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Review Article

The role of SGLT2 inhibitors in protecting cardiovascular health: beyond glycaemic control

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ABSTRACT

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, also known as Gliflozins, are a class of anti-diabetic medications initially developed for glycemic control in patients with type 2 diabetes mellitus (T2DM). T2DM patients are at a significantly higher risk of adverse outcomes, including heart failure, atherosclerotic cardiovascular disease, and renal diseases. Unlike traditional hypoglycemic agents, SGLT2 inhibitors have demonstrated notable cardiovascular benefits. Four SGLT2 inhibitors-Canagliflozin, Empagliflozin, Ertugliflozin, and Dapagliflozin—are currently approved by regulatory agencies such as the European Medicines Agency and the US Food and Drug Administration. Various mechanisms have been proposed to explain the cardioprotective effects of SGLT2 inhibitors, extending their therapeutic potential beyond glycemic control. The renal benefits of SGLT2 inhibitors contribute to cardiovascular outcomes, including reductions in albuminuria and slowing of chronic kidney disease progression. This review explores the impact of SGLT2 inhibitors on cardiovascular health in diabetic and non-diabetic populations, highlighting their ability to reduce renal and cardiovascular risks. Current evidence underscores their transformative role in managing T2DM and cardiovascular diseases. Furthermore, these findings pave the way for the development of innovative therapeutic strategies targeting diabetes and cardiovascular comorbidities. Additional research is needed to better understand the potential benefits of SGLT2 inhibitors in non-diabetic individuals**.**

Keywords: Sodium-glucose cotransporter type 2 inhibitors, SGLT2 inhibitors, Gliflozins, Cardiovascular health, cardioprotective effects, Empagliflozin, Dapagliflozin

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, posing significant challenges to global healthcare systems. Individuals with T2DM have a high risk of developing cardiovascular complications, including heart failure, atherosclerotic cardiovascular disease, and renal disease. As a result, the coexistence of diabetes and cardio-renal comorbidities leads to a significant risk of cardiovascular events and mortality.[1]

Approximately one-third (32.2%) of the individuals with T2DM are affected by some sort of CVDs, mainly from coronary heart disease (21.2%), followed by heart failure (14.9%), angina (14.6%), myocardial infarction (MI) (10.0%), and stroke (7.6%). These CVDs also cause approximately half of all deaths among them.[2]

Sodium-glucose cotransporter type 2 inhibitors, or gliflozins, are a class of anti-diabetic medication. SGLT2 inhibitors inhibit SGLT2 protein in the renal tubules, reducing glucose reabsorption, which lowers the renal glucose threshold and initiates the excretion of glucose in the urine.[3] Besides their use in treating T2DM, they have shown cardiovascular benefits unlike other traditional hypoglycemic drugs.

Multiple studies measuring cardiovascular outcomes found that SGLT2 inhibitors can decrease the incidence of hospitalization due to heart failure.[4-6] Currently, the original 'golden triangle' of heart failure medications is replaced by the 'new tetrad' including beta-blockers, renin-angiotensin system inhibitors, aldosterone receptor antagonists, and SGLT2 inhibitors.[7,8]

Four SGLT2 inhibitors—Canagliflozin, Empagliflozin, Ertugliflozin, and Dapagliflozin—have been approved by the European Medicines Agency and the US Food and Drug Administration. These agents are extensively utilized in clinical practice for the management of T2DM and associated comorbidities.[9]

Specifically, empagliflozin and dapagliflozin are regularly used for heart failure prevention and treatment.[7,8] SGLT2 inhibitors have also shown a potential protective effect against cancer treatment–related cardiotoxicity. Additionally, multiple preclinical studies have stated that SGLT2 inhibitors may exert anticancer effects across various malignancies, including bladder, prostate, breast, and colorectal cancer.[10-12]

Traditional hypoglycemic agents have largely focused on glycemic control without addressing the cardiovascular and renal risks associated with T2DM. The introduction of SGLT2 inhibitors has transformed the therapeutic landscape by offering the dual benefits of glucose regulation and cardiovascular protection. Given the increasing burden of cardiovascular diseases in diabetic and non-diabetic populations, it is critical to explore and understand the broader applications of SGLT2 inhibitors. Investigating their role in cardiovascular health beyond glycemic control provides valuable insights into their mechanisms of action and their potential to redefine clinical practice guidelines for managing high-risk patients.

The aim of this review is to discuss the effects of Sodium-glucose cotransporter type 2 inhibitors on cardiovascular health beyond glycemic control in diabetic and non-diabetic patients, focusing on the mechanisms of these effects. In addition, we are going to review the cardiac outcomes of different trials assessing the efficacy of SGLT2 inhibitors.

REVIEW

The following databases were used in systematic research, medline (PubMed), Web of Science, and Scopus till January 5, 2025. The MeSH database was used to retrieve the synonyms of the search strategy. Search terms were then combined by ("and" and "or") Boolean operators according to the Cochrane handbook for systematic reviews of interventions as follows: "sodium glucose transporter 2 inhibitors" or "sodium-glucose transporter 2 inhibitor" or "SGLT-2 inhibitors" or "SGLT 2 inhibitors" or "gliflozins" and "cardiovascular health" or "cardiovascular system" or "circulatory system" or "cardiovascular disease".

Summaries of the found studies were exported by endnote X8, and duplicate studies were removed. Any study that discusses the role of SGLT2 inhibitors in protecting cardiovascular health and is published in peer-reviewed journals was included with the inclusion of full-text articles, abstracts, and case series with the related topics included. All languages are included. Case reports, letters, and comments were excluded.[13]

DISCUSSION

Sodium-glucose cotransporter 2 inhibitors are an important class of anti-diabetic drugs. It has proven efficacy in lowering glucose in diabetic patients. Recently, multiple studies found that SGLT2 inhibitors have cardioprotective effects reflected in non-fatal stroke rates, non-fatal MI rates, and heart failure hospitalizations. Here is a summary of SGLT2 inhibitors effects on cardiovascular health.

SGLT2 inhibitors effects on cardiovascular health

SGLT2 inhibitors led to a paradigm shift in managing T2DM through recent years due to their additional cardioprotective effects beyond glucose control. Various trials focused on the cardioprotective effects of SGLT2 inhibitors by measuring the major adverse cardiovascular events (MACE) risk in patients treated by this type of drug, such as CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME.[14] The EMPA-REG outcome

trial assessed the effect of empagliflozin, an SGLT2 inhibitor, on cardiovascular outcomes in T2DM and established CVD patients. The trial showed a 14% reduction in relative risk of different MACE outcomes, including non-fatal stroke and non-fatal MI, during a median follow-up of 3.1 years. It was also associated with a 38% reduction in relative risk of cardiovascular death.[6]

Canagliflozin, another SGLT2 inhibitor, was evaluated by the CANVAS program in patients with T2DM and a high risk of CVD. A 14% reduction in the risk of MACE was found in this study. Reduced heart failure hospitalizations were also observed after the use of Canagliflozin.[15] Another trial called the DECLARE-TIMI 58 trial examined another type of SGLT2 inhibitor called Dapagliflozin. It was examined in patients with T2DM, including patients without CVD. Although the primary endpoint of MACE reduction was not observed, a remarkable reduction in hospitalization due to heart failure was found. However, the MACE primary endpoint showed no reduction.[16]

Sodium-glucose cotransporter 2 inhibitors have become a cornerstone therapy for heart failure, as they have significantly changed the therapeutic outcomes of these patients. It was initially introduced as an agent for treating heart failure by the pivotal study EMPA-REG OUTCOME trial. It highlighted their cardiovascular benefits by reducing hospitalization for heart failure patients treated with empagliflozin compared to a placebo.[17]

Heart failure can be classified based on the ejection fraction (EF) into HF with preserved EF (HFpEF) EF>50%, HF with mildly reduced EF (HFmrEF) EF between 40% to 50%, and HF with reduced EF (HFrEF) EF ≤40%.[18] The DAPA-HF trial assessed the benefits of SGLT2 inhibitors in patients with heart failure with a reduced ejection fraction (HFrEF). The DAPA-HF trial examined the effectiveness of dapagliflozin and found a 24% reduction in a composite of cardiovascular outcomes such as hospitalization for heart failure, urgent hospital visits requiring intravenous heart failure treatment, and death from cardiovascular causes in in Dapagliflozin group.[19]

In recent studies, the beneficial effect of the SGLT2 inhibitors was only assessed among patients with HFrEF. However, the EMPEROR-Preserved trial in 2022 showed that cardiovascular outcomes in patients with HFpEF were also improved by empagliflozin. The study found a 19% reduction in the primary composite outcome of cardiovascular death and heart failure after the use of empagliflozin in patients with HFmrEF and HFpEF regardless of whether they had diabetes or not.[20]

As discussed, SGLT2 inhibitors have significant cardioprotective effects improving outcomes in CVD patients. This highlights their potential role in improving cardiac outcomes in cancer patients treated with cardiotoxic cancer drugs. Cardiovascular disease is considered the second most common cause of morbidity and mortality in cancer survivors, after the recurrence of the primary cancer.[21] Serious cardiovascular complications such as hypertension, heart failure, arrhythmias, and coronary artery disease may occur as a result of using anticancer therapy. Anthracyclines are among the most widely used drugs in cancer treatment. This type of drug has the highest risk for cardiotoxicity.[22] SGLT2 inhibitors showed promising potential in managing cardiovascular complications in cancer survivors. Recently, different retrospective observational studies stated the beneficial effects of SGLT2 inhibitors in cancer patients receiving various potentially cardiotoxic therapies.[23,24]

A recent retrospective study evaluated the efficacy of SGLT2 inhibitors in cancer and diabetes mellitus patients who were treated with anthracyclines comparing them with those on anthracyclines, without SGLT2 inhibitors.[23] The study found that during 1.5 years of follow-up, patients who commenced SGLT2 inhibitors had a lower rate of cardiac complications, such as cardiomyopathy and heart failure admissions, compared with those who did not receive SGLT2 inhibitors. Lower rates of sepsis and improved overall mortality were also observed, supporting the safety of SGLT2 inhibitors. However, there is a need for more studies addressing the effectiveness of SGLT2 inhibitors in the field of cardio-oncology.

Mechanisms underlying cardiovascular protection

Various mechanisms have been proposed explaining how SGLT2 inhibitors exert their cardioprotective effects (Figure 1). Studies stated that SGLT2 inhibitors exert their cardioprotective effects through indirect mechanisms (such as renal and hemodynamic mechanisms) and direct cardiac mechanisms.[25,26] In order to recognize SGLT2 inhibitors clinical significance, the mechanisms underlying their actions should be understood.

Indirect cardioprotective mechanisms of SGLT2 inhibitors

The proximal renal tubules of the kidneys contain the SGLT2 protein, which is responsible for glucose reabsorption from the circulation. This protein is the primary target of SGLT2 inhibitors; by inhibiting it, a reduction in renal glucose reabsorption and an increase in urinary glucose excretion occur.[27] Studies showed that SGLT2 inhibitors are also effective in enhancing insulin sensitivity and in reducing HbA1c levels, when used alone or combined with other anti-diabetic drugs.[14] Notably, their effect is independent of insulin, so they are convenient for patients with insulin resistance and T2DM.[27]

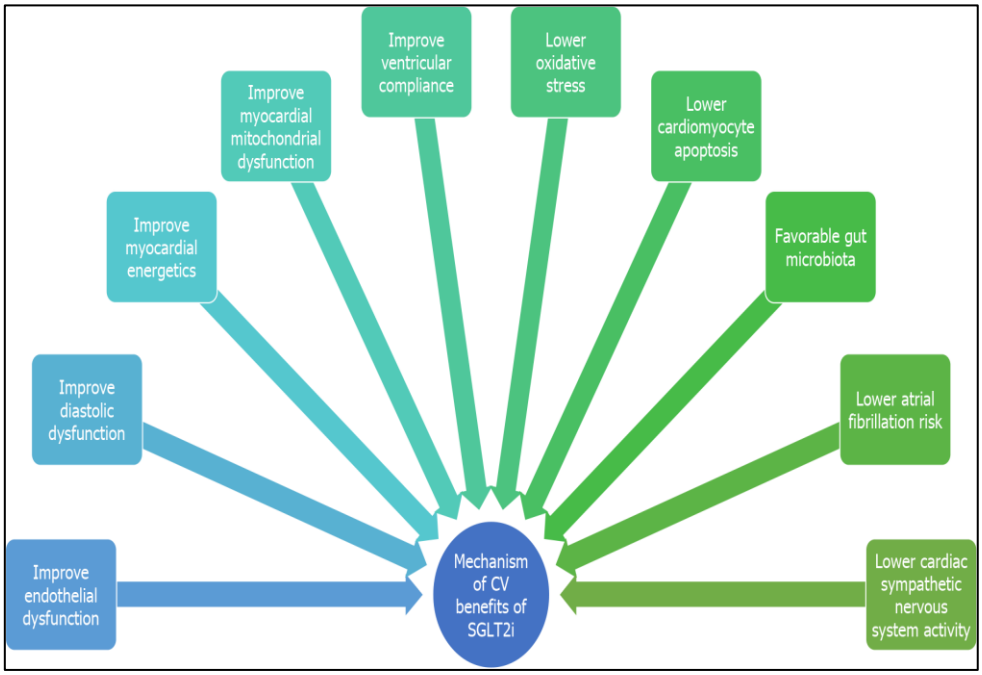

Figure 1: Mechanisms of cardiovascular benefits of sodium glucose cotransporter 2 inhibitors. CV: cardiovascular; SGLT2i: Sodium glucose otransporter-2 inhibitors.[1] Mondal 2024: sodium glucose cotransporter-2 inhibitors and heart disease: current perspectives.

In addition, SGLT2 inhibitors have indirect effects on glycemic control beyond their immediate effect through influencing different metabolic health parameters. SGLT2 inhibitors can lead to weight loss due to increased glucose excretion in urine, which precipitates loss of calories and may improve lipid profiles by increasing (HDL) cholesterol and reducing triglycerides.[28,29] These benefits of SGLT2 inhibitors make them suitable for obese or overweight T2DM patients.[30] By controlling blood glucose levels and enhancing metabolic and lipid profiles, SGLT2 inhibitors reduce the risk of cardiovascular diseases.

As discussed above, SGLT2 inhibitors exert their glycemic control by targeting the kidneys. Their action on the kidney has a renoprotective effect besides glycemic control. SGLT2 inhibitors can induce natriuresis and reduce sodium reabsorption, leading to reduced intraglomerular pressure and hyperfiltration. This effect mitigates the stress on the renal vasculature and retards renal damage.[31] They are also associated with a significant reduction in albuminuria, which is a hallmark of diabetic kidney disease. The decrease in glomerular pressure and inflammation associated with SGLT2 inhibitors and their impact on the tubuloglomerular feedback mechanisms may lead to this reduction in albuminuria.[32] These effects on the kidney provide a diuretic effect, which can reduce cardiac load and blood volume, thus protecting the heart by decreasing myocardial oxygen consumption.

Sodium-glucose cotransporter 2 inhibitors are associated with a significant reduction in blood pressure.[33] Studies have shown that SGLT2 inhibitors cause modest but clinically meaningful decreases in both systolic and diastolic blood pressure. This effect is likely due to increased glucose excretion, natriuresis and osmotic diuresis. They are also effective in improving vascular health and endothelial function by reducing arterial stiffness, which is a significant risk factor for cardiovascular diseases. This improvement in vascular health can lead to decreased vascular resistance and lower blood pressure by enhancing vasodilation.[33] These positive hemodynamic effects further enhance the cardioprotective effects of SGLT2 inhibitors.

Additionally, SGLT2 inhibitors demonstrate cardioprotective effects by targeting multiple cellular processes involved in cardiac remodeling and dysfunction. Pathological cardiac remodeling and heart failure progression can result from chronic inflammation via various cytokines like IL-6 and TNF-α.[34] SGLT2 inhibitors can inhibit pro-inflammatory cytokines, which mitigates cardiac fibrosis and inflammation in different models of heart failure and myocarditis.[35]

Oxidative stress leads to disruption of mitochondrial function, which results in cardiac hypertrophy, fibrosis, and apoptosis.[34] SGLT2 inhibitors improve mitochondrial biogenesis through reducing ROS production. This also may improve oxidative phosphorylation through pathways like AMPK-Nrf2 signaling.[36] Energy metabolism is shifted from fatty acids to glucose during heart failure, resulting in insufficient energy production.[37] Empagliflozin can enhance fatty acid oxidation and increase ketone body utilization, which improves

myocardial ATP production and reduces remodeling, thus improving cardiac energy metabolism.[38]

Direct cardioprotective mechanisms of SGLT2 inhibitors

Studies confirmed that the cardiac tissue lacks SGLT2 expression on its surface. This finding prompted the need for more studies assessing the cardioprotective effect of SGLT2 inhibitors.[39] It has been suggested that SGLT2 inhibitors do its cardioprotective effect through exerting a diuretic effect via glomerular reabsorption, which can reduce cardiac load and blood volume, thus protecting the heart by decreasing myocardial oxygen consumption.

Assuming that SGLT2 inhibitors cardioprotective effect is attributed to its diuretic effect and this diuretic effect relies on blood glucose concentration, the cardiac benefit of SGLT2 inhibitors in non-diabetic patients remains unclear.[40] As a result, it is proposed that the SGLT2 inhibitors exert protective effects directly on the heart. Several studies indicated that the SGLT2 inhibitors can reverse cardiac remodeling. This finding suggests that SGLT2 inhibitors not only have a cardioprotective effect through their systemic effect (diuretic effect), but they also have a direct effect on the heart.[41,42]

Sodium-glucose cotransporter 2 inhibitors affect the heart through countering the pathological cardiac remodeling. Pathological cardiac remodeling is characterized by changes in the size and morphology of the left ventricle. Additionally, cardiac structural function is evaluated by the LV ejection fraction (LVEF) and left ventricular (LV) mass index (LVMI).[43] It is also assessed by left atrial volume index (LAVI), LV end-systolic volume (LVESV), and LV end-diastolic volume (LVEDV). It was found that SGLT2 inhibitors improved cardiac function through increasing LVEF and decreasing LVEDV, LVESV, LAVI and LVMI.[44,45] Cardiac fibrosis and cardiac hypertrophy are also among the pathological processes in cardiac remodeling. These changes can significantly affect the prognosis of different cardiovascular diseases.[46,47]

It was stated that SGLT2 inhibitors are associated with an inhibition or attenuation in cardiac fibrosis and cardiomyocyte hypertrophy. SGLT2 inhibitors can regulate various signaling pathways in numerous models, such as left coronary artery ligation MI, transverse aortic constriction and diabetes.[48,49]

Future directions and research gaps

Ongoing research is investigating the potential clinical applications of SGLT2 inhibitors in various medical conditions. Using SGLT2 inhibitors as an obesity treatment is being assessed due to their weight loss effect through enhancing loss of glucose in urine and appetite control.[50] The DAPA-CKD trial examined the renoprotective effects of SGLT2 inhibitors in chronic kidney disease in diabetic and non-diabetic patients, and the results are promising.[51] They also show potentially improved liver function and decreased hepatic fat in non-alcoholic fatty liver disease.[52]

However, crucial research gaps still need to be discussed. The exact mechanisms of SGLT2 inhibitors in cardiovascular and renal fields remain unclear. Other challenges such as deciding the most suitable individuals for SGLT2 inhibitors and the interaction between these inhibitors and other diabetes drugs remain unclear. Additionally, there is a need to address the long-term safety of SGLT2 inhibitors.[14]

CONCLUSION

Recently, SGLT2 inhibitors showed a great improvement in the management of type 2 DM and cardiovascular diseases. Studies proved that SGLT2 inhibitors can reduce renal and cardiovascular risks and are associated with improved metabolic profiles, decreased hospitalizations, reduced cardiovascular mortality, and improved heart function in different heart failure phenotypes, as shown by multiple clinical trials, such as EMPEROR-Reduced and EMPA-REG OUTCOME. In addition, SGLT2 inhibitors show potential in cardio-oncology, as they have proven effective in mitigating cardiotoxicity in cancer patients. SGLT2 inhibitors are leading a paradigm shift toward integrated, multi-faceted disease management. New therapeutic strategies are going to be developed for patients with diabetes and cardiovascular diseases. More research is necessary to assess their benefits in non-diabetic populations and other clinical applications.

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REFERENCES

1. Mondal S, Pramanik S, Khare VR, Fernandez CJ, Pappachan JM. Sodium glucose cotransporter-2 inhibitors and heart disease: Current perspectives. World J Cardiol. 2024;16(5):240-59.
2. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovascular Diabetol. 2018;17(1):83.
3. Ni L, Yuan C, Chen G, Zhang C, Wu X. SGLT2i: beyond the glucose-lowering effect. Cardiovas. 2020;19(1):98.
4. Home PD, Pocock SJ, Beck-Nielsen H. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet (London, England). 2009;373(9681):2125-35.

5. Wilcox T, De Block C, Schwartzbard AZ, Newman JD. Diabetic Agents, From Metformin to SGLT2 Inhibitors and GLP1 Receptor Agonists: JACC Focus Seminar. J Am Coll Cardiol. 2020;75(16):1956-74.
6. Zinman B, Lachin JM, Inzucchi SE. Empagliflozin, Cardiovascular outcomes, and mortality in type 2 diabetes. The New England J Med. 2016;374(11):1094.
7. Lawton JS, Tamis-Holland JE, Bangalore S. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(3):e18-114.
8. 8. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European heart journal. 2021;42(36):3599-3726.
9. Braunwald E. Gliflozins in the Management of Cardiovascular Disease. The New England J Med. 2022;386(21):2024-34.
10. Nasiri AR, Rodrigues MR, Li Z, Leitner BP, Perry RJ. SGLT2 inhibition slows tumor growth in mice by reversing hyperinsulinemia. Cancer & Metabol. 2019;7:10.
11. Villani LA, Smith BK, Marcinko K. The diabetes medication Canagliflozin reduces cancer cell proliferation by inhibiting mitochondrial complex-I supported respiration. Molecular Metabol. 2016;5(10):1048-56.
12. Wu W, Zhang Z, Jing D, et al. SGLT2 inhibitor activates the STING/IRF3/IFN-β pathway and induces immune infiltration in osteosarcoma. Cell Death Dis. 2022;13(6):523.
13. Training C. Chapter 4: Searching for and selecting studies. Available at: https://training.cochrane. Accessed on 13 November 2024.
14. Fatima A, Rasool S, Devi S. Exploring the cardiovascular benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors: expanding horizons beyond diabetes management. Cureus. 2023;15(9):46243.
15. Neal B, Perkovic V, Mahaffey KW. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377(7):644-57.
16. Johnston R, Uthman O, Cummins E, et al. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. Health technology assessment (Winchester, England). 2017;21(2):1-218.
17. Packer M, Anker SD, Butler J, Filippatos G, Zannad F. Effects of Sodium-Glucose Cotransporter 2 Inhibitors for the Treatment of Patients With Heart Failure: Proposal of a Novel Mechanism of Action. JAMA Cardiol. 2017;2(9):1025-9.
18. Heidenreich PA, Bozkurt B, Aguilar D. AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):895-1032.
19. McMurray JJV, DeMets DL, Inzucchi SE. 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). European J Heart Fail. 2019;21(5):665-75.
20. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. The New England J Med. 2021;385(16):1451-61.
21. Lenneman CG, Sawyer DB. Cardio-Oncology: An Update on Cardiotoxicity of Cancer-Related Treatment. Circulation. 2016;118(6):1008-20.
22. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of Anthracyclines. Frontiers in Cardiovas. 2020;7:26.
23. Gongora CA, Drobni ZD, Quinaglia Araujo Costa Silva T. Sodium-glucose co-transporter-2 inhibitors and cardiac outcomes among patients treated with anthracyclines. JACC Heart. 2022;10(8):559-67.
24. Abdel-Qadir H, Carrasco R, Austin PC. The association of sodium-glucose cotransporter 2 inhibitors with cardiovascular outcomes in anthracycline-treated patients with cancer. JACC Cardio Oncol. 2023;5(3):318-28.
25. Zelniker TA, Wiviott SD, Raz I. 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 (London, England). 2019;393(10166):31-9.
26. 26. Chen B, Guo J, Ye H, Wang X, Feng Y. Role and molecular mechanisms of SGLT2 inhibitors in pathological cardiac remodeling (Review). Molecular medicine reports. 2024;29(5).
27. Wiviott SD, Raz I, Bonaca MP. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. The New England J Med. 2019;380(4):347-57.
28. Bose D, Maurya M, Konwar M. Impact of sodium-glucose co-transporter 2 inhibitors on renal outcomes in patients of diabetes mellitus: A meta-analysis of landmark renal and cardiovascular outcome trials. Indian J Pharmacol. 2023;55(2):119-27.
29. Vaduganathan M, Docherty KF, Claggett BL. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet (London, England). 2022;400(10354):757-67.
30. Heerspink HJL, Stefánsson BV, Correa-Rotter R. Dapagliflozin in patients with chronic kidney disease. The New England J Med. 2020;383(15):1436-46.
31. Verma S, Rawat S, Ho KL. Empagliflozin increases cardiac energy production in diabetes: novel translational insights into the heart failure benefits

of sglt2 inhibitors. JACC Basic to Translational Sci. 2018;3(5):575-87.
32. Wada T, Mori-Anai K, Kawaguchi Y. Renal, cardiovascular and safety outcomes of canagliflozin in patients with type 2 diabetes and nephropathy in East and South-East Asian countries: results from the canagliflozin and renal events in diabetes with established nephropathy clinical evaluation trial. J of Diabetes Investig. 2022;13(1):54-64.
33. Jyotsna F, Mahfooz K, Patel T, et al. A Systematic Review and Meta-Analysis on the Efficacy and Safety of Finerenone Therapy in Patients with Cardiovascular and Chronic Kidney Diseases in Type 2 Diabetes Mellitus. Cureus. 2023;15(7):41746.
34. Aimo A, Castiglione V, Borrelli C. Oxidative stress and inflammation in the evolution of heart failure: From pathophysiology to therapeutic strategies. European journal of preventive cardiology. 2020;27(5):494-510.
35. Kolijn D, Pabel S, Tian Y, et al. Empagliflozin improves endothelial and cardiomyocyte function in human heart failure with preserved ejection fraction via reduced pro-inflammatory-oxidative pathways and protein kinase Gα oxidation. Cardiovascular research. 2021;117(2):495-507.
36. Wang J, Huang X, Liu H. Empagliflozin ameliorates diabetic cardiomyopathy via attenuating oxidative stress and improving mitochondrial function. Oxidative medicine and cellular longevity. 2022;2:1122494.
37. De Jong KA, Lopaschuk GD. Complex energy metabolic changes in heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. The Canadian J of Cardiol. 2017;33(7):860-71.
38. Li X, Lu Q, Qiu Y. Direct cardiac actions of the sodium glucose co-transporter 2 inhibitor empagliflozin improve myocardial oxidative phosphorylation and attenuate pressure-overload heart failure. J Am Heart Associ. 2021;10(6):e018298.
39. Van Steenbergen A, Balteau M, Ginion A. Sodium-myoinositol cotransporter-1, SMIT1, mediates the production of reactive oxygen species induced by hyperglycemia in the heart. Scientific reports. 2017;7:41166.
40. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nature reviews Cardiology. 2020;17(12):761-72.
41. Tripolt NJ, Kolesnik E, Pferschy PN. Impact of EMpagliflozin on cardiac function and biomarkers of heart failure in patients with acute MYocardial infarction-The EMMY trial. American heart journal. 2020;221:39-47.
42. Lewinski D, Tripolt NJ, Sourij H. Ertugliflozin to reduce arrhythmic burden in ICD/CRT patients (ERASe-trial) - A phase III study. Am Heart J. 2022;246:152-60.
43. Aimo A, Vergaro G, González A. Cardiac remodelling-part 2: clinical, imaging and laboratory findings. a review from the study group on biomarkers of the heart failure association of the european society of cardiology. European J Heart Fai. 2022;24(6):944-58.
44. Lee MMY, Brooksbank KJM, Wetherall K. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). Circulation. 2021;143(6):516-25.
45. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA. Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction. J Am Coll Card. 2021;77(3):243-55.
46. Wu QQ, Xiao Y, Yuan Y. Mechanisms contributing to cardiac remodelling. Clinical Sci. 2017;131(18):2319-45.
47. Frangogiannis NG. Cardiac fibrosis. Cardiovas. 2021;117(6):1450-88.
48. Yurista SR, Silljé HHW, Oberdorf-Maass SU. Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. European J Heart Failure. 2019;21(7):862-73.
49. Habibi J, Aroor AR, Sowers JR. Sodium glucose transporter 2 (SGLT2) inhibition with empagliflozin improves cardiac diastolic function in a female rodent model of diabetes. Cardiovas Diabetol. 2017;16(1):9.
50. Anker SD, Khan MS, Butler J. Weight change and clinical outcomes in heart failure with reduced ejection fraction: insights from EMPEROR-Reduced. European J Heart Fail. 2023;25(1):117-27.
51. Wheeler DC, Stefánsson BV, Jongs N. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. The lancet Diabetes & Endocrinol. 2021;9(1):22-31.
52. Huang G, Cheng Z, Hildebrand A. Diabetes impairs cardioprotective function of endothelial progenitor cell-derived extracellular vesicles via H3K9Ac inhibition. Theranostics. 2022;12(9):4415-30.

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