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REVIEW ARTICLE

The Role of SGLT2 Inhibitors in Cardiovascular Protection Beyond Diabetes: A Comprehensive Review

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ABSTRACT

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have evolved from a new glucose-lowering medication class to essential treatments for managing cardiovascular and kidney diseases. The review investigates SGLT2 inhibitors through their operational mechanisms and their strong clinical results and their growing medical use cases. The study examines the effects of these inhibitors on disease progression for both diabetic and non-diabetic patients.

Background: Sodium-glucose cotransporter 2 inhibitors started as glucose-lowering medications but now serve as drugs that protect both heart and kidney function for every patient who has cardiovascular disease or chronic kidney disease and also present benefits beyond their blood sugar-lowering properties.

Objectives: The review studies SGLT2 inhibitors through their cardiovascular and renal benefits together with their operational mechanisms and major clinical trial results, while showing its increasing usage among people who do not have diabetes.

Methods: The researchers conducted a complete literature review through PubMed and clinicaltrials.gov to discover important randomized controlled trials and meta-analyses and mechanistic investigations which studied cardiovascular results and heart failure and chronic kidney disease and treatment comparison studies from 2015 until 2025.

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Key Findings: The trials from EMPA-REG OUTCOME DAPA-HF EMPEROR-Reduced DAPA-CKD and CREDENCE show that SGLT2 inhibitors decrease cardiovascular mortality and heart failure-related hospital admissions and advancing kidney disease at rates between 25 to 39 percent for people with diabetes and those without. Patients start to see advantages within weeks after starting treatment, which continue to exist for an extended period. The cardioprotective mechanisms function through four main processes which include natriuresis, enhanced cardiac energy metabolism, oxidative stress reduction, and decreased myocardial fibrosis. SGLT2 inhibitors provide higher kidney protection to patients than GLP-1 receptor agonists do.

Limitations: The majority of clinical studies enrolled white participants, while there was insufficient evidence to study acute coronary syndromes and heart failure with preserved ejection fraction in non-diabetic patients.

Conclusions: SGLT2 inhibitors have developed into essential treatment for heart failure and chronic kidney disease because their primary function has changed from glucose reduction. The medication serves as the initial treatment option for protecting heart and kidney health because it demonstrates excellent safety results and strong cardiovascular and kidney protection effects.

KEYWORDS:

• SGLT2 Inhibitors • Cardiovascular Protection • Heart Failure • Chronic Kidney Disease • Renal Outcomes • Dapagliflozin • Empagliflozin • Non-Diabetic Populations • Clinical Trials

INTRODUCTION

The Burden of Cardiovascular Disease and Its Intersection with Diabetes.

Cardiovascular disease is the foremost worldwide health issue, causing 17.9 million deaths annually, along with significant morbidity. Individuals with type 2 diabetes encounter a two to threefold increased risk of heart disease compared to those without diabetes, as their condition heightens the likelihood of acquiring cardiovascular disease. The coexistence of diabetes and cardiovascular disease is a medical challenge that physicians find difficult to manage. Individuals with type 2 diabetes who do not attain comprehensive risk mitigation by conventional glycemic control techniques exhibit a heightened prevalence of three conditions, namely myocardial infarction, stroke, and heart failure. Researchers aimed to develop novel molecules capable of safeguarding cardiovascular health through diverse protective mechanisms that do not rely on glucose reduction for therapeutic applications.[1]

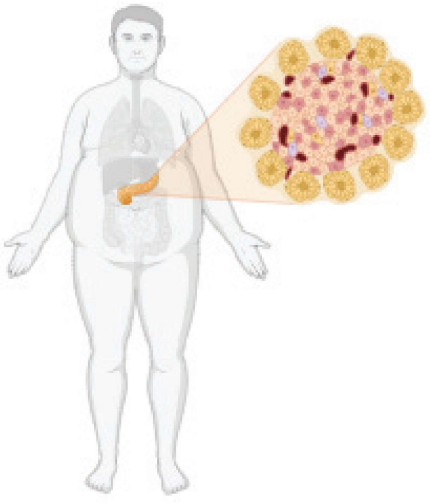

Figure 1: Adult male (obese, anterior, eyes open, with highlighted pancreas) ***Source:*** BioRender.com

Historical Context and the Paradigm Shift

Sodium-glucose cotransporter 2 inhibitors were created as a primary medication following research initiated in 2013, aimed at achieving reductions in hemoglobin A1c

levels between 0.5 and 1.0 percent. The 2015 EMPA-REG OUTCOME experiment fundamentally transformed medical treatment protocols. The pivotal trial demonstrated that empagliflozin reduces cardiovascular mortality by 38 percent and hospitalizations for heart failure by 35 percent in patients with pre-existing cardiovascular illness, far surpassing the standard outcomes of glucose-lowering therapies. Researchers initiated their inquiry into SGLT2 inhibition following an unexpected outcome, which prompted them to explore the mechanisms of SGLT2 inhibitors in the treatment of heart disease and chronic kidney disease in both diabetic and non-diabetic patients.

CURRENT CLINICAL RELEVANCE

The COVID-19 pandemic demonstrated the impact of the virus on heart failure patients, resulting in the expedited implementation of SGLT2 inhibitors based on scientific research in clinical practice. The regulatory agencies expedited the approval of these drugs for diverse medical applications. The American Heart Association, European Society of Cardiology, and American College of Cardiology designated SGLT2 inhibitors as crucial therapies for heart failure and chronic renal disease in their 2024 international guidelines. Current cardiologists, nephrologists, and primary care physicians must comprehend these three facets of the therapy process for their medical practice.[2]

Scope of This Review

The study investigates three research methodologies to analyze the protective effects of SGLT2 inhibitors on cardiac and renal functions. The study investigates the mechanisms by which these materials promote cardiovascular health, utilizing clinical research findings to demonstrate their advantages in treating heart failure and managing chronic kidney disease, as well as their efficacy in non-diabetic patients, safety profile, and comparative performance against novel cardioprotective therapies employing GLP-1 receptor agonists. The evidence-based synthesis furnishes doctors with critical information that aids in patient selection and optimal treatment application.

MECHANISM OF ACTION: FOCUS ON CARDIOPROTECTION

Primary Mechanism: Renal Glucose and Sodium Handling

SGLT2 inhibitors operate by inhibiting the sodium-glucose cotransporter-2 proteins located in the proximal tubules of human renal tissue. The human body typically reabsorbs almost all glucose filtered from the bloodstream back into circulation. The body eliminates glucose via urine when these transporters are obstructed, resulting in a loss of the ability to reabsorb glucose. The mechanism leads to osmotic diuresis as the body eliminates both water and glucose. The body undergoes two concurrent processes, including heightened sodium excretion via natriuresis, whereas studies demonstrate a significant rise in urine sodium levels. The body undergoes several hemodynamic and metabolic changes due to the depletion of glucose and salt. The cardiovascular benefits of SGLT2 inhibitors rely on these physiological changes that occur over time.[3]

Hemodynamic Effects and Cardiac Loading Conditions

SGLT2 inhibitors positively influence the heart's capacity to regulate blood volume and pressure through their diuretic and natriuretic properties. The medications exert their therapeutic effect by enhancing the excretion of sodium and water from the body, leading to a reduction in blood volume and fluid retention. The outcome results in a diminution of left ventricular end-diastolic volume, subsequently lowering left ventricular pressure. The heart requires a reduced blood volume for filling because it receives a smaller volume for processing. The body undergoes a continuous reduction in systolic blood pressure, averaging between 2 to 4 mmHg, hence diminishing afterload. The heart enhances its function as the two systems collaborate to achieve superior ventricular–arterial connection. This illness impacts patients with heart failure as their bodies lose the capacity to regulate regular blood pressure levels. Investigations utilizing biomarkers provide evidence supporting this assertion. SGLT2 inhibitors reduce BNP and NT-proBNP levels, as these biomarkers indicate myocardial wall stress. The DAPA-HF trial results indicate that dapagliflozin medication resulted in a 20% reduction in NT-proBNP levels among patients, whereas the

placebo group exhibited negligible variation. The interval between biomarker alterations and clinical advancement indicates that these hemodynamic effects serve as a principal catalyst for the cardiovascular benefits conferred by these drugs.

Improved Cardiac Energy Metabolism

The scientific accomplishment attained by researchers regarding SGLT2 inhibitors demonstrates its paramount significance in elucidating the impact of these medications on human cardiac metabolism. SGLT2 inhibitors induce cardiac myocytes to transition their principal energy substrate from glucose to fatty acids and ketone bodies. The metabolic change transpires due to elevated amounts of beta-hydroxybutyrate, which the heart utilizes as its principal energy substrate. The cardiac muscle operates more efficiently as fatty acid oxidation generates greater adenosine triphosphate via oxygen utilization compared to glucose oxidation. The heart employs metabolic flexibility to manage its energy demands during episodes of heart failure. Heart failure transpires when the heart depletes its energy stores due to the inability of sick hearts to synthesize ATP and the impairment of their mitochondria. SGLT2 inhibitors induce metabolic alterations that allow mitochondria to regain their oxidative phosphorylation capabilities, thereby increasing ATP generation. Research indicates that empagliflozin and dapagliflozin safeguard mitochondrial complex I and II oxidative phosphorylation by averting the energy depletion associated with progressive heart failure. The body restores its energy through mechanisms that do not necessitate glucose lowering, elucidating why non-diabetic individuals observe favorable outcomes, such as improved cardiac function and enhanced exercise capacity, when treated with SGLT2 inhibitors.[4]

Reduction of Oxidative Stress and Inflammatory Signaling

Oxidative stress serves as a crucial mechanism that leads to the onset and advancement of heart failure and other cardiovascular conditions. SGLT2 inhibitors decrease reactive oxygen species (ROS) production in heart and blood vessel systems through their various operational methods. The drugs boost mitochondrial activity, which results in decreased production of ROS that normally occurs during mitochondrial dysfunction. SGLT2 inhibitors reduce sodium concentration in heart cells through their influence on Na^+/H^+ exchanger activities. The process of sodium overload prevention helps to stop the mitochondrial calcium buildup, which leads to increased ROS generation. SGLT2 inhibitors demonstrate their ability to decrease oxidative stress while simultaneously providing powerful anti-inflammatory benefits. The studies demonstrate that these compounds can impact several signaling networks by activating both STAT3 and PI3K pathways, which result in the inhibition of NF-κB-driven inflammatory responses. The result leads to a decrease in pro-inflammatory cytokines, which include tumor necrosis factor-alpha and interleukin-6. The effects occur in cardiac tissues and throughout the body system, which contributes to improved endothelial functionality and decreased vascular inflammation.

Prevention of Adverse Cardiac Remodeling and Fibrosis

Heart failure progresses through three phases, beginning with myocardial destruction, advancing to cardiac chamber dilation, and culminating in loss of cardiac function. The SGLT2 inhibitors prevent unfavorable remodeling by employing distinct methods that collaboratively obstruct this process. The medication inhibits myocyte fibroblast activation and decreases levels of fibrogenic proteins, including transforming growth factor-beta and CTGF. SGLT2 inhibition leads to diminished macrophage and immune cell infiltration in cardiac tissue, thereby mitigating inflammation that promotes fibrosis progression. The DAPA-LVH trial demonstrated that dapagliflozin medication initiated the reversal of left ventricular remodeling by decreasing left ventricular mass in both diabetic and non-diabetic subjects. The EMMY trial indicated that empagliflozin administration promptly following a myocardial infarction enhanced left ventricular ejection fraction and decreased NT-proBNP levels, signifying the cessation of infarct-related cardiac remodeling.

MAJOR CLINICAL TRIALS: CARDIOVASCULAR OUTCOMES IN DIABETIC POPULATIONS

EMPA-REG OUTCOME: The Watershed Trial

The EMPA-REG OUTCOME trial, released in 2015, provided a foundational framework for researchers to investigate the impact of

SGLT2 inhibitors on cardiovascular health. The researchers executed an extensive investigation across many institutions employing a double-blind methodology to evaluate 7,020 patients with type 2 diabetes and pre-existing cardiac disease. The participants in the study received either empagliflozin at doses of 10 mg or 25 mg or a placebo. The researchers designated the primary endpoint as a composite outcome that included three specific events: cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The data revealed major outcomes that researchers did not anticipate. Empagliflozin treatment yielded primary outcome data indicating a 14 percent reduction, with a hazard ratio of 0.86 and a 95 percent confidence interval ranging from 0.74 to 0.99. Moreover, cardiovascular mortality reduced by 38% (HR 0.62, 95% CI 0.49–0.77), and hospitalizations due to heart failure diminished by 35% (HR 0.65, 95% CI 0.50–0.85). All-cause mortality decreased by 32% (HR 0.68, 95% CI 0.53–0.87). The treatment benefits manifested rapidly, as evidenced by the Kaplan-Meier curves, which indicated disparities between the treatment and placebo groups within the initial months of therapy, suggesting that early hemodynamic alterations were responsible for the effects rather than gradual metabolic changes. The EMPA-REG OUTCOME experiment identified numerous significant findings. The study showed that SGLT2 inhibitors are better for the heart than they are for lowering blood sugar. The study findings indicated a reduction in heart failure hospitalizations attributable to particular cardiac advantages. The study indicated that hemodynamic impacts manifest more rapidly than metabolic processes due to their significant influence on human health, particularly in the context of improving cardiovascular outcomes in patients with heart failure. The experiment resulted in subsequent research that investigated SGLT2 inhibitors in particular groups of heart failure patients.[5]

CANVAS and CANVAS-R: Canagliflozin's Cardiovascular Effects

The CANVAS and CANVAS-R trials examined the effects of canagliflozin on 10,142 people with diabetes who also had cardiovascular disease or were at elevated risk for heart disease. The study concentrated on a triad of medical occurrences: cardiovascular mortality, nonfatal myocardial infarction, and nonfatal cerebrovascular accident. The study's results demonstrated that canagliflozin decreased the composite occurrence of these events by 14 percent, yielding a hazard ratio of 0.86, with a 95 percent confidence interval of 0.75 to 0.97. The findings revealed a 27 percent reduction in hospitalizations due to heart failure, resulting in a hazard rate of 0.73, with a 95 percent confidence interval between 0.55 and 0.97.

The CANVAS program also highlighted safety concerns in conjunction with its research findings. A physician who prescribes canagliflozin bears significant responsibility, as patients may face an elevated risk of lower limb amputations, including those of the toes and feet, as highlighted in a black box warning that delineates this association. The study's results demonstrated that SGLT2 inhibitors possess varying safety profiles, necessitating ongoing monitoring post-clinical studies.

DECLARE-TIMI 58: Dapagliflozin in Established Disease

In the trial titled Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DATE), one cohort was administered a placebo, while the other cohort received dapagliflozin, a medication that inhibits glucose reabsorption in the kidneys. Both groups consisted of people diagnosed with type 2 diabetes. All patients had a history of cardiovascular disease (CVD), as only those with CVD (38%) were included in the study. Researchers aimed to determine if dapagliflozin could mitigate the risk of future cardiovascular events (e.g., heart attacks, heart failure, stroke), irrespective of the participants' prior CVD status. Patients administered dapagliflozin exhibited a notable reduction in the risk of mortality from cardiovascular disease and hospitalization owing to heart failure (17% reduction) relative to those receiving a placebo (HR 0.83; CI 0.73-0.95). Further analysis of the results indicated that the predominant portion of the overall effect is ascribed to a 26% decrease in the number of study participants hospitalized for heart failure (HR 0.74; CI 0.65-0.85). This study's findings further substantiate the efficacy of SGLT2 inhibitors in patients with established cardiovascular disease (CVD) and demonstrate their effectiveness as therapeutic and preventative agents for mitigating future cardiovascular events in individuals without CVD.[6]

HEART FAILURE: PARADIGM-SHIFTING EVIDENCE FROM DEDICATED TRIALS

DAPA-HF: The First Dedicated Heart Failure Trial

The findings from the 2019 study on the effects of Dapagliflozin on the incidence of heart failure deterioration or cardiovascular mortality in individuals with chronic heart failure (DAPA-HF) established that SGLT2 inhibitors are critically significant in the management of heart failure. The DAPA-HF study comprised a total of 6,801 individuals diagnosed with heart failure with reduced ejection fraction (HFrEF). Clinical practice guidelines describe HFrEF as a left ventricular ejection fraction (LVEF) of 40% or lower, regardless of diabetes status. The findings of the DAPA-HF study indicated that 51.4% of individuals that developed heart failure were diagnosed with type 2 diabetes. This information enhances the generalizability of the findings from this research. The primary composite endpoint of the trial was cardiovascular mortality or exacerbation of heart failure, characterized by hospitalization for heart failure, administration of intravenous diuretics in the emergency room, or outpatient treatment with intravenous diuretics. Cardiovascular mortality decreased by 26% (HR = 0.74, 95% CI = 0.65-0.85) and by 18% (HR = 0.82, 95% CI = 0.60-1.12) in comparison to the progression of heart failure. Twenty-one patients needed to be treated to prevent one composite event. The study revealed that dapagliflozin conferred advantages to all patients with varying diabetic situations, as well as to those exhibiting diverse baseline cardiac function and natriuretic peptide levels. Patients began to observe therapeutic advantages within the initial month of treatment, corresponding with the effects of acute hemodynamic processes. Dapagliflozin demonstrated beneficial impacts on patient quality of life and symptom alleviation, as evidenced by its Kansas City (State of Missouri) Cardiomyopathy Questionnaire scores, which revealed both clinical and prognostic improvements. The DAPA-HF trial resulted in the inaugural approval of an SGLT2 inhibitor for a non-glycemic indication when the FDA sanctioned dapagliflozin for heart failure with low ejection fraction in May 2020.

EMPEROR-Reduced: Empagliflozin in Advanced Heart Failure

The EMPROR-Reduced trial examined patients with heart failure with reduced ejection fraction (HFrEF) who had an average left-ventricular ejection fraction (LVEF) of 27% and exhibited persistent heart failure symptoms. This cohort included a substantial number of individuals with prior heart failure treatment in hospitals, as evidenced by markedly elevated heart failure-related natriuretic peptide levels compared to those in the DAPA-HF trial. Approximately 50% of the trial's total participants did not satisfy either of the necessary diagnostic criteria for Type 2 Diabetes (T2D), nor were they on treatment with T2D medications at the time of enrollment in the trial. Empagliflozin therapy led to a 25% decrease in the major endpoints of heart failure readmission and cardiovascular death in the trial (HR=0.75, 95% CI=0.65-0.86). Despite HR estimates indicating no significant reduction in the risk of cardiovascular death linked with empagliflozin (HR=0.92, 95% CI=0.66-1.28), the available data revealed a potential decrease in the risk of cardiovascular mortality. The trial showed significant efficacy, as the incidence of deteriorating heart failure episodes decreased by 71% (HR=0.71, 95% CI=0.55-0.92). Empagliflozin treatment demonstrated initial clinical benefits starting around 4 to 6 weeks after therapy commencement, consistently observed across all pertinent T2D and non-T2D patient cohorts.[7]

Meta-Analysis of DAPA-HF and EMPEROR-Reduced

The DAPA-HF and EMPEROR-Reduced investigations, qualifying for a predefined meta-analysis, encompassed 10,531 HFrEF patients who demonstrated treatment outcomes with SGLT2 inhibition across various patient demographics. The data indicated a 26 percent reduction in both cardiovascular mortality and hospitalizations attributable to heart failure (HR 0.74, 95% CI 0.68-0.82), demonstrating consistent benefits across all predefined subgroups, including age, sex, diabetes status, baseline ejection fraction, and ARNI (angiotensin receptor neprilysin inhibitor) utilization. The meta-analysis demonstrated that patients with HFrEF benefit from SGLT2 inhibitors, which provide universal therapy effects rather than

being specific to individual medications, as empagliflozin and dapagliflozin yield identical risk reductions in both relative and absolute terms.

EMPEROR-Preserved: Expanding Beyond Reduced Ejection Fraction

The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) expanded the examination of SGLT2 inhibitors to heart failure with preserved ejection fraction (HFpEF), a condition previously deemed a "no-drug" phenotype lacking effective therapeutic alternatives. The trial enrolled 4,128 patients with HFpEF and an LVEF of at least 40%, irrespective of their diabetes status. Empagliflozin demonstrated a 21% reduction in the primary outcome, which encompassed cardiovascular mortality and heart failure hospitalization (HR 0.79, 95% CI 0.64-0.98), mostly due to a decrease in heart failure hospitalizations (HR 0.75, 95% CI 0.55-1.02 for cardiovascular mortality). Empagliflozin also improved patient symptoms and exercise capacity, as evaluated by the Kansas City (State of Missouri) Cardiomyopathy Questionnaire. The results indicated that SGLT2 inhibitors serve as one of the few drugs that provide benefits to patients at all levels of left ventricular ejection fraction in the treatment of heart failure.

CHRONIC KIDNEY DISEASE: RENAL PROTECTION IN DIABETIC AND NON-DIABETIC POPULATIONS

DAPA-CKD: Watershed Evidence in Non-Diabetic Chronic Kidney Disease

The Dapagliflozin and Prevention of Adverse Effects in Chronic Kidney Disease (DAPA-CKD) trial, released in 2020, developed new treatment guidelines for chronic kidney disease. The study encompassed 4,304 volunteers with eGFR measurements ranging from 25 to 75 mL/min/1.73 m², who had albuminuria as indicated by a urine albumin-to-creatinine ratio beyond the 200 mg/g threshold. The study revealed that 32.5% of individuals exhibited no indications of type 2 diabetes, thereby contributing evidence to clarify the persistent discussion over the renal benefits of SGLT2 inhibitors experienced by hemodialysis patients. The primary outcome encompassed three events demonstrating a persistent reduction in eGFR of at least 50%, as well as patients progressing to end-stage renal disease and fatalities resulting from renal or cardiovascular complications. The composite treatment with Dapagliflozin led to a 39% reduction (HR 0.61, 95% CI 0.51-0.72), encompassing distinct component reductions: a 47% decrease in ≥50% eGFR decline (HR 0.53, 95% CI 0.43-0.66) and a 36% reduction in end-stage renal disease (HR 0.64, 95% CI 0.50-0.82). The research indicated that overall mortality declined to 31% (HR 0.69, 95% CI 0.53-0.88). The trial's design enabled researchers to categorize participants based on their diabetes status, revealing that both diabetic patients (HR 0.64, 95% CI 0.52-0.79) and non-diabetic patients (HR 0.50, 95% CI 0.35-0.72) experienced comparable treatment benefits, although the findings indicated more pronounced advantages for individuals without diabetes. The study showed that SGLT2 inhibitors protect the kidneys in ways that don't depend on their ability to lower blood sugar levels. This means that they protect everyone with chronic kidney disease, no matter what the cause is. The eGFR slope analysis indicated that dapagliflozin treatment diminished the eGFR decline rate from -3.79 mL/min/1.73 m² annually on placebo to -2.86 mL/min/1.73 m² annually on dapagliflozin, resulting in a difference of 0.93 mL/min/1.73 m² each year. The disparity in eGFR slope across treatments will prolong the onset of end-stage renal disease by 10 to 15 years for patients with typical medical circumstances.[8]

USE IN NON-DIABETIC PATIENTS: EXPANDING BEYOND THE DIABETIC POPULATION

The application of SGLT2 inhibitors in non-diabetic individuals represents a significant advancement in modern cardiology and nephrology. The broadened application of SGLT2 inhibitors beyond their initial role in diabetes treatment presents a significant challenge to their original development as diabetes medicines, as it raises questions about their long-term safety and efficacy in non-diabetic populations.

Table: 01 Modern cardiology has shifted from "treating glucose" to "treating cardiovascular and renal risk," regardless of diabetes status

Trial Name	Drug (Class)	Population (Non-Diabetic?)	Primary Outcome	Key Results	Clinical Impact
DAPA-HF	Dapagliflozin (SGLT2i)	HFrEF (± diabetes)	CV death / HF hospitalization	↓ events (~26%)	First major proof SGLT2 works without diabetes
EMPEROR-Reduced	Empagliflozin (SGLT2i)	HFrEF (± diabetes)	CV death / HF hospitalization	↓ HF hospitalization	Confirms class effect
EMPEROR-Preserved	Empagliflozin (SGLT2i)	HFpEF (± diabetes)	CV death / HF hospitalization	↓ composite outcome	Breakthrough in HFpEF
DELIVER	Dapagliflozin (SGLT2i)	HFpEF/HFmrEF (± diabetes)	CV death / HF hospitalization	↓ events	Broad HF indication
DAPA-CKD	Dapagliflozin (SGLT2i)	CKD (many non-diabetics)	Renal decline / CV death	↓ CKD progression & mortality	Strong kidney protection
EMPA-KIDNEY	Empagliflozin (SGLT2i)	CKD (large non-DM group)	Kidney disease progression	↓ progression	Expands to non-diabetic CKD
SELECT	Semaglutide (GLP-1 RA)	Overweight/obese WITHOUT diabetes + CVD	3-point MACE	↓ MACE (~20%)	Landmark obesity-CV prevention trial
STEP Trials	Semaglutide	Obesity (non-diabetic)	Weight loss	~15% weight loss	Indirect CV benefit
SURMOUNT-1	Tirzepatide (dual GIP/GLP-1)	Obesity (non-diabetic)	Weight loss	Up to ~20% weight loss	Emerging CV implications

Non-Diabetic Heart Failure: From Exception to Standard

Approximately 50% of individuals in the DAPA-HF and EMPEROR-Reduced studies did not have Type 2 Diabetes Mellitus (T2DM). The analysis of the hazard ratios between the two subgroups indicated that the anticipated advantage of the two studies for nondiabetics was greater due to the relative risk reduction attained by nondiabetics compared to diabetics. Although the confidence intervals of the hazard ratios exhibited significant overlap, the nondiabetic patient groups revealed a hazard ratio for cardiovascular mortality or exacerbation of heart failure of 0.71 (95% CI 0.57-0.89) for dapagliflozin and 0.74 (95% CI 0.59-0.91) for empagliflozin, which were equivalent to the hazard ratios observed in the diabetic populations. These discoveries facilitated the swift execution of regulatory approvals. Dapagliflozin gained FDA clearance for HFrEF in 2022; empagliflozin obtained the same approval for HFrEF in nondiabetic individuals. Both medicines have obtained approval for the treatment of HFpEF in nondiabetic patients. SGLT2 inhibitors have received strong support from global guidelines for use in all HFrEF patients and some HFpEF patients who do not have diabetes.[9]

Non-Diabetic Chronic Kidney Disease: Fundamental Redefinition of Treatment

DAPA-CKD offers compelling evidence that non-diabetic individuals can derive benefits from SGLT2 inhibitors. The trial design incorporated a subgroup analysis, enabling researchers to examine various diabetes status groups, which demonstrated that all groups derived equivalent benefits from the medication. The revelation necessitated the development of novel treatment modalities for chronic renal disease. For almost twenty years, renin-angiotensin-aldosterone system (RAAS) inhibitors have been the sole pharmacological treatment demonstrated to decelerate chronic kidney disease (CKD) progression. DAPA-CKD and EMPA-KIDNEY have introduced the inaugural novel medication class that offers protection against chronic kidney disease (CKD) since the advent of ACE inhibitors.[10]

Current Guidelines for Non-Diabetic Applications

The 2023 ACC/AHA/HFSA Heart Failure Guidelines designate SGLT2 inhibitors with a Class 2a recommendation for the management of heart failure with preserved ejection fraction (HFpEF), regardless of the patient's diabetic status. This classification stems from recent clinical experience and data. SGLT2 inhibitors

have been assigned a Class 1 recommendation for the management of heart failure with decreased ejection fraction (HFrEF) in patients without diabetes. The 2022 KDIGO Clinical Practice Guideline for Diabetes Management in patients with CKD recommends SGLT2 inhibitors as a primary treatment option for individuals with CKD and albuminuria, alongside RAAS inhibitors, irrespective of the patient's diabetes status.

SAFETY PROFILE: NAVIGATING ADVERSE EVENTS IN CLINICAL PRACTICE

Common Adverse Events and Their Management

The safety profile of SGLT2 inhibitors is attributable to their design, which operates through a unique mechanism. Genital mycotic infections are the most commonly reported side effects, occurring around 3 to 5 times more often than with a placebo. The predominant patient-reported side effects arise from infections that occur due to alterations in osmotic conditions within the urine environment. The majority of infections present as straightforward cases that rapidly respond to conventional antifungal therapy. Female patients exhibit a higher prevalence than males, with a previous history of recurrent vaginal infections significantly elevating the risk. The management options encompass educating patients on genital hygiene routines and recognizing symptoms of infection. Clinicians must promptly address infections while employing preventative strategies rather than discontinuing SGLT2 medications in instances of recurrent vaginal infections. Most guidelines do not advocate for permanent cessation purely based on a history of genital infections, considering the critical cardiovascular and renal advantages. Meta-analyses indicate that urinary tract infections occur at marginally elevated rates, with significant variability across various studies. The trend of heightened risk exhibits a less discernible pattern in comparison to genital infections. Healthcare personnel must monitor severe upper tract infections, such as pyelonephritis and urosepsis, due to their infrequent occurrence and the necessity for supervision.[11]

Volume Depletion and Hypotension

The first two weeks of SGLT2 inhibitor therapy result in natriuresis and diuresis, leading individuals with specific medical conditions to encounter symptomatic hypotension and volume depletion. Patients with loop diuretics require ongoing monitoring, a necessity that becomes particularly crucial for individuals with severe heart failure. The research suggests that significant hypotensive episodes occurred at comparable rates in both the SGLT2 inhibitor and placebo groups during the majority of randomized trials, suggesting that clinical deterioration due to volume depletion arises solely when medical personnel appropriately choose and monitor their patients.

Acute Kidney Injury and Transient eGFR Decline

Concerns regarding SGLT2 inhibitors inducing acute renal damage have significantly diminished. Meta-analysis evidence indicates that SGLT2 inhibitors significantly diminish the risk of acute renal damage compared to placebo treatment (RR 0.75, 95% CI 0.66-0.85). The treatment interval from weeks 2 to 4 exhibited a transient reduction in eGFR (estimated glomerular filtration rate), averaging between 10% and 15% due to hemodynamic adaptation; however, it did not result in any renal parenchymal injury. The DAPA-CKD and CREDENCE trials, shown through pre-specified studies, indicate that transient declines in eGFR do not adversely affect kidney health outcomes and do not impede patients from attaining substantial future gains in eGFR slope. The existing practice guidelines mandate eGFR monitoring following the commencement of SGLT2 inhibitors, commencing with a baseline evaluation and subsequently doing follow-up assessments at 1–3 months to ensure patient stabilization. The physician must perform additional tests to ascertain the cause of the eGFR decline if it decreases by more than 30% from the baseline level during the designated timeframe.[12]

Diabetic Ketoacidosis: Risk Stratification and Prevention

The most significant adverse impact of SGLT2 inhibitors arises from the uncommon medical syndrome termed euglycemic diabetic ketoacidosis. The meta-analysis indicates that two to five patients develop the condition for every ten thousand patient-years examined. The condition arises when an individual has metabolic acidosis while maintaining

normal blood glucose levels. The body expels glucose via glucosuria, resulting in elevated glucagon production and subsequent hepatic ketogenesis. Individuals with type 1 diabetes mellitus should refrain from using SGLT2 inhibitors, as this drug elevates their risk of developing euglycemic diabetic ketoacidosis (eudKA). Individuals requiring insulin during acute medical emergencies, post-surgical recovery, or in instances of significant fluid depletion are at an elevated risk of acquiring type 2 diabetes. Acute pancreatitis, although uncommon, may elevate risk. Women exhibit a marginally elevated relative risk compared to men, however the absolute incidence remains low.

EudKA manifests by modest symptoms, including nonspecific dyspnea and fatigue, accompanied with stomach discomfort, occurring when blood glucose levels remain within normal limits or exhibit only minor elevations. A diagnosis necessitates the presence of anion gap metabolic acidosis alongside positive serum and urine ketones, with blood glucose levels remaining within near-normal or low ranges. The management protocol necessitates the prompt discontinuation of SGLT2 inhibitors, alongside insulin therapy, rigorous fluid replacement, and the rectification of metabolic acidosis. The prevention techniques involve identifying appropriate patients, educating them on risk factors, and discontinuing SGLT2 inhibitor usage during acute medical conditions, prior to surgical procedures, and throughout prolonged fasting intervals. Current evidence does not endorse systematic screening for eudKA in asymptomatic individuals; however, clinical vigilance is necessary.[13]

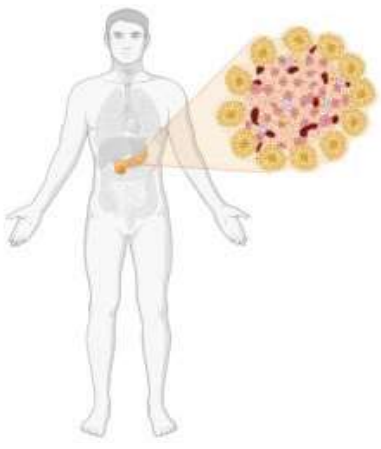

Figure 2: Adult male (anterior, eyes open, with highlighted pancreas and islet callout) ***Source:*** BioRender.com

Drug-Specific Safety Considerations

SGLT2 inhibitors operate as a pharmacological class; however, each medication within this class has distinct side effect profiles. Dapagliflozin and empagliflozin exhibit reduced incidences of genital infections and amputation risks compared to canagliflozin. Dapagliflozin exhibits a marginally elevated incidence of urinary tract infections in certain assessments. Empagliflozin has specific renal safety benefits for patients with advanced chronic kidney disease (CKD), such as a lower risk of worsening renal function and improved cardiovascular outcomes compared to other treatments. Physicians must utilize distinct pharmacological attributes to select drugs that correspond to the unique risk factors of their patient.[14]

DISCUSSION AND FUTURE DIRECTIONS

Current Practice Integration and Guideline Recommendations

Prominent international guidelines have swiftly incorporated the research endorsing SGLT2 inhibitors. The 2022 AHA/ACC/HFSA Heart Failure Guidelines recommend SGLT2 inhibitors as a top treatment for HFrEF, regardless of whether the patient has diabetes. The 2023 ESC Guidelines provide key treatment recommendations for heart failure, stating that SGLT2 inhibitors should be a primary treatment for all levels of ejection fraction. The 2022 KDIGO guideline, in conjunction with the European Society of Nephrology policy statements, advocates for SGLT2 inhibitors and RAAS inhibitors as co-first-line therapies for patients with chronic kidney disease and albuminuria, irrespective of their diabetic status. The clinical data strongly supports medical guidelines; yet, their application in practice is still inadequate. SGLT2 inhibitors remain inaccessible to eligible patients due to therapeutic inertia hindering healthcare professionals from prescribing this medicine across diverse healthcare systems. The interplay of financial factors, formulary restrictions, and clinician unawareness regarding non-glycemic applications results in underutilization of SGLT2 inhibitors, which could significantly benefit patients with heart failure and chronic kidney disease. The organization must implement educational

programs that integrate with systems-based solutions to promote precise prescribing procedures as fundamental goals for its development, particularly focusing on the benefits of SGLT2 inhibitors in various clinical applications and addressing the barriers to their utilization.

Novel Clinical Applications and Current Trials

Current research studies on SGLT2 inhibitors explore their potential use in treating acute coronary syndromes and post-myocardial infarction disorders. The DAPA-MI trial evaluated the impact of dapagliflozin prescribed to non-diabetic patients following acute myocardial infarction. The preliminary data indicate enhancements in both symptoms and biomarkers; however, the researchers have yet to release their primary endpoint findings. EMPACT-MI investigates empagliflozin therapy in acute myocardial infarction patients with varying ejection fraction values. The forthcoming trials allow researchers to examine SGLT2 inhibitors as prospective therapies for acute coronary syndromes. The EMPULSE research evaluated empagliflozin as a therapeutic alternative for hospitalized patients with acute decompensated heart failure, encompassing various ejection fraction levels. The results indicated that empagliflozin medication yielded superior clinical outcomes, as the hierarchical composite results established empagliflozin as the optimal treatment option. The findings suggest possible therapeutic advantages for patients with acute medical conditions experiencing various forms of heart failure, particularly in terms of improved clinical outcomes and reduced hospital readmission rates associated with empagliflozin treatment. The RENAL LIFECYCLE study examines the utilization of SGLT2 inhibitors in patients undergoing dialysis to fulfill the therapeutic needs of individuals with advanced renal impairment during their transition to kidney replacement treatment.

Comprehending Individual Variability and Precision Medicine

The advantages of SGLT2 inhibitors demonstrate uniform efficacy across all patient groups. Research findings indicate that SGLT2 inhibitors provide elderly individuals aged 75 and older with equivalent therapy benefits as those seen by younger patients. The SOLD (SGLT2 Inhibitors in elderly Diabetic Patients) trial evaluated SGLT2 inhibitors in elderly patients, demonstrating that the medication was both safe and effective. SGLT2 inhibitors confer advantages to all racial and ethnic demographics; nevertheless, certain research predominantly involved white participants, hence limiting the generalizability of their findings to other groups. Researchers must ascertain which patient traits yield optimal treatment outcomes, as this knowledge will facilitate the advancement of precision medicine strategies. Employing biomarker selection techniques, such as baseline NT-proBNP measurement and evaluation of albuminuria severity, will improve treatment outcomes and optimize resource allocation. Researchers must examine the genetic determinants that govern SGLT2 expression, along with its metabolic pathways and response mechanisms.

Mechanistic Insights Propelling Innovative Development

Researchers persist in examining the mechanisms of SGLT2 inhibitors, as their discoveries yield critical insights for the advancement of novel therapies. The revelation that the advantages of SGLT2 inhibitors in cardiomyopathy transcend renal effects via direct cardiac influences and metabolic reconfiguration has motivated researchers to investigate SGLT2 inhibitors for prospective applications in non-ischemic cardiomyopathy, cardiac amyloidosis, and myocarditis. Current case reports and limited mechanistic investigations suggest that the medication may benefit individuals with different types of cardiac disease; however, randomized studies provide inadequate data. SGLT2 inhibitors demonstrate promise as a novel therapeutic approach to prevent cardiac injury following acute myocardial infarction. The EMMY trial results indicated that post-myocardial infarction empagliflozin enhances left ventricular ejection fraction and other remodeling measures, prompting researchers to design larger trials to investigate this idea.

Surveillance of Safety in Distinct Demographics

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discovery that the benefits of SGLT2 inhibitors in cardiomyopathy exceed their renal effects, impacting direct cardiac function and metabolic reorganization, has prompted researchers to explore SGLT2 inhibitors for potential applications in non-ischemic cardiomyopathy, cardiac amyloidosis, and myocarditis. Current case reports and limited mechanistic investigations suggest that the medication may benefit individuals with different types of cardiac disease; nevertheless, there is a lack of solid data from randomized trials. SGLT2 inhibitors demonstrate promise as a novel therapeutic approach to prevent cardiac injury following acute myocardial infarction. The EMMY trial results indicated that post-myocardial infarction empagliflozin enhances left ventricular ejection fraction and other remodeling measures, prompting researchers to design larger trials to investigate this idea.[15]

Considerations for Health Equity and Access

Research indicates that SGLT2 inhibitors are beneficial; yet, significant issues about their accessibility persist across many countries. The exorbitant expense of treatment continues to be a barrier globally, particularly impacting low- and middle-income nations that face the highest prevalence of cardiovascular and renal diseases. The forthcoming availability of generic products will improve consumer accessibility in the future years. Health systems that establish initiatives to ensure equitable access to SGLT2 inhibitors will realize significant health advantages by reducing the incidence of cardiovascular and renal diseases in their most vulnerable populations.

CONCLUSION

The evolution of SGLT2 inhibitors from glucose-lowering medications to vital therapies that safeguard cardiac and renal functioning illustrates a significant achievement in translational medicine. Twenty years of clinical research have converted preliminary findings regarding heart failure advantages in the EMPA-REG OUTCOME trial into extensive evidence endorsing the use of SGLT2 inhibitors in various patient demographics: individuals with and without diabetes, those with reduced and preserved ejection fractions, and patients with chronic kidney disease of any origin. The mechanisms by which SGLT2 inhibitors confer cardioprotective effects operate through various biological pathways, resulting in pleiotropic effects that include hemodynamic improvements, metabolic alterations, decreased oxidative damage, reduced myocardial fibrosis, and renal protective advantages. The mechanism operates via numerous paths that medicine employs to yield consistent clinical outcomes across all patient demographics. The pivotal studies encompassed EMPA-REG OUTCOME, DAPA-HF, EMPEROR-Reduced, DAPA-CKD, and CREDENCE, which provided Level 1 evidence that SGLT2 inhibitors reduce the incidence of cardiovascular mortality, heart failure hospitalization, and the development of kidney disease. Patients who underwent treatment began to experience improvements that persisted for several months and extended into the future. This therapy method has advantages beyond diabetic populations, as it also benefits non-diabetic individuals with heart failure and chronic renal disease, demonstrating that SGLT2 inhibitors function as disease-modifying medications rather than conventional metabolic therapies. The studies delineate the safety profiles of the medicine, identifying vaginal mycotic infections and volume-related effects as the principal side effects. Serious consequences, such as diabetic ketoacidosis, pyelonephritis, and amputations, occur seldom, and patient outcomes enhance through appropriate patient selection and monitoring techniques. SGLT2 inhibitors yield superior outcomes in mitigating heart failure and preserving eGFR levels relative to GLP-1 receptor agonists, but GLP-1 agonists facilitate more significant weight reduction and enhanced glycemic control. The synergistic application of these processes offers advantages to patients who satisfy the criteria for this treatment, particularly in improving heart failure outcomes and managing diabetes effectively. Notwithstanding robust guideline endorsements for SGLT2 inhibitors, the medical community has not yet embraced these medications as conventional therapy. The medical community must eliminate treatment inertia by educating healthcare providers on appropriate prescribing practices and instituting systemic improvements that facilitate proper prescribing, such as implementing training programs and creating easy access to updated clinical guidelines. The global demand for SGLT2 inhibitors must be addressed, particularly in resource-limited

regions that have an elevated prevalence of cardiovascular and renal disorders. The research project will lead to heightened approvals of SGLT2 inhibitors since it will evaluate these medications in individuals with acute coronary syndromes, cardiac amyloidosis, myocarditis, and other cardiac conditions. The two precision medicine approaches that identify ideal patient cohorts for therapy and elucidate disease mechanisms leading to novel therapeutics will advance cardio-renal protection research. The contemporary medical practice employing SGLT2 inhibitors for the management of cardiovascular and renal illnesses signifies a pivotal shift from symptom alleviation to altering disease development. SGLT2 inhibitors hold potential for better health outcomes and a better quality of life for millions of people with heart failure and chronic kidney disease. The forthcoming research endeavor should focus on three objectives: establishing global treatment accessibility, utilizing clinical practice standards to improve medical treatment, and doing fundamental research to identify novel cardio-renal protective therapies.

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