovasc Diabetol. 2021 Oct 4;20(1):199. [PubMed: 34607570]
65. Sayour AA, Celeng C, Olah A, et al. Sodium-glucose cotransporter 2 inhibitors reduce myocardial infarct size in preclinical animal models of myocardial ischaemia-reperfusion injury: a meta-analysis. Diabetologia. 2021 Apr;64(4):737–748. [PubMed: 33483761]
66. Schulze PC, Bogoviku J, Westphal J, et al. Effects of Early Empagliflozin Initiation on Diuresis and Kidney Function in Patients With Acute Decompensated Heart Failure (EMPAG-HF). Circulation. 2022 Jul 26;146(4):289–298. [PubMed: 35766022]
67. Damman K, Beusekamp JC, Boorsma EM, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). Eur J Heart Fail. 2020 Apr;22(4):713–722. [PubMed: 31912605]
68. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med. 2022 Mar;28(3):568–574. [PubMed: 35228754] (••) Multinational randomized clinical trial indicating that initiation of empagliflozin in patients hospitalized for acute HF results in significant clinical benefit in the 90 days after starting treatment.
69. Biegus J, Voors AA, Collins SP, et al. Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial. Eur Heart J. 2023 Jan 1;44(1):41–50. [PubMed: 36254693]
70. Tromp J, Ponikowski P, Salsali A, et al. Sodium-glucose co-transporter 2 inhibition in patients hospitalized for acute decompensated heart failure: rationale for and design of the EMPULSE trial. Eur J Heart Fail. 2021 May;23(5):826–834. [PubMed: 33609072]

71. Kosiborod MN, Angermann CE, Collins SP, et al. Effects of Empagliflozin on Symptoms, Physical Limitations, and Quality of Life in Patients Hospitalized for Acute Heart Failure: Results From the EMPULSE Trial. Circulation. 2022 Jul 26;146(4):279–288. [PubMed: 35377706]
72. Cesaro A, Gragnano F, Paolisso P, et al. In-hospital arrhythmic burden reduction in diabetic patients with acute myocardial infarction treated with SGLT2-inhibitors: Insights from the SGLT2-I AMI PROTECT study. Front Cardiovasc Med. 2022;9:1012220. [PubMed: 36237914]
73. Paolisso P, Bergamaschi L, Cesaro A, et al. Impact of SGLT2-inhibitors on contrast-induced acute kidney injury in diabetic patients with acute myocardial infarction with and without chronic kidney disease: Insight from SGLT2-I AMI PROTECT registry. Diabetes Res Clin Pract. 2023 Aug;202:110766. [PubMed: 37276980]
74. Paolisso P, Bergamaschi L, Santulli G, et al. Infarct size, inflammatory burden, and admission hyperglycemia in diabetic patients with acute myocardial infarction treated with SGLT2-inhibitors: a multicenter international registry. Cardiovasc Diabetol. 2022 May 15;21(1):77. [PubMed: 35570280]
75. von Lewinski D, Kolesnik E, Tripolt NJ, et al. Empagliflozin in acute myocardial infarction: the EMMY trial. Eur Heart J. 2022 Nov 1;43(41):4421–4432. [PubMed: 36036746] (•) Clinical trial showing that in patients with a recent myocardial infarction, empagliflozin shows a significant improvement in echocardiographic functional and structural parameters.
76. Andelova K, Bacova BS, Sykora M, et al. Mechanisms Underlying Antiarrhythmic Properties of Cardioprotective Agents Impacting Inflammation and Oxidative Stress. Int J Mol Sci. 2022 Jan 26;23(3).
77. Bossi AC, Forloni F, Colombelli PL. A Response To: Sodium-Glucose Cotransporter 2 Inhibitors and Major COVID-19 Outcomes: Promising Mechanisms, Conflicting Data, and Intriguing Clinical Decisions. Diabetes Ther. 2020 Dec;11(12):3007–3009. [PubMed: 33052537]
78. Shimizu W, Kubota Y, Hoshika Y, et al. Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: the EMBODY trial. Cardiovasc Diabetol. 2020 Sep 25;19(1):148. [PubMed: 32977831]
79. Curtain JP, Docherty KF, Jhund PS, et al. Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. Eur Heart J. 2021 Sep 21;42(36):3727–3738. [PubMed: 34448003]
80. Olsson LG, Swedberg K, Ducharme A, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. J Am Coll Cardiol. 2006 May 16;47(10):1997–2004. [PubMed: 16697316]
81. Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994 Mar 16;271(11):840–4. [PubMed: 8114238]
82. Sato T, Aizawa Y, Yuasa S, et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. Cardiovasc Diabetol. 2018 Jan 4;17(1):6. [PubMed: 29301516]
83. Thanassoulis G, Massaro JM, O'Donnell CJ, et al. Pericardial fat is associated with prevalent atrial fibrillation: the Framingham Heart Study. Circ Arrhythm Electrophysiol. 2010 Aug;3(4):345–50. [PubMed: 20558845]
84. Zelniker TA, Bonaca MP, Furtado RHM, et al. Effect of Dapagliflozin on Atrial Fibrillation in Patients With Type 2 Diabetes Mellitus: Insights From the DECLARE-TIMI 58 Trial. Circulation. 2020 Apr 14;141(15):1227–1234. [PubMed: 31983236]
85. Pandey AK, Okaj I, Kaur H, et al. Sodium-Glucose Co-Transporter Inhibitors and Atrial Fibrillation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc. 2021 Sep 7;10(17):e022222. [PubMed: 34459238]
86. Granger CB, Mahaffey KW. Preventing Atrial Fibrillation With Treatments for Diabetes Mellitus. Circulation. 2020 Apr 14;141(15):1235–1237. [PubMed: 32282249]
87. Packer M, Wilcox CS, Testani JM. Critical Analysis of the Effects of SGLT2 Inhibitors on Renal Tubular Sodium, Water and Chloride Homeostasis and Their Role in Influencing Heart Failure Outcomes. Circulation. 2023 Jul 25;148(4):354–372. [PubMed: 37486998]

88. Yau K, Dharia A, Alrowiyti I, et al. Prescribing SGLT2 Inhibitors in Patients With CKD: Expanding Indications and Practical Considerations. Kidney Int Rep. 2022 Jul;7(7):1463–1476. [PubMed: 35812300]

89. Packer M. Mechanisms Leading to Differential Hypoxia-Inducible Factor Signaling in the Diabetic Kidney: Modulation by SGLT2 Inhibitors and Hypoxia Mimetics. American Journal of Kidney Diseases. 2021 2021/02/01/;77(2):280–286. [PubMed: 32711072]

90. Onishi A, Fu Y, Darshi M, et al. Effect of renal tubule-specific knockdown of the Na+/H+ exchanger NHE3 in Akita diabetic mice. American Journal of Physiology-Renal Physiology. 2019;317(2):F419–F434. [PubMed: 31166707]

91. Kwon O, Myong JP, Lee Y, et al. Sodium-Glucose Cotransporter-2 Inhibitors After Acute Myocardial Infarction in Patients With Type 2 Diabetes: A Population-Based Investigation. J Am Heart Assoc. 2023 Jul 18;12(14):e027824. [PubMed: 37421263]

92. ElSayed NA, Aleppo G, Aroda VR, et al. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2023. Diabetes Care. 2023 Jan 1;46(Suppl 1):S158–S190. [PubMed: 36507632]

93. Writing C, Maddox TM, Januzzi JL Jr., et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021 Feb 16;77(6):772–810. [PubMed: 33446410]

94. Santulli G, Varzideh F, Forzano I, et al. Functional and Clinical Importance of SGLT2-inhibitors in Frailty: From the Kidney to the Heart. Hypertension. 2023 Jul 5.

95. Chen S, Wang Q, Christodoulou A, et al. Sodium Glucose Cotransporter-2 Inhibitor Empagliflozin Reduces Infarct Size Independently of Sodium Glucose Cotransporter-2. Circulation. 2023 Jan 17;147(3):276–279. [PubMed: 36649392] (•) Research letter showing in a SGLT2 KO mouse model that empagliflozin reduces infarct size independently of the presence of SGLT2.

96. Baartscheer A, Schumacher CA, Wust RC, et al. Empagliflozin decreases myocardial cytoplasmic Na(+) through inhibition of the cardiac Na(+)/H(+) exchanger in rats and rabbits. Diabetologia. 2017 Mar;60(3):568–573. [PubMed: 27752710]

97. Iborra-Egea O, Santiago-Vacas E, Yurista SR, et al. Unraveling the Molecular Mechanism of Action of Empagliflozin in Heart Failure With Reduced Ejection Fraction With or Without Diabetes. JACC Basic Transl Sci. 2019 Nov;4(7):831–840. [PubMed: 31998851]

98. Striepe K, Jumar A, Ott C, et al. Effects of the Selective Sodium-Glucose Cotransporter 2 Inhibitor Empagliflozin on Vascular Function and Central Hemodynamics in Patients With Type 2 Diabetes Mellitus. Circulation. 2017 Sep 19;136(12):1167–1169. [PubMed: 28923906]

99. Mone P, Varzideh F, Jankauskas SS, et al. SGLT2 Inhibition via Empagliflozin Improves Endothelial Function and Reduces Mitochondrial Oxidative Stress: Insights From Frail Hypertensive and Diabetic Patients. Hypertension. 2022 Aug;79(8):1633–1643. [PubMed: 35703100]

100. Varzideh F, Kansakar U, Santulli G. SGLT2 inhibitors in cardiovascu-lar medicine. Eur Heart J Cardiovasc Pharmacother. 2021 Jul 23;7(4):e67–e68. doi: 10.1093/ehjcvp/pvab039. [PubMed: 33964138]

## Article highlights

- Sodium Glucose co-Transporter 2 (SGLT2) inhibitors emerged as a main therapeutic option for patients with type 2 diabetes mellitus.
- Recent randomized clinical trials unveiled unprecedented cardioprotective actions of SGLT2 inhibitors.
- The favorable effects of SGLT2 inhibitors on cardiovascular outcome are not dependent on the presence of diabetes.
- We present an overview of the recent therapeutic progress in the cardiovascular field obtained with SGLT2 inhibitors, including ongoing clinical trials.

**Table 1.**

Main preclinical studies testing the effects of SGLT2 inhibitors on cardiac function.

| Year | First Author | SGLT2 inhibitor(s) tested | Main conclusions | Novel Information | Reference |
|---|---|---|---|---|---|
| 2017 | Byrne | Empagliflozin | Empagliflozin decreased worsening of cardiac function in a mouse model of pressure overload-induced HF. | SGLT2 inhibition prevents the progressive decline of cardiac function even in non-diabetic murine models with reduced EF both in vivo and ex vivo. | [7] |
| 2017 | Andreadou | Empagliflozin | Empagliflozin improved myocardial function, reduced infarct size, decreased iNOS expression and lipid peroxidation in mice. | Identification of the anti-oxidant and anti-inflammatory properties of empagliflozin mediated by the activation of STAT3 pathway. | [8] |
| 2017 | Lee | Dapagliflozin | Dapagliflozin reduced myofibroblast infiltration during postinfarction remodeling in infarcted rat hearts. | Demonstration of the regulation of macrophage polarization via STAT3 by dapagliflozin. | [14] |
| 2018 | Aroor | Empagliflozin | Empagliflozin improved kidney injury causing glycosuria and reducing systemic and renal artery stiffness in a mouse model of T2DM. | SGLT2 inhibition enhances eNOS activation and mitigates the hyperglycemia-induced suppression of the antifibrotic factor RECK in the kidney. | [10] |
| 2019 | Shao | Empagliflozin | Empagliflozin reduced the remodeling of atrial structural and electrical conformation reducing left atrial diameter, interstitial fibrosis. | Demonstration of the beneficial effects of empagliflozin on atrial fibrillation in diabetic rats. | [9] |
| 2020 | Lahwong | Dapagliflozin | Dapagliflozin administration in acute setting reduced cardiac infarct size, increased LV function and reduced rate of arrhythmias in rats with I/R injury. | Evidence of the direct effects of dapagliflozin on cardiac apoptosis, inflammation, ionic homeostasis, and oxidative stress pathways. | [13] |
| 2021 | Quagliariello | Empagliflozin | Empagliflozin reduced doxorubicin toxic effects on cardiomyocytes. | Identification of new anti-inflammatory and cardioprotective mechanisms of empagliflozin involving NLRP3 and MyD88-related pathways. | [11] |
| 2021 | Sayour | Canagliflozin, Dapagliflozin, Empagliflozin | SGLT2 inhibitors reduced myocardial infarct size in animal models independent of diabetes. | The reduction of infarct size is equal for the different types of SGLT2 inhibitors, suggesting a class effect. | [65] |
| 2023 | Chen | Empagliflozin | Empagliflozin (10 mg/kg/day) has protective effects in a model of cardiac ischemia/reperfusion despite the ablation of SGLT2 (global knock-out mouse). | The demonstration of the beneficial heart effects of SGLT2 inhibitors in a SGLT2 KO mouse model suggests that the reduction of the infarct size is not directly mediated by the SGLT2 protein. | [95] |

EF: Ejection Fraction; I/R: Ischemia/Reperfusion; HF: Heart Failure; HFD + STZ: high-fat diet /streptozotocin; KO: Knock-Out; LV: Left Ventricular; SGLT2: Sodium–glucose cotransporter 2; T2DM: Type 2 Diabetes Mellitus.

**Table 2.**

Ongoing trials testing SGLT2 inhibitors.

| Acronym, NCT | Official Name | Current primary outcome | State | Estimated completion date |
|---|---|---|---|---|
| DAPA-AF, NCT04792190 | Use of Dapagliflozin to Reduce Burden of Atrial Fibrillation in Patients Undergoing Catheter Ablation of Symptomatic Atrial Fibrillation (DAPA-AF) | Mean percentage of time spent in AF | Active, not recruiting | June, 2023 |
| EMPACT-MI, NCT04509674 | A Streamlined, Multicenter, Randomized, Parallel Group, Double-blind Placebo-controlled Superiority Trial to Evaluate the Effect of EMPAgliflozin on Hospitalization for HF and Mortality in Patients With aCuTe Myocardial Infarction | Composite of time to first HF hospitalization or all-cause mortality | Recruiting | August, 2023 |
| DAPA-MI, NCT04564742 | A Registry-based, Randomized, Double-blind, Placebo-Controlled Cardiovascular Outcomes Trial to Evaluate the Effect of Dapagliflozin on the Incidence of HF or Cardiovascular Death in Patients Without Diabetes With Acute Myocardial Infarction at Increased Risk for Subsequent Development of HF | Time to the first occurrence of any of the components of this composite: hospitalization for HF or cardiovascular death | Recruiting | September, 2023 |
| EMPA-AF, NCT04583813 | Efficacy of Empagliflozin in Patients With HF and Atrial Fibrillation | Maintenance of sinus rhythm after the blanking period | Not yet recruiting | January, 2024 |
| ERASe, NCT04600921 | Ertugliflozin to Reduce Arrhythmic Burden in ICD/CRT patientS - a Phase III Study | Episodes of supraventricular tachycardia and ventricular fibrillation. | Recruiting | April, 2024 |

AF: Atrial Fibrillation; CRT: Cardiac Resynchronization Therapy; HF: Heart Failure; ICD: Implantable Cardioverter-defibrillators.