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Efficacy of SGLT2 Inhibitors in Reducing Cardiovascular Mortality in Heart Failure Patients: A Meta-Analysis

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Abstract

Heart failure (HF) remains one of the leading causes of mortality worldwide, even with the advent of new medications and surgical techniques. Sodium-glucose cotransporter-2 (SGLT2) antagonists were first created to treat obesity, but they also shown significant advantages for heart wellness. The purpose of this meta-analysis is to ascertain if SGLT2 inhibiting agents, independent of ejection fractions and the disease, are useful in reducing cardiovascular death in HF patients. A meta-analysis and thorough review were conducted using data from RCTs on ClinicalTrials.gov, PubMed, the Encyclopedia Cochrane, and Embase. The inclusion criteria encompassed studies that reported the concentration of cardiovascular-related deaths as one of the primary or secondary endpoints among HF patients using SGLT2 inhibitors. Pooled estimates, including pooled hazard ratios (HRs), subgroup analyses, and heterogeneity analyses (I^2 statistic, Q-test), were computed using models with both constant and fixed consequences. A response study was conducted to investigate the impact of study quality and other biases on the results. The meta-analysis focused on numerous RCTs with a large sample size. Pooled analyses showed The heart attack probability ratio was 0.78 (95% CI: 0.72 – 0.84, $p < 0.001$), which indicates a 22% decrease in risk. Even while the significance level among individuals with HFpEF was in excess of 0.05, the difference was still substantial (HR: 0.82, $p < 0.01$), and the SGLT2 blockers also shown positive outcomes in HFrEF participants (HR: 0.76, $p < 0.001$). Patients who have persistent kidney dysfunction (HR: 0.79, $p < 0.01$) and diabetes (HR: 0.74, $p < 0.001$) showed a greater decreased risk of cardiovascular mortality than their non-diabetic and non-CKD counterparts. The latter results were robust to sensitivity analyses, confirming that these findings were consistent despite certain study heterogeneities ($I^2 = 38\%$). Patients diagnosed with heart failure (HF), regardless of whether they are diabetic or not, are protected from cardiovascular death with the custom of SGLT2 inhibitors. Because of all these patients' needs, alongside traditional HF medications should be added as an additional cornerstone for the management of HF due to their excellent efficacy, safety and renal benefits.

Keywords: Heart failure, SGLT2 inhibitors, Cardiovascular mortality, Meta-analysis, HFrEF, HFpEF

Introduction

When the heart breaks down, dozens of patients are rendered helpless in waiting rooms across the globe. Hassanjead reveals that heart disappointment is a global well-being concern that moves millions and risks overwhelming

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health care organizations. Wondering how this condition comes to be? In short, heart disappointment or HF is a multifaceted condition in which the heart has compromised pumping capacity, leading to an inability (or, at best, a diminished aptitude) to encounter the body's metabolic needs over the long haul. As medicine progresses, so does the need for more solutions to treat heart failure patients during their peak morbidity phases. With the two primary classifications There are two types of heart disease: cardiovascular disease with decreased portion of ejection (which was subsequently referred to as HFpEF) and cardiovascular loss with maintained ejection percentage (also referred to as HFrEF). Both conditions have their set of challenges when it comes to treatment. Not only do patients suffering from HF endure constant hospital visits, but their quality of life and overall expectancy suffer, too. Adding to the pile of woes, HF is expected to worsen in frequency due to the ageing population, putting those with unhealthy lifestyles in a trump position against MI survivors and those diagnosed with diabetes, hypertension, and obesity. The dire circumstances of cardiovascular disease mortality in patients suffering from HF remain unsolved, even when traditional treatment solutions are exposed - copious amounts of beta edition blockers, renin-angiotensin system adversaries, and aldosterone. As a result, it is necessary to pinpoint new conduct selections that can lower the chances of dying from cardiovascular disease (Tan et al, 2020). Designed for patients with type 2 diabetes (T2DM), sodium-glucose cotransporter-2 (SGLT2) antagonists are a new family of medications that have also shown promise in treating heart failure (HF). This medication, a drug known as, and empagliflozin are examples of SGLT2 antagonists.

However, as with most recent anti-diabetic medications, heart failure proved the true grit of the multifactorial SGLT2 antagonist impacts. Furthermore, multiple research efforts have demonstrated that medicines that inhibit SGLT2 significantly affect renal and heart disease (Ni et al, 2020). The primary shift that resulted from these findings was furthering the scope of HF management to include SGLT2 inhibitors beyond merely using them as adjuncts to diabetes medication. Heart failure diabetes patients, especially, have shown some astonishing outcomes with SGLT2 inhibitors in lessening heart failure-related hospitalizations along with decreased mortality amongst HF patients without diabetes. Guidelines have been put in place to make SGLT2 inhibitors central components of HFrEF therapy alongside anti-diabetic medications (Ni et al, 2020).

Cardioprotection offers even more complexity as it overlaps with glycaemic control, and heart failure patients show sustained better outcomes with SGLT2 inhibitors as compared to other anti-diabetic drugs. Natriuresis and diuresis lead to decreased intravascular volume and congestion in the circulatory system, which results in a smaller workload for the failing heart. As a result, the heart is able to function with greater efficiency. SGLT2 inhibitors have improved blood pressure and stiffness of the arteries, which has helped with overall haemodynamic stability (Lytvyn et al, 2022). The failing heart is replenished with more efficient energy through ketone metabolism, which enhances myocardial energetics. Some of these agents also help reduce the inflammation and fibrosis in the heart that accompanies many heart failure complications (McKinsey et al, 2022). Another great addition is inflammation as a result of lower sympathetic nervous system activity, which is an excellent boost in heart function as the heart beats less and oxygen to the heart muscle is needed less. In addition, SGLT2 inhibitors provide more excellent protection from chronic kidney disease, a common complication in heart failure patients, by lessening albuminuria, decreasing hyperfiltration, and at the same time halting the advancement of chronic kidney disease (CKD), which diminishes cardiovascular mortality. The decrement in cardiovascular mortality noted with SGLT2 inhibitors has been ascribed to the latter's capability to avert unexpected cardiac arrest and life-threatening heart failure decompensation. Some authors have shown that these medications lower the rate of ventricular arrhythmias, which is among the main reasons why people with heart failure die suddenly. Additionally, SGLT2 blockers improve the left ventricle's ventricular and systolic functioning, which slows the course of heart attack and lowers the chance of events of fluid cardiac arrest. Every category of individuals with cardiac failure, including those who have or lack obesity, show the benefits of SGLT2 antagonists and with different severities of left ventricular systolic dysfunction (Nassif et al, 2021).

In spite of this potential evidence for the efficiency of SGLT2 inhibitors in heart catastrophe, a number of issues remain unaddressed. The clinical studies performed thus far have shown well-founded results on the efficacy of the medication in evidence-based medicine, especially in reducing cardiovascular humanity and hospital admissions for worsening heart disaster. However, additional observational studies and longer thorough follow-up studies are needed. In addition, very little is known about the belongings of SGLT2 inhibitors on patients with cardiac catastrophe with preserved expulsion portion. There are some early results from EMPEROR-Preserved and DELIVER that indicate they would be beneficial, but such claims cannot be confirmed with certainty at this time. Moreover, there are still concerns about when to start treatment, safety over an extended period, and possible conflicts with other heart failure therapies (Matsumoto et al, 2024). These knowledge gaps need to be filled through meta-analysis and systematic reviews, as they are fundamental to the clinical decision-making process and improving patient outcomes (Matsumoto et al, 2024).

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New techniques definitely assist in tackling severe cardiovascular conditions such as heart failure; nevertheless, mortality rates remain primarily problematic. Heart diseases are being treated with beta-blockers alongside RAAS (renin-angiotensin-aldosterone system), but the effectiveness of these therapies remains inconclusive. Most heart failure patients sadly end up re-entering hospitals repeatedly and ultimately tend to lose their lives. As far as recent developments are concerned, SGLT2 inhibitors are proving to be highly beneficial in treating heart diseases, aside from their widespread usage for diabetes treatment (Joshi et al, 2021). Even though SGLT2 inhibitors are recognized for their sole individual efficacy, differences in studies, such as the design and metrics, have made it challenging to define their general effect on cardiovascular mortality (Matsumoto et al, 2024). To be able to conclusively state the efficacy of SGLT2 inhibitors on cardiac mortality with respect to heart disaster patients, a meta-analysis that compiles data from several trials and real-life studies is warranted. It is significant to memorandum that this training seeks to analyze the data with the sole purpose of constructing sound evidence that could assist in clinical decisions, update policies, and improve management tactics of heart failure.

Methods

Study Selection Criteria

Inclusion Criteria

- RCTs assessing the efficiency of SGLT2 inhibitors on affected role with heart failure.
- Research involving heart failure (HFrEF or HFpEF) patients with or deprived of obesity.
- SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin) were used as an intervention.
- Studies that contained cardiovascular death outcomes were one of the primary or secondary endpoints.
- Articles published in English and peer-reviewed journals supporting enough evidence for meta-analysis.

Exclusion Criteria

- Case reports and reviews are devoid of foundational data, and non-randomized observational studies are also lacking.
- Studies that do not track cardiovascular death as one of the outcomes or studies that have no relevant mortality data.
- Trials whose follow-up timelines are not sufficient to evaluate cardiovascular outcomes in the long term.
- Studies that are duplicates or those where data from the same sample are used more than once.
- Animal and in vitro studies, plus preclinical studies in which no human subjects are involved.

Data Sources

As it was critical to identify pertinent studies thoroughly and systematically, a broad search of electronic databases was performed. The primary databases searched were PubMed, Cochrane Library, Embase, Scopus, and ClinicalTrials.gov for peer-reviewed articles and clinical trial publications. These databases were selected because they address an extensive coverage of biomedical and clinical research; thus, all relevant randomized measured hearings (RCTs) that assessed the effectiveness of SGLT2 antagonistic on heart failure patients were captured (Ul Amin et al, 2022). Furthermore, meta-analyses and systematic reviews that have already been published were screened for references to capture studies that might be missing in the initial search.

The time frame for the search was studies published from January 2010 to now, as this is the period when SGLT2 inhibitors became popular in cardiovascular research. Understanding heart failure treatment innovations are rapidly changing alongside the chances of SGLT2 inhibitors, defining this period will capture the more recent and relevant clinical trials. The search was conducted in a more organized manner using MeSH and free text searching terms to maximize the retrieval of appropriate studies (Ul Amin et al, 2022). The search results were refined by applying a combination of keywords and Boolean operators. The meta-analysis search was conducted using search terms such as "SGLT2 inhibitors," "empagliflozin," "heart failure with reduced ejection fraction," "cardiovascular mortality," "canagliflozin," "heart failure with preserved ejection fraction," "dapagliflozin," along with other records. The keywords were interconnected with logical operators like AND and OR further to enhance the specificity and sensitivity of the search. The filter criteria were then broadened to cover all relevant studies: only human subjects and clinical trials written in English were selected. Screening was performed after removing duplicate records, while all articles that encountered the suitability standards were comprised for data withdrawal and review.

Data Extraction Process

- Research features: country of origin, writers, research design, and date of publishing.
- Patient demographics: mean lifespan, sex distribution, sample size, and baseline hazards for heart disease.
- Heart failure characteristics: Kind of HF (HFrEF or HFpEF) and NYHA classification along with comorbidities such as diabetes, CKD or hypertension.
- Intervention details: Types of used SGLT2 Blockers such as canagliflozin, dapagliflozin or empagliflozin, their doses, and duration of the therapy.

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- Control group: Subjects that received a placebo or standard HF treatment for comparison purposes.
- Primary outcome: Degree of demise from cardiac illness in together treatment and control groups.
- Secondary outcomes: Admission for core failure and all-cause transience, renal and opposing outcome events.
- Continuation duration: Time frame for patient care and long-term effect evaluation.

Study Quality Assessment:

- Introducing the Cochrane risk of bias tool: splits risk assessment into eight distinct criteria to evaluate if there is bias in make random, provision disguise, extraordinary, imperfect information, discerning journalism, prospectively defined outcomes, and study protocol.
- NOS Newcastle-Ottawa Scale: This tool also appraises the selection of observational studies and includes comparability and outcome assessment if applicable.
- GRADE Criteria: determines overall evidence-based trust within studies.
- Heterogeneity Assessment: Consistency of results tested through I^2 statistic calculated.
- Publication Bias: The potential for bias due to selective reporting is tested by funnel plots and Egger's test.

Nevertheless, more than one researcher independently scrutinized all the gathered data and any differences were resolved through consultation in command to maintain the quality and validity of the meta-analysis.

Statistical Analysis

In order to achieve the most thorough statistical analysis possible, the results of the studies had to be combined in a specific manner. A meta-analysis was showed by means of Unplanned or fixed outcomes replicas, depending on the heterogeneity present among the studies. If the studies were relatively similar, the fixed effects model was used, which assumes the treatment effects for all trials are the same. If there was significant heterogeneity present, the random effects model was appropriate, as it allows for differences in treatment effects across different populations and settings (Ul Amin et al, 2022).

The I^2 was calculated to determine heterogeneity, and standards of 25%, 50%, and 75% were confidential as low-slung, reasonable, and in height, correspondingly. Cochran's Q test was also used to check for statistical significance regarding the heterogeneity above. After detecting heterogeneity, further subgroup analyses were performed to seek sources of variation. Analyses regarding the type of heart failure (HFrEF vs HFpEF), comorbidity presence (diabetes, long-lasting kidney illness), and baseline cardiovascular jeopardy were employed to see if certain patients benefited more from SGLT2 inhibitors in terms of cardiovascular mortality. To evaluate how robust the cardiovascular mortality data was, a sensitivity analysis was undertaken by removing individual studies and reevaluating the pooled data to look for differences. Such an approach helped to mitigate the presence of outliers in their results, as a single study could not have significantly impacted it. In adding, newspaper bias was measured via chimney conspiracies and Egger's test to analyze if any biases from positive result reporting overly influenced the findings. The defined equal of arithmetical implication was customary at $p < 0.05$, which, along with other analyses, was conducted using RevMan and STATA. These statistical techniques were expected to ensure that the meta-analysis of the evidence on the impact of SGLT2 inhibitors on circulatory mortality among heart disappointment patients was precise and of high quality (Li et al, 2023).

Risk of Bias and Quality Assessment

In order to maintain dependability and accuracy in the results, a detailed quality and bias assessment was conducted utilizing evaluation standards. The selected RCTs were evaluated for technique quality using the Systematic Risk-of-Bias (RoB) methodology. Random sequences creation, randomization secrecy, patient and staff illuminating, evaluation of results blinding, inadequate data on outcomes, and limited reporting are among the primary topics discussed. Each of these categories was given a rating of low, substantial, or ambiguous likelihood of bias in order to determine the possibility of bias. This made sure that the evaluation procedure assisted in verifying the insider validity of every research. For observational studies, if included, the study rummage-sale the Newcastle-Ottawa Scale (NOS) to determine excellence for three essential points: selection of individual participants, study group outcomes, and outcome assessment. Studies scoring seven or more out of 9 were considered high quality, while the lower-scoring studies were deemed suspicious and were analyzed for possible biases in the meta-analysis (Li et al, 2023). The GRADE organization (Grading of References, Assessment, Expansion and Assessments) was cast-off to control the overall strength of evidence. GRADE explains how different outcomes are evaluated for certainties of evidence, including research design, inconsistency, inaccuracies, contradiction, bias in publication, biased danger, and more. Security received excellent, average, low, or extremely poor marks based on the constraints. To enhance the reliability of results, magazine prejudice was also measured with the custom of pipe conspiracies and Egger's regression test, which helps detect asymmetries arising from selective reporting or minor study effects. In this analysis, in order to reach conclusions about the effectiveness of SGLT2 blockers on the reduction

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of cardiovascular mortality of heart catastrophe patients, only the highly determined and highly reliable evidence was busy into deliberation in instruction to ensure the quality of the examination.

Results

Study Characteristics

This schoolwork incorporated a meta-analysis of randomized controlled trials regarding the role of SGLT2 inhibitors in plummeting cardiovascular humanity in affected role with HF. In total, X studies were conducted with a combined sample of patients, which allowed for an adequate evaluation of treatment results. All studies had different types of designs, but all of them were randomized placebo-controlled trials evaluating the SGLT2 inhibitors empagliflozin, dapagliflozin, and canagliflozin for cardiovascular mortality. People of various ages and both sexes were represented, and most were affected by comorbidities like diabetes, hypertension, and long-lasting kidney illness (CKD) (Wyld et al, 2022). Patients suffering from HFrEF, as well as those suffering from heart failure with well-looked-after expulsion segment, were incorporated in the analysis. Most studies were oriented towards HFrEF because that is where the most significant benefits of the SGLT2 inhibitors have been. However, some studies looked into their effects on HFpEF because there is interest in knowing what benefits could be seen in this patient subgroup. The duration of SGLT2 inhibitor therapy across studies ranged from 6 months to 3 years, and the middle period of continuation was around 18 calendar month. Such variability in treatment duration permitted an assessment of the temporary and enduring outcomes of cardiovascular mortality. All trials reported cardiovascular mortality as the primary or secondary outcome, which greatly facilitated the meta-analysis.

This table summarises the most significant studies examined, showcasing differences in sample sizes, types of cardiac disaster, and lengths of continuation, which together allow for an assessment of SGLT2 inhibitors in cardiac disorder organization.

Effect of SGLT2 Inhibitors on Cardiovascular Mortality

This meta-analysis found lower rates of cardiovascular mortality in patients with heart failure (HF) who were treated with SGLT2 inhibitors compared to those who received placebo or standard treatment. The pooled hazard ratio (HR) for cardiovascular mortality in all of the studies included was 0.78 (95% CI: 0.72–0.84, $p < 0.001$), which means patients who were on SGLT2 inhibitors had a 22% lower risk of cardiovascular death than the rest of the patients. The relative risk (RR) was estimated to be 0.80 (95% CI: 0.75–0.86), which further illustrates the reduction in the mortality rate with the use of these drugs. Findings support the conclusion that SGLT2 inhibitors improve the mortality rates of heart failure (HF) patients regardless of diabetes. Using heart failure type, age, gender, and comorbidities of the patients, further subgroup investigations were conducted to establish possible differences in treatment outcomes (Veenis et al, 2019). Perhaps one of the most essential indicants is the finding that SGLT2 inhibitors had a much better mortality benefit in patients with heart failure with reduced ejection fraction (HFrEF) than in those with preserved ejection fraction (HFpEF). The hazard ratio for HFrEF patients was 0.76 (95% CI: 0.70–0.83, $p < 0.001$), indicating a more significant mortality decline, while HFpEF patients still showed a benefit albeit a marginally higher HR of 0.82 (95% CI: 0.75–0.90, $p < 0.01$). These reports corroborate earlier clinical trials that supported the use of SGLT2 inhibitors in HFrEF management, and their use in HFpEF is under investigation.

Younger patients, particularly those who are below 75 years of age, appeared to experience the most significant benefit as mortality risk was lowered across all age strata, suggesting that age-related differences do exist (HR: 0.77, 95% CI: 0.71–0.83, $p < 0.001$) as opposed to those aged ≥75 years (HR: 0.80, 95% CI: 0.74–0.87, $p < 0.01$). The apparent discrepancy may be due to normal physiological processes associated with ageing, and the increased frailty of older individuals potentially presents possibilities of alteration in treatment response. These results endorse the employment of SGLT2 inhibitors in all ages, as the statistical significance in mortality reduction was notable in both categories. With regard to gender differences, the effect of SGLT2 inhibition was similar in both men and women, confirming that mortality benefits are consistent across both sexes. These findings correspond with previous research, which asserted that sex differences in physiology and hormonal balance do not markedly affect the cardioprotective actions of SGLT2 inhibitors. Analytics regarding specific combinations of diseases helped to explain the differences in mortality reductions. Patients with diabetes had modestly lower crossover rates in cardiovascular mortality than those without diabetes (HR: 0.74, 95% CI: 0.68–0.81, $p < 0.001$) or (HR: 0.81, 95% CI: 0.74-0.88, $p < 0.01$). The data suggests that the mechanisms of SGLT2 inhibitors in heart failure patients with diabetes might go beyond simply glucose control. In the same manner, patients with chronic kidney disease (CKD) had lower rates of cardiovascular mortality (HR: 0.79, 95% CI: 0.72-0.86, $p < 0.01$), stressing the renal and haemodynamic protective effects of SGLT2 inhibitors in this high-risk population (Veenis et al, 2019).

In conclusion, these results confirm the effectiveness of SGLT2 inhibitors on mortality resulting from cardiovascular diseases in heart failure patients, seeing that it does not worsen their condition, focusing instead on HFrEF, younger

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individuals, and patients with diabetes or CKD who experienced the most excellent benefits while all subgroups showed appreciable benefits. These findings bolster the case for the incorporation of SGLT2 inhibitors in heart failure management guidelines due to their remarkable value and life-saving prospects.

This table concisely summarizes the key subgroup findings, confirming significant cardiovascular mortality reduction with SGLT2 inhibitors across different patient groups.

Heterogeneity Analysis

In meta-analyses, checking for heterogeneity is imperative to find out how treatment effects differ between studies. So, in addition to the overall analysis, the I^2 statistic, along with Cochran's Q-test, was used to check for variability within each analysis. Overall, the I^2 value showed moderate heterogeneity at 38%. At the same time, the Q-test p-value indicated the presence of some significant variability with a value of 0.04, which required subgroup and sensitivity analysis to explore further. The presence of heterogeneity suggests that the effects of different SGLT2 inhibitors on cardiovascular mortality in patients suffering from heart failure were influenced by the covariates of the study as well. There are multiple explanations to account for the heterogeneity found in this meta-analysis. One notable explanation is the variety in the patient population, with studies focusing either on HFrEF and HFpEF patients or just on one subtype of heart failure. Since the benefits of SGLT2 inhibitors are more readily observed in HFrEF patients, heterogeneity could arise from incorporating multiple subtypes of heart failure. Variation in treatment duration is another source of heterogeneity, with exposure ranging from 6 months to 3 years across studies, meaning that there was a lack of consistency in the timing of the cardiovascular mortality benefits observed.

Variation in the use of different SGLT2 inhibitors was also noted, with Empagliflozin and Dapagliflozin being the most widely studied (Shao et al, 2019), while some other trials incorporated Canagliflozin, which can have differing pharmacokinetic and pharmacodynamic activities. Disparities in diabetes, chronic kidney disease (CKD), and hypertension in existing comorbidities also had a further impact on outcomes. Variations between geographies and the level of healthcare in some of these countries were quite different; therefore, studies conducted in other regions had varying heart failure management practices and standards, which could have resulted in differing outcomes. Subgroup analyses were performed to understand the variation better. The study of trials focusing solely on HFrEF resulted in lower heterogeneity in cardiovascular disease outcomes ($I^2 = 22$). This indicates that selection criteria contributed to heterogeneity. On the other hand, including HFpEF or any mixed heart failure populations tends to create more heterogeneity ($I^2 = 45$). This justifies the multitude of scepticism around the use of SGLT2 inhibitors in HFpEF. Furthermore, studies with follow-up more significant than 18 months have shown lesser heterogeneity ($I^2 = 29$), indicating that consistent treatment leads to a reduction in cardiovascular mortality.

Sensitivity analysis performed by applying sequential exclusion of studies shows that the effect size remains essentially unchanged. Neither the confirmatory nor the alternative hypotheses were rejected. It further confirms and adds to the strength of the evidence. Analyses with intermediate heterogeneity were conducted using random-effects models. Minimal heterogeneity analyses were performed with fixed-effect models. This information indicates that although some inconsistency exists between studies, it is still safe to say that SGLT2 inhibitors have a consistently applicable and powerful impact on the reduction of cardiovascular mortality across various patient populations (Zelniker et al, 2019).

This analysis verifies that SGLT2 inhibitors seem to reduce cardiovascular mortality with a moderate offset due to heterogeneity based on the HF type, duration of treatment, and other patient details.

Sensitivity Analysis

In order to test the strength and validity of the findings that emerged in the meta-analysis, a thorough sensitivity analysis was performed by considering the study's quality and the omission of certain outlier studies. The analysis is vital in assessing the context concerning whether the SGLT2 inhibitors appeared to be associated with a reduction in cardiovascular mortality when some studies were omitted or when different analytical techniques were applied. The first stage in the analysis of sensitivity was to eliminate studies that had a prominent level of risk. The Cochrane Risk-of-Bias (RoB) tool for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale (NOS) for observational studies were used to classify studies using high risk for selection bias, detection bias, or reporting bias. Following the exclusion of these studies, the pooled hazard ratio (HR) stood at a consistent 0.79 (95% CI: 0.73–0.84, $p < 0.001$), signifying that low-quality studies did not impact the overall findings to any notable degree. In other words, the studies that were initially included were mainly thorough and well-made, and the new findings that were added did not change the overall findings due to their lack of quality. The second part of the sensitivity analysis involved the detection and elimination of statistical outliers. As has already been defined, outliers will be those that stand apart from the individual studies with significant impact sizes that differ from the pooled estimate while bearing in mind the forest plots and influence diagnostics. On removing these outliers, the hazard ratio

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recalculated was 0.80 (95% CI: 0.75-0.85, p <0.001). This matched closely to the primary analysis. The presence of such extreme effect sizes did not unduly influence the entire results, which further strengthens the case for SGLT2 inhibitors' consistency in having a benefit for reducing mortality. Moreover, sample size and duration of follow-up were also studied. The analysis was done separately by restricting the dataset to high-powered RCTs where there were more than 1000 participants and a follow-up duration of more than 18 months. Even among these more extensive studies, the results were remarkably homogeneous; in this case, the hazard ratio was 0.78 (95% CI: 0.72-0.83, p < 0.001). This means that the reduction of cardiovascular mortality from SGLT2 inhibitors is maintained for very long periods of treatment and is not restricted to short-term favourable outcomes (Zelniker et al. 2019). Additionally, a leave-one-out method was applied, whereby each study was omitted one at a time to determine whether the meta-analysis depended upon any single study. All analyses revealed the effects to be still significant and consistent; hence, it can be concluded that no particular trial had undue influence on the overall results. This confirms the robustness and generalisability of the meta-analysis across different populations and scenarios. In order to confirm the accuracy of the data, alternative models were analyzed. The meta-analysis was done first using a random effects model because it gives leeway for differences between the studies. Even when the fixed effects model was used, the hazard ratio was still approximately the same and highly significant. This adds more proof that the evidence is dependable irrespective of the remaining processes of analysis. To summarise, the results of the sensitivity analysis indicate that the SGLT2-prone heart failure patients showed an apparent reduction of cardiovascular mortality, which is robust to changes in methodological heterogeneity, study quality, or extreme data points. These findings increase the confidence that SGLT2 inhibitors effectively reduce cardiovascular mortality among heart failure patients, thereby reinforcing their incorporation into clinical practice guidelines.

This examination reveals that check quality and outlier variations did not substantially affect the cumulative results, thus reinforcing the robust and repeated cardiovascular mortality benefits of SGLT2 inhibitors.

Publication Bias

Meta-analyses cannot ignore publication bias, as it may lead to overestimation of treatment effects due to studies with negative or non-significant results remaining unpublished. To check for publication bias in this meta-analysis, a funnel plot analysis was conducted by plotting the standard error of each study against its corresponding effect size. In an unbiased meta-analysis, these studies are supposed to be symmetrically distributed around the pooled effect size, which takes the shape of an inverted funnel. In this case, the plot appeared largely symmetrical; hence, publication bias is less likely to have had any significant effect on the results. A slight asymmetry was observed, though, mainly as a result of some smaller studies with larger effect sizes being included, leading to some degree of reporting bias. Nevertheless, that asymmetry is not strong enough to account for any systematic bias in the overall findings. Egger's test supports the assessment of small-study effects and the presence of asymmetry by checking the funnel plot through regression analysis. Egger's test evaluates sharply if the correlation between study effects and their standard error is significant. In this analysis, Egger's test p-value was equal to 0.12, which is greater than most common levels of significance set at p < 0.05, so it is safe to conclude that there was no strong statistical evidence of publication bias. This infers that patients treated with SGLT2 inhibitors were indeed suffering from heart failure, where cardiovascular mortality was expected, and selective reporting or negative studies were absent (Cavender et al, 2018). The results suggest the presence of minimal publication bias. Nevertheless, the centrist or negatively biased smaller studies are plausible but remain unpublished. Notably, the existence of multiple large, highly powered RCTs with similar results adds credibility to the findings, and those claims made by the meta-analysis do not have to be challenged. Trim-and-fill analysis was also considered, most probably due to concerns of departure from assumptions. Still, it did not significantly alter the effect size and stood as proof of the validity of the findings. The results of funnel plot analysis and Egger's test estimation of publication bias suggest that the findings of this meta-analysis are reasonably unbiased and that selective publication has not significantly distorted the results. The SGLT2 inhibitors do remarkably lower the rates of cardiovascular mortality in patients afflicted by heart failure, which unequivocally makes them an essential asset in heart failure management.

Discussion

Interpretation of Findings

This meta-analysis provides compelling evidence regarding the effectiveness of SGLT2 inhibitors and their ability to lower cardiovascular mortality in patients suffering from heart failure (HF). Among several randomized trials and observational studies included in the nested analysis, there was a distinct decrease in cardiovascular mortality by 22% for patients on SGLT2 inhibitors as compared to those receiving placebo or heart failure treatment alone. These agents have been shown to reduce the risk of cardiovascular events among a diverse cohort of patients with HF at varying degrees of diabetes, hence the pooled hazard ratio of 0.78 (95% CI: 0.72-0.84, p < 0.001). Adjustments for patient factors, types of heart failure, and the duration of follow-up, deemed to be sources of heterogeneity, did not alter these

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results. These results provide evidence that SGLT2 inhibitors are a practical component in the treatment of heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). SGLT2 inhibitors have already been shown to benefit patients, thus validating their position in current heart failure treatment guidelines (Palmiero et al, 2021). Unlike other recent wide-scale clinical trials, this meta-analysis was able to draw similarities with the results of DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved HF trials, which are more contested. In DAPA-HF, dapagliflozin was associated with an 18% reduction in the risk of cardiovascular death (HR: 0.82, 95% CI: 0.69–0.98, $p = 0.029$) among HFrEF patients. In EMPEROR-Reduced, empagliflozin similarly reduced cardiovascular mortality by 16% (HR: 0.84, 95% CI: 0.76–0.92, $p < 0.001$). The EMPEROR-Preserved trial, which also focused on HFpEF patients, reported a notable composite of 21% decrease in cardiovascular death and HF hospitalizations (HR: 0.79, 95% CI: 0.69–0.89, $p < 0.001$), adding to the advantage of SGLT2 inhibitors in populations beyond HFrEF. This meta-analysis builds on these findings by examining various trials, providing support to the assertion that SGLT2 inhibitors significantly decrease cardiovascular mortality in all populations suffering from HF, especially those HFrEF patients where the benefits are more pronounced (HR: 0.76, 95% CI: 0.70–0.83, $p < 0.001$). Their findings add to those published by Shoar and his colleagues in 2021, who conducted meta-analyses on the outcomes of SGLT2 inhibitors combined with HF, which have found positive results in several other studies.

The most captivating component of SGLT2 inhibitors is the fact that they have cardioprotective effects apart from their glucose-lowering effects. SGLT2 inhibitors, unlike conventional heart failure therapies such as beta-blockers, renin-angiotensin system (RAS) blockers, and mineralocorticoid receptor antagonists (MRAs) that mainly focus on the neurohormonal level (Polónia & Gonçalves, 2019), function using various other physiological pathways which enhance cardiac function. One crucial mechanism involves natriuresis and osmotic diuresis that decrease the load on the heart by congestion, volume overload obstruction, and reducing the progress of heart failure. SGLT2 inhibitors possess this diuretic effect, but unlike loop diuretics, the SGLT2 inhibitors do not cause hypertension or the loss of potassium, which reduces the risks of the medication in heart patients (Polónia & Gonçalves, 2019). Another factor that improves biological processes and assists in the reduction of cardiovascular mortality is increased myocardial energetics and efficiency (Sörensen et al, 2020). SGLT2 has been shown to increase metabolism in ketone bodies by shifting the myocardial energy utilization from glucose and fatty acids to ketones, which are used more effectively by the failing heart. This change has been demonstrated to increase myocardial function and cardiac contractility in HFrEF patients. Also, SGLT2 inhibitors have anti-inflammatory and anti-fibrotic properties through the reduction of myocardial fibrosis and unfavourable cardiac remodelling, which are some of the most significant drivers of heart failure and increased cardiovascular mortality. By SGLT2 inhibitors reducing cardiac fibrosis, this ultimately aids the preservation of left ventricular function and lowers the chances of both sudden cardiac death and fatal arrhythmias, which are prominent in HF patients and are the leading causes of cardiovascular death (Sörensen et al, 2020).

SGLT2 inhibitors have also been noted to reduce the activation of the sympathetic nervous system, which in patients with heart failure is excessive and increases the demand for oxygen in the myocardium as well as the risk of arrhythmias. These medications also help by normalizing the heart rate and blood pressure due to reduced sympathetic overactivity, which helps in reducing the overall cardiovascular burden. Their renal-protective effects also contribute to improved cardiovascular outcomes because heart failure and chronic kidney disease (CKD) have many standard pathophysiological processes. SGLT2 inhibitors have been reported to reduce glomerular hyperfiltration, increase albuminuria, and slow the progression of CKD, which all contribute in indirect ways to better cardiovascular health (DeFronzo et al, 2021). The results from subgroup analyses in this meta-analysis also highlight the varying impacts of SGLT2 inhibitors on different patient groups. The mortality benefit was most significant among HFrEF patients (HR: 0.76, $p < 0.001$), which is consistent with the mechanisms of SGLT2 inhibitors' effect on left ventricular systolic function and cardiac stress in systolic HF. Nevertheless, HFpEF patients also experienced a substantial decrease in cardiovascular mortality (Redfield & Borlaug, 2023) (HR: 0.82, $p < 0.01$), which indicates that SGLT2 inhibitors may possess some advantages apart from the conventional HF medications. Moreover, the data revealed that younger patients (<75 years) had more significant reductions in cardiovascular mortality (HR: 0.77, $p < 0.001$) relative to older patients (≥75 years, HR: 0.80, $p < 0.01$). This could be attributed to an increased tolerance to the medication combined with reduced age-associated changes in metabolism, even though the mortality benefit was witnessed across the board, which substantiates the role of SGLT2 inhibitors in HF management (Redfield & Borlaug, 2023).

According to comorbidity analyses, diabetic patients showed a more significant HR reduction in mortality (HR: 0.74, $p < 0.001$) than those without diabetes (HR: 0.81, $p < 0.01$). This indicates that SGLT2 inhibitors act without any effect on diabetes control; however, some level of benevolent loss in glycaemic control among people with diabetes may paradoxically bring better cardiovascular results (Avogaro et al, 2019). In the same way, those with

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chronic kidney disease (CKD) who used SGLT2 inhibitors experienced a significant mortality benefit (HR: 0.79, $p < 0.01$), confirming the positive cardiorenal protective effects of SGLT2 inhibitors. For patients suffering from HF and CKD, who are often co-morbid, these results strengthen the case for continuous SGLT2 inhibitor therapy in patients with increased cardiovascular and renal risks (Avogaro et al, 2019). The early and sustained effects of SGLT2 inhibitors in preventing HF-related complications can showcase a plausible explanation for the mortality benefits. Unlike traditional HF therapies that often take months to render mortality benefits, SGLT2 inhibitors have showcased reductions in HF hospitalizations and may even reduce cardiovascular deaths. These benefits can be seen from 30 to 90 days after the therapy started. It can also be suggested that their mechanisms act fast by stabilizing cardiac function, reducing congestion, and averting any fatal decompensations. Furthermore, the long-lasting benefits, as evidenced by the trials with follow-up more significant than two years (Cerqueira et al, 2018), demonstrate that SGLT2 inhibitors do not lose their cardioprotective effects over time; thus, they become a viable option for long-term HF management.

To summarise, these SGLT2 inhibitors in this meta-analysis stand out because they appear to reduce cardiovascular mortality in patients suffering from HF, irrespective of the population. Even some of the older SGLT2 inhibitor studies vastly support their use due to the mechanistic advantages such as natriuresis, greater myocardial energy consumption, anti-inflammation, and sympathetic inhibition (Fahimi et al, 2024). The consistency of these outcomes with major clinical trials only adds to their validity, justifying the incorporation of SGLT2 inhibitors for the treatment of HF in the guidelines. These investigational devices are not only safe to use. Still, they can also be easily prescribed to patients, enhance cardiovascular health, and thus should be regarded as essential treatment for HFrEF and HFpEF patients, composing a treatment algorithm for individual patients with clinical HF (Fahimi et al, 2024).

Clinical Implications

These findings have clinical relevance in the management of heart failure (HF) because they emphasize the SGLT2 inhibitors as one of the key therapies in managing cardiovascular mortality. Due to the wide range of effectiveness in both HFrEF and HFpEF, as well as in patients with and without diabetes, SGLT2 inhibitors ought to be added as an essential medicine to the traditional medications of heart failure, which include beta-blockers, renin–angiotensin–aldosterone system (RAAS) inhibitors, and mineralocorticoid receptor antagonists (MRAs). These factors all together make SGLT2 inhibitors an effective therapy for reducing CVD mortality, preventing heart failure hospitalizations, and improving health-related quality of life in heart failure patients. Furthermore, their nephroprotective effects are especially beneficial for patients with concomitant chronic kidney disease (CKD), adding to their rationale for widespread use in clinical practice. In light of these findings, heart failure treatment guidelines will need to be amended to recommend the routine use of SGLT2 inhibitors in all eligible HF patients. Current guidelines from the American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) have already endorsed SGLT2 inhibitors as class I recommendations for HFrEF and emerging data support their use in HFpEF as well. The findings of this meta-analysis arguably provide more substantial support for expanding guideline recommendations so that SGLT2 inhibitors are invoked earlier in the HF treatment algorithm instead of as a supplementary treatment, which is how most guidelines recommend it. Healthcare professionals should be advised to include SGLT2 inhibitors in standard HF management, particularly for these patients with SGLT2-optimised treatment to the greatest extent attainable for improved mortality and long-term outcomes in this vulnerable population (Fahimi et al, 2024).

Limitations

This meta-analysis has found some compelling evidence; however, there is insufficient quantitative and qualitative information available to provide a basis for the analysis. One of the critical issues is divergence in sample sizes and the duration of trials among the included studies. There is other evidence as well to support other correlational studies as some trials were multi-centric, while others had a small sample size, thereby increasing the effect estimate variance. In addition, the follow-up periods were from 6 months to 3 years, which means that any prolonged cardiovascular mortality benefits after this time frame are not clear. Considering that HF is an ongoing ailment, there is a need for long-duration studies to analyze the effect of SGLT2 inhibitors on survival and mortality beyond the timeline of the current trial. It is also plausible as a limitation that some reporting bias may come into play as smaller studies with no or negative findings may not have been submitted despite attempting to do so for publication bias using funnel plot and Egger's test. While these analyses showed no substantial bias, it is essential to note that selective bias cannot be eliminated. Some of the trials were also designed differently, where some were only aimed at HFrEF patients, and some used a mixed population of HFrEF and HFpEF, so this finding may suffer from heterogeneity, which would lead to variability in the patient population and treatment modalities. Statistically, some of the included studies displayed moderate heterogeneity (I value greater than 25%), and that was expected in the data set by $I^2 = 38$. While subgroup and sensitivity analyses reveal possible aspects of heterogeneity, such as specific types of HF,

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comorbidity patterns, and follow-up duration, some elements of heterogeneity still exist. The implementation of these variations was assisted by the combined use of both fixed and random effects models; however, differences in study designs, primary patient demographics, and other institutional factors may still affect the external validity of the findings. Perhaps future individual patient-level meta-analyses will shed light on the effects of clinically meaningful heterogeneity and enhance the clinical utility of SGLT2 inhibitors.

Future Research Directions

This meta-analysis strongly supports SGLT2 inhibitors as pivotal in lowering cardiovascular mortality for patients suffering from heart failure (HF). Yet, there are a number of aspects that can be explored further. Long-term clinical studies designed to assess the continued efficacy and safety of SGLT2 inhibitors beyond three years of follow-up would be one such focus. Most available studies have limited timeframes, making it challenging to evaluate prolonged survival rates, possible surgery adverse effects, and the long-term efficacy of cardiovascular and renal preservation. Subsequent research ought to focus on progressive HF patients across the globe. It should have SGLT2 inhibitors as the focus, determining whether the short-term mortality reduction seen in past studies will continue decades later. One more primary focus is placed on the recruitment of patients from a broader range of clinics. Some studies have focused on high-income countries which have well-developed healthcare systems. Due to such restrictive parameters, it may be challenging to evaluate the effectiveness of SGLT2 inhibitors in lower-resourced countries. Trials are also required to examine ethnic minority, underserved, and rural population strata where the availability of universal HF therapeutics and medication compliance is likely to vary. In addition, further research should evaluate the performance of SGLT2 inhibitors in other particular groups like advanced HF patients (NYHA Class III-IV) with preserved ejection fraction (HFpEF) or patients with multi-organ failure, including severe chronic kidney disease or liver failure. Similarly significant is the area of research focusing on individualized treatment modalities for heart failure patients on SGLT2 inhibitor therapy. While an overall mortality advantage is well accepted, not all patients improve to the same extent. More effort is needed to determine markers or clinical parameters that can personalize therapy and identify patients who will receive the maximum benefit from SGLT2 inhibitors. Precision medicine, mainly genetic and proteomic approaches, might shed more light on the different responses of various patient subgroups towards treatment for heart failure. Further development is also required for combination therapy techniques. Though independent SGLT2 inhibitor benefits exist, their relationships with other new heart failure treatment tactics, such as sodium-glucose cotransporter-1 (SGLT1) inhibitors, new RAAS blockers, and GLP-1 receptor agonists, are of scientific interest. New studies ought to explore optimal combinations of medications, possible synergistic effects, and the best order for using heart failure therapies in order to improve the results for patients. SGLT2 inhibitors changed the approach to the management of heart failure. Still, more thorough research needs to be done concerning the long-term effects on various populations, precision treatment, and different combinations for the world's best heart failure management practices.

Conclusion

This meta-analysis strengthens the rationale for employing SGLT2 inhibitors as pharmacological agents intended to attenuate cardiovascular mortality in patients with heart failure (HF). The analysis from different randomized controlled trials showed that there is a 22% decrease in cardiovascular mortality, which supports the decisive cardioprotective actions of these agents beyond their glucose-lowering effects. These "other" effects seem to be very consistent for all types of heart failure patients (HFrEF, HFpEF), different ages, and in both types of diabetes, affirming the "one size fits all" approach for these drugs in HF treatment. Suggested reasons for the underlying biological mechanisms and attributed protective effects are linked to natriuresis, osmotic diuresis, decreased stress on myocardial tissues, cardiac metabolism, anti-inflammatory processes, as well as sympathetic modulation, anti-inflammatory effects, and improved cardiac metabolism. Sensitivity analyses confirmed the robustness of these findings, whereas subgroup analyses underscored the fact that more substantial effects were noted among patients with HFrEF, diabetes, and chronic kidney disease (CKD). Considering these observations, policymakers and practitioners should focus on establishing a framework to support the use of SGLT2 inhibitors for treatment in clinical settings. Due to the favourable safety profile, ease of administration, and early realization of benefits, these drugs should be among the first line of treatment for those diagnosed with heart failure instead of deploying them at an advanced stage of treatment. SGLT2 inhibitors are the most prescribed medication in heart failure cases and seem to improve cases of CKD and diabetes. Clinicians are responsible for proper patient selection while tracking volume depletion or genitourinary infections that may arise, all the while making the patients aware of the long-term advantages of taking SGLT2 inhibitors.

The integration of these findings goes beyond clinical practice. These results could impact future strategies for cardiovascular disease public health management. Adoption of SGLT2 inhibitors on a grander scale could result in fewer hospitalizations due to heart failure, lower expenditures in healthcare, better rates of survival among patients, and significantly change the 'gold standard' in the treatment of

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heart failure. Additionally, the work on combination therapies, precision medicine, and real-world evidence-generated studies will further define their place in the treatment of cardiovascular diseases. To summarise, SGLT2 inhibitors have changed the outlook of treatment for heart failure for good, providing drastic reductions in cardiovascular mortality. The diversity of their mechanisms of action, a wide range of indications for use, and documented efficacy make SGLT2 inhibitors the foundation of pharmacotherapy for heart failure. With the advancement of heart failure treatment strategies, more patients are expected to receive these medications, which will have the greatest impact on the patient's quality of life and the overall cardiovascular health of populations around the world.

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