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Non-Diabetic Indications of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors: A review Study

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Abstract

Background: In 2018, Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i) were approved as a strong second-line therapy after metformin for diabetic patients with defined atherosclerotic cardiovascular diseases (ASCVD), heart failure (HF), and chronic kidney disease (CKD). Large-scale clinical trials showed a considerable decline in the cardiovascular death, hospitalization for heart failure, and prognosis for kidney disease.

Objective: To determine if patients without diabetes could benefit clinically from using SGLT2i.

Methods: Review the impact of SGLT2i in the non-diabetic arm in eight large-scale trials. The patients that were recruited had established heart failure (reduced or preserved ejection fraction), myocardial infarction, or chronic kidney disease.

Results: In four large-scale trials that included non-diabetic patients with heart failure, two trials that recruited patients with myocardial infarction, and two studies involving chronic renal diseases, SGLT2i approved a significant reduction of cardiovascular death and/or the rate of hospitalization.

Conclusion: SGLT2i have shown proven clinical benefits beyond glycemic control. Multiple mechanisms contribute to the therapeutic impact of SGLT2i in non-diabetic patients with heart failure, chronic kidney disease, and myocardial infarction.

الاستخدامات غير السكريّة لمثبطات ناقل الصوديوم والجلوكوز المشترك 2 (SGLT2): دراسة مراجعة

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الخلاصة

المقدمه: في عام 2018، اعتُمدت مثبطات ناقل الصوديوم والجلوكوز المشترك 2 (SGLT2i) كعلاج مؤثر من الخط الثاني بعد "الميتفورمين" لمرضى السكري الذين يعانون من أمراض القلب والأوعية الدموية الناجمة عن تصلب الشرايين (ASCVD)، وفشل القلب (HF)، وأمراض الكلى المزمنة (CKD). وقد أظهرت تجارب سريرية واسعة النطاق انخفاضاً ملحوظاً في وفيات القلب والأوعية الدموية، وحالات دخول المستشفى بسبب فشل القلب، وتحسناً في مآل أمراض الكلى.

الهدف: تحديد مدى الاستفادة السريرية للمرضى غير المصابين بالسكري من استخدام مثبطات (SGLT2i).

المنهجية: مراجعة تأثير (SGLT2i) على المجموعات غير المصابة بالسكري ضمن ثماني تجارب سريرية واسعة النطاق. شملت الدراسة مرضى يعانون من فشل القلب المؤكد (مع كسر قذفي منخفض أو محفوظ)، واحتشاء عضلة القلب، أو أمراض الكلى المزمنة.

النتائج: أثبتت مثبطات (SGLT2i) من خلال أربع تجارب واسعة النطاق شملت مرضى فشل القلب غير المصابين بالسكري، وتجربتين شملتا مرضى احتشاء عضلة القلب، ودراستين حول أمراض الكلى المزمنة؛ وجود انخفاض جوهري في وفيات القلب والأوعية الدموية و/أو معدلات الاستشفاء (دخول المستشفى).

الاستنتاج: أظهرت مثبطات (SGLT2i) فوائد سريرية مثبتة تتجاوز السيطرة على مستويات السكر في الدم. وتساهم آليات متعددة في التأثير العلاجي لهذه المثبطات لدى المرضى غير المصابين بالسكري ممن يعانون من فشل القلب، وأمراض الكلى المزمنة، واحتشاء عضلة القلب.

1. Introduction

The twenty-first century has witnessed the emergence of novel extra-pancreatic approaches in the management of Type 2 Diabetes Mellitus (T2DM). These new pathways aim to improve glycemic control and reduce common adverse events, such as hypoglycemia, as ultimate goals (Dave, 2023). These extra-pancreatic mechanisms have exhibited potential therapeutic advantages, with accumulated evidence capable of reshaping the clinical guidelines for the interrelated metabolic disorders, including cardiovascular diseases, chronic kidney disease, metabolically unhealthy obesity, Non-alcoholic fatty liver disease (NAFLD), and polycystic ovarian syndrome (PCOS) (Iriowen et al., 2023). Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors were among the newly emerged oral antihyperglycemic agents with a high possibility of advantages and cumulative evidences beyond T2DM

1.1.SGLT2 Physiological Function in Glucose Hemostasis

In the renal proximal convoluted tubules, specifically on the brush border of the apical epithelial surface, SGLT2 appears as a principal mechanism responsible for glucose reabsorption after being freely filtered from the glomerulus (Wright, 2021). The vast majority of glucose molecules are absorbed via SGLT2 at a rate of 80-90%; the remainder is handled by the low-capacity SGLT1 in the terminal proximal tubules (Liu and Defronzo, 2012). A secondary active transportation process governs glucose reabsorption, where a basolateral-positioned Na/K pump ensures the creation of an electrochemical sodium gradient. This gradient is then utilized by the apical SGLT2 for the reabsorption of a glucose molecule accompanied by a sodium ion. The intracellular glucose then diffuses into the bloodstream via the GLUT2 transporter (Han et al., 2022). SGLT2 is predominantly distributed in the S1 and S2 segments of the proximal convoluted tubules in the kidneys, where glucose reabsorption occurs. However, it is essential to note that in the CNS, SGLT2 plays a possible role in regulating glucose transportation through the blood-brain barrier (Hummel et al., 2022). They were detected, for example, in the hypothalamus, nucleus tractus solitarius, and amygdala. A neuroprotective activity of SGLT2 inhibitors can be result from their ability to reduce the neuroinflammatory process, providing neuronal plasticity in stroke and Alzheimer's disease (Pawlos et al., 2021). These transporters have been detected to a less abundance in the cardiomyocytes (Cinti et al., 2025).

1.2.SGLT2 Inhibitors: Structure and Function

Generally, SGLT2 inhibitors comprise two moieties, glycone and aglycone. All SGLT2i share the possessing of a glucose moiety as a glycone part, which competes the filtrated glucose on the SGLT2 protein binding site in the convoluted proximal tubules. Conversely, the aglycone part tends to stabilize the binding of SGLT2i sugar moiety to the SGLT2 receptors (Scheen, 2014). This, in turn, inhibits glucose transporting for a relatively long duration, approximately 12 hours, depending on the affinity of the SGLT2i member to the aromatic residue of the transporter protein. The variation among different SGLT2i, in terms of pharmacokinetic properties, is mainly determined by the chemical structure of the aglycone part (Isaji, 2011). This structural diversity contributes to the distinct pharmacological profiles and clinical outcomes observed with different SGLT2 inhibitors.

1.3.The Timely Evolution of SGLT2 Inhibitors' Impact on Guidelines of Diabetes and Beyond

The discovery of SGLT2 inhibitor dates back to 1835, when Phlorizin, a naturally occurring substance from the bark of apple trees, was isolated. Phlorizin was believed to possess potential antipyretic, antimalarial, and anti-infectious activity (Choi, 2016). During the thirteen of the last century, Phlorizin was tested to induce glycosuria through blocking glucose reabsorption with an ability to reduce blood glucose levels. However, its poor oral absorbability and interfering with glucose reabsorption

with organs other than kidneys were serious obstacles to develop it as an antihyperglycemic agent. Anyhow, this was the spark that the concept of SGLT2 inhibitors was developed as promised extra-pancreatic drug to manage T2DM (Tian et al., 2021).

The European Medicine Agency (EMA) was the first institution to approve Dapagliflozin as the prototype of newly-emerged antihyperglycemic family, named SGLT2 Inhibitors, in 2012. On March 29th 2013, Canagliflozin was approved by the Food and Drug Administration (FDA) as a first SGLT2 inhibitor in USA. Empagliflozin was then approved in August 2014. Ertugliflozin, Bexagliflozin, and Ipragliflozin were approved later, bringing the total number of approved SGLT2 inhibitors worldwide to six (Braunwald, 2022). For five years (2013-2018), SGLT2 inhibitors were mentioned in the American Diabetic Association and European Association for the Studies of Diabetes (ADA/EASD) guidelines as one of the antihyperglycemic agents. A dramatic update was conducted by these institutions in 2018 when new essential approach for managing T2DM in patients with established cardiovascular diseases and/or chronic kidney diseases was born, based on the cardiovascular and renal protective capabilities of SGLT2i and Glucoagn-like peptide receptor agonists (GLP-1 agonists) (Wilcox et al, 2020). The clinical evidences have decisively ensured the impact of SGLT2i even in non-diabetic patients when certain agents, like Dapagliflozin and Empagliflozin, gotten FDA approval in patients with heart failure and chronic kidney diseases (Mark et al., 2023). SGLT2i were officially adopted in several clinical practice guidelines for non-diabetic patients, for example not limited to, KDIGO (Kidney Disease: Improving Global Outcomes) 2020 guidelines which SGLT2i mentioned as an option in the treatment of chronic kidney disease when the glomerular filtration rate falls below 30ml/min/1.73m^2. The limit was redefined in 2022 down to 20ml/min/1.73m^2, because of its continuously noticed nephroprotective activity (Lv et al., 2023). In 2023, European Society of Cardiology (ESC) also expanded the use of SGLT2i for all patients with heart failure including early initiation of SGLT2i in hospitalized patients with acute heart failure (Mazzotta et al., 2025). This paper reviewed eight large-scale clinical trials in which non-diabetic patients were included. All of them are randomized, double-blind, multicenter, placebo-controlled, with different clinical end-points. These evidences represent the milestone of sglt2i activity beyond diabetes. The patients' profile can be categorized into three clinical domains: heart failure, chronic kidney disease, and myocardial infarction. The sequence of studies depends on the time of publication in each of these three domains:

2. SGLT2i in Nondiabetic Patients with Heart Failure

2.1.Dapagliflozin And Prevention of Adverse Outcomes in Heart Failure (DAPA-HF)

The DAPA-HF trial enrolled 4,744 patients with reduced heart failure (Ejection Fraction ≤ 40%), classified as class II-IV New York Heart Association definition. Of these, 2,605 were non-diabetic patients. The non-diabetic patients received 10mg of Dapagliflozin once daily for a median duration of 18.2 months. The primary goal was to assess the benefits of adding SGLT2i to usual care in reducing cardiovascular death, heart failure hospitalization, or visits. Dapagliflozin demonstrated an absolute risk reduction of 4.95% compared to the placebo arm. Notably, a significant reduction in all-cause mortality was observed among non-diabetic patients (9.6% vs. 11.5% of cardiovascular death in favor of Dapagliflozin). The study concluded that Dapagliflozin provided consistent clinical benefits for both diabetic and non-diabetic patients (McMurray et al., 2019).

2.2.Empagliflozin Prognosis Evaluation Reduction in Outcomes in Real-world Effects Data (EMPEROR REDUCED)

The EMPEROR-REDUCED trial involved 3,730 patients with symptomatic heart failure and reduced left ventricular pumping activity, in which the Left Ventricular Ejection Fraction (LVEF) was ≤ 40%. Non diabetic patients comprised approximately 50% of the total enrolled patients (1,874), with 1,268 classified as prediabetic and 606 patients were normoglycemic. Patients received 10mg of Empagliflozin once daily for a median of 16 months. The primary goal was to a composite endpoint assessing

time to first death or hospitalization due to heart failure complications. Empagliflozin reduced cardiovascular death by 25% and heart failure hospitalization by 30% with consistent results in diabetic and non-diabetic patients (Packer et al., 2020).

2.3.Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-PRESERVED)

The EMPEROR-PRESERVED trial recruited 5,988 patients with preserved ejection fraction (HFpEF, ejection fraction > 40%). Patients received 10 mg Empagliflozin once daily for 26.2 months. However, the study outcomes did not clarify the number of nondiabetic patients. The composite cardiovascular death, event and hospitalization was significantly lower in the Empagliflozin group (13.8% vs. 17.1% in placebo group), with a notion that lower risk of hospitalization contributes to a greater extent in these findings. The authors ensured that Empagliflozin effect was consistent in both diabetic and nondiabetic patients (Anker et al., 2021).

2.4.Dapagliflozin Evaluation to Improve the LIVES of Patients with Preserved Ejection Fraction Heart Failure (DELIVER)

The DELIVER trial enrolled 6,263 patients with left ventricular ejection fraction ≥ 40, symptomatic heart failure (NYHA Class II-IV, natriuretic peptide level of ≥ 300 pg/ml), and structural heart disease (valves, cahmbers, or walls). The patients received 10mg of Dapagliflozin for a mean duration of 27.6 months. Non-diabetic patients comprised 55% of the study population (3,457). Dapagliflozin reduced the composite endpoint of cardiovascular death or worsening heart failure by 18%, with a significant reduction in cardiovascular death and heart failure hospitalization (Solomon et al., 2022).

3. SGLT2i in Non-diabetic patients with Chronic Kidney Disease

3.1.Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (Dapa-CKD)

The DAPA-CKD trial enrolled 4,304 patients with chronic kidney disease (eGFR 25-75 ml/min/1.73 m^2, urinary albumin-to-creatinine ratio of 200-5000mg/g in both diabetic and non-diabetic patients). Non-diabetic patients comprised 32.5% of the study population (1,398). The main causes of CKD in non-diabetic patients were ischemic nephropathy, hypertensive nephropathy, or chronic glomerulonephritis. The primary goals of this trial was a composite end-point gathers a sustained decline in eGFR ≥ 50% of its initial value, end stage kidney disease, death due to renal or cardiovascular reasons. Dapagliflozin reduced the composite endpoint of kidney disease progression or cardiovascular death by 39%. It also showed a significant reduction in all-cause mortality by 31%. In concern to non-diabetic patients, Dapagliflozin arm exhibited 49% relative risk reduction of the composite primary end-point, 52% reduction of relative risk of all-cause of death. This indicates a significant Reno protectivity in non-diabetic patients with CKD (Heerspink et al., 2020).

3.2.The Study of Heart and Kidney Protection with Empagliflozin (EMPA-Kidney)

The EMPA-Kidney trial recruited 6,609 patients with chronic kidney disease (eGFR was either ranging from 20-45 ml/min./1.73m^2, or between 45-90 ml/min./1.73m^2 with a urinary albumin-to-creatinine ratio ≤ 200 mg/g).10mg of Empagliflozin once a day was given to the non-diabetic enrolled patients. On the other hand, the diabetic patients received 20mg of Empagliflozin once a day. 54% of the study population was non-diabetic (3,569). The primary end-point of this trial was a composite of CKD progression or cardiovascular-related death. Kidney disease progression was defined in term of occurrence of end-stage kidney disease or ≥ 40% reduction of eGFR. Regardless to diabetes, the total population exhibited 28% reduction of composite end-point comparing to placebo. 14% reduction of all-cause hospitalization was seen in Empagliflozin arm. No significant reduction was noticed in the reduction of cardiovascular death. However, almost 50% reduction in eGFR decline was reported in patients on Empagliflozin. In non-diabetic patients, there was a statistical

significance in the reduction of the primary end-point in favor of Empagliflozin (12.3% vs. 16.8%). The reduction of cardiovascular death and kidney disease progression was consistent in both diabetic and non-diabetic groups (The EMPA-KIDNEY Collaborative Group, 2023).

4. SGLT2i in non-diabetic patients with defined myocardial infarction

4.1.Dapagliflozin After Patients with Myocardial Infarction (DAPA-MI)

It's the first large-scale clinical trials recruited only non-diabetic patients for the use of SGLT2i. 10mg of Dapagliflozin once a day for a mean of 12 months. The total number of the study was 4,017 patients, in which all of them were neither have diabetes mellitus nor chronic heart failure. The primary end-point was set as a hierarchical composite outcome involving the following components arranged based on the following order: all-cause of death, hospitalization for heart failure, nonfatal myocardial infarction, atrial flutter or fibrillation, new diagnosis of diabetes mellitus type 2, improvement in New York Heart Association functional class, and finally 5% reduction of body weight or more. In November 2023, the findings of this trial demonstrated. There was a win ratio of the hierarchical composite endpoint in 1.34 in favor of Dapagliflozin arm ($P < 0.001$). Diving in the details, while there was a significant improvement in the NYHA functional class and the cardiometabolic findings (such as newly development of T2DM, 5% reduction of body weight); there were no significant results regarding death, hospitalization due to heart failure, non-fatal MI, and atrial fibrillation/flutter. No unexpected adverse events were noted. Urinary genital infection and diabetic ketoacidosis were, as expected, higher in Dapagliflozin arm (Petrie et al., 2025).

4.2.EMPAgliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction (EMPACT-MI)

EMPACT-MI enrolled 6522 patients received 10mg of Empagliflozin once a day for median of 17.9 months. The non-diabetic patients represented 60.4% out of the total enrolled patients (3920). The study enrolled patients with acute myocardial infarction. The patients also should be defined at a high risk to develop heart failure (symptomatic congestion or newly reduced left ventricular ejection fraction ($\leq 45\%$). In addition, one more high-risk indicator should be present like, age, T2DM, prior MI or others). The primary goal of the trial was a composite outcome which included first hospitalization for heart failure or death. While Empagliflozin did not show a significant reduction in the composite end-point, however, there was a significant reduction in the first and total number of heart failure hospitalization in patients with lower risk cardiac risk. Those results were consistent with the non-diabetic patients (James et al., 2024). Table1 simply summarizes the details the demographic, the clinical characteristics, and the descriptive statistics of the reviewed clinical trials.

Table1: Summary of The Reviewed Clinical Trials Involved Nondiabetic Patients on SGLT2 Inhibitors

Study Name, year of publication, journal	Non-Diabetic/Total Population	Patients' clinical main condition	Study duration in month	Drug received	Primary Study End-point	Primary Outcome		
						Total Study Population	Diabetic Patients	Non-diabetic Patients
DAPA-HF 2019, NEJM	2605/4744 (55%)	HFrEF	18.2	Dapagliflozin 10mg	Composite: Worsening heart failure. Cardiovascular death.	Hazard Ratio **0.74** p<0.001	**0.75**	**0.73**
EMPEROR-Reduced 2020,NEJM	1874/3730 (50%)	HFrEF	16	Empagliflozin 10mg	Composite: time-to- 1st event: Cardiovascular death. Hospitalization for HF.	Hazard Ratio **0.75** p<0.001	**0.72**	**0.78**
EMPEROR-Preserved 2021, NEJM	3050/5988 (51%)	HFpEF	26.2	Empagliflozin 10mg	Composite: Cardiovascular death. Hospitalization for HF.	Hazard Ratio **0.79** p<0.001	**0.79**	**0.78**
DELIVER 2022,NEJM	3457/ 6263 (55%)	HFpEF	27.6	Dapagliflozin 10mg	Composite: Worsening HF event. Cardiovascular death.	Hazard Ratio **0.82** p<0.001	**0.83**	**0.81**
DAPA-CKD 2020, NEJM	1398/3404 (41%)	CKD	29	Dapagliflozin 10mg	Composite: 1st occurrence of any of: ≥50% of eGFR. ESKD. Death due kidney or CV Causes.	Hazard Ratio **0.61** p<0.001	**0.64**	**0.50**
EMPA-KIDNEY 2023, NEJM	3569/6609 (54%)	CKD	24	Empagliflozin 10mg	Composite: Kidney disease progression. Death Due to CV death.	Hazard Ratio **0.72** p<0.001	0.64	0.82
EMPACT-MI 2024, NEJM	4441/6522 (60%)	MI	17.9	Empagliflozin 10mg	Composite: Time to 1st hospitalization for HF. All-cause mortality.	Hazard Ratio **0.9** p<0.21	0.97	0.85
DAPA-MI 2023, NEJM	0/4017	MI	30	Dapagliflozin 10mg	Hierarchical Composite Outcome: Death. Hospitalization for HF. Nonfatal MI. Atrial Fibrillation/ Flutter. New-onset T2DM NYHA Functional Classification. Body weight reduction≥5%.	Win Ratio **1.34** p>0.001	-	1.34

4.3.Suggested Mechanisms of SGLT2 Inhibitors in Multifaceted Indications other than T2DM

Heart Failure: Due to the early observation of reduced hospitalization of patients with HFrEF in the DAPA-HF trial, it was believed that the underlying mechanism diverges from the time-consuming impact of SGLT2i to achieve cardiovascular benefits. The diuretic activity of SGLT2i plays a crucial role in alleviating heart failure symptoms by reducing preload volume. This is accomplished through interaction with Sodium-Hydrogen Exchanger 3 (NHE3), located adjacent to SGLT2 on the brush boarder of proximal tubules. NHE3 activity is markedly increased in heart failure patients, leading to a blunted natriuretic response, which reduces sodium reabsorption and increases diuresis (Verma, Patel, and Waikar, 2020). In the myocardium, SGLT2i may modulate NHE1 function, a regulatory protein that exhibits overactivity in heart failure patients in response to compensatory activation of sympathetic neurons and the renin-angiotensin-aldosterone system, resulting in chronically elevated sodium ions in cardiomyocytes. The progressive elevation of intracellular sodium reverses the mode of action of sodium-calcium exchange, leading to calcium intracellular overload. Elevated calcium levels trigger myocardial damage, inducing ventricular hypertrophy, apoptosis, and myocardial fibrosis. SGLT2i's ability to inhibit NHE1 slows this cascade (Packer, 2017). Heart failure is also a predisposing factor of cardiac fibrosis. Injured cardiomyocytes activate macrophages, perivascular and endothelial cells to produce inflammatory mediators, profibrotic signals, and growth factors, such as transforming growth-factor (TGF-β), triggering fibroblast transformation into myofibroblasts, which excessively produce collagen and other extracellular proteins, leading to cardiac fibrosis (Aujla and Kssiri, 2021; Travers et al., 2016). SGLT2i induce a negative caloric state due to decreased renal glucose reabsorption, potentially activating 5'-adenosine monophosphate-activated protein kinase (AMPK), which exhibits a pro-fibrotic inhibitory role through downregulating TGF-β growth factor and inhibiting fibroblast transformation (Qi et al., 2017; Rolski and Maczewski, 2025). As illustrated in the EMPEROR-PRESERVED trial, SGLT2i significantly reduces cardiovascular death and hospitalization rates for heart failure in patients with HFpEF, where obesity-related factors like adipokines contribute to disease progression (Theodorakis et al., 2024). Retinol-binding protein4 (RBP4), Interlukein-6, and tumor necrosis factor-α (TNF-α) are examples of pro-inflammatory adipokines elevated in HFpEF patients (Mazurkiewicz et al., 2025). SGLT2i modulate macrophages activity, attenuating pro-inflammatory adipokines production through Toll-like receptor 4/nuclear factor kappa-B (TLR4/NF-Kb) signaling inhibition and increasing. On the other hand, SGLT2i increase anit-inflammatory adipokines like adiponektin (Cinti et al., 2025). Chronic Kidney Disease: Although evidences for renal protection activity of SGLT2i in non-diabetic patients are significant; they are not as robust as cardiac protection evidences. Trials designs were primarily tailored for diabetic patients, excluding important CKD subgroups like dialysis, polycystic kidney disease, hyperkalemia, and very low eGFR (Lv et al., 2023; Mark et al., 2023, Nuffield Department of Population Health Renal Studies Group, 2022; Yau et al., 2022). However, large-scale clinical trials for CKD patients were fewer than those assessing other common diseases, consistent with the fact that only angiotensin-converting-enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonist finerenone have proven effective in slowing kidney function decline (Bakris et al., 2020; Ruggenenti et al., 1999). Hemodynamic effects of SGLT2i may represent major nephroprotective influences in non-diabetic patients (Vallon, 2022), reducing intraglomerular pressure secondary to natriuretic effects and osmotic diuresis, lowering physical stress on the glomerular barrier (Miyata, Zhang, and Chan, 2021). Another suggested mechanism is the metabolic theory, where SGLT2i shift cellular energy production to lipolysis, reducing oxidative stress, pro-inflammatory signals, and fibrosis (Afsar B. and Afsar R.E, 2023; Vasquez-Rios and Nadhkarni, 2020). Myocardial Infarction: with consistently emerging evidences for reducing hospitalization and major adverse cardiac events, including cardiovascular death, yet, the evidences for SGLT2i use in post-MI are limited so far compared to heart failure

and renoprotective activity (Vallon, 2022). While EMPACT-MI primary end point did not been met; the significant DAPA-MI primary outcome was driven by the win-ratio approached that used to calculate the endpoint. Win ratio approach was mostly driven by the cardiometabolic benefits, like weight reduction (Hernandez et al., 2024). SGLT2i's beneficial impact in non-diabetic post-MI patients is achieved by reduced heart failure hospitalization, improved left ventricular ejection fraction, and enhanced metabolic parameters (Yoo et al., 2024). The mechanisms underlying SGLT2i benefits in heart failure and post-MI patients are closely similar, involving antioxidant and anti-inflammatory activity, improved cardiac energy efficiency, inhibited ventricular remodeling and fibrosis, restoring ionic homeostasis by reducing intracellular concentration of sodium and normalizing that of calcium (Uthman et al., 2018).

Conclusion

In non-diabetic patients, Dapagliflozin and Empagliflozin exhibited consistent reduction in cardiovascular death and hospitalization rates in eight large-scale clinical trials, where the recruited non-diabetic patients were also suffering from heart failure (reduced or heart failure), chronic kidney disease, and myocardial infarction.

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