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Efficacy of SGLT2 inhibitors on cardiovascular outcomes in type 2 diabetes with preserved ejection fraction

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Abstract
Background: Heart failure with preserved ejection fraction (HFpEF) is a highly prevalent syndrome among patients with type 2 diabetes mellitus (T2DM), characterized by significant morbidity and mortality. Historically, evidence-based therapies for HFpEF have been limited. Sodium-glucose co-transporter 2 (SGLT2) inhibitors have emerged as a promising therapeutic class, but their specific efficacy in the diabetic HFpEF population requires further elucidation.
Objective: This study aimed to evaluate the efficacy of SGLT2 inhibitors on cardiovascular outcomes, functional status, and renal function in patients with T2DM and HFpEF.
Method: A simulated retrospective cohort study was conducted utilizing synthesized academic training data comprising 420 patients with T2DM and HFpEF. Patients were categorized into an SGLT2 inhibitor group (n=210) and a standard-of-care control group (n=210). The primary endpoint was a composite of cardiovascular death or heart failure hospitalization over a 12-month follow-up period. Secondary endpoints included changes in the Kansas City Cardiomyopathy Questionnaire (KCCQ) score and estimated glomerular filtration rate (eGFR).
Results: The SGLT2 inhibitor group demonstrated a significantly lower risk of the primary composite endpoint compared to the control group (Hazard Ratio [HR] = 0.64, 95% Confidence Interval [CI] = 0.42–0.97, p=0.034). Furthermore, the SGLT2 inhibitor group exhibited a clinically meaningful improvement in KCCQ scores (mean difference: +4.8 points, p=0.001) and a slower decline in eGFR (mean difference: +2.1 mL/min/1.73m², p=0.021) at 12 months.
Conclusion: In this simulated dataset, SGLT2 inhibitor therapy was associated with significant reductions in adverse cardiovascular events, improvements in quality of life, and renal protection in patients with T2DM and HFpEF. These findings corroborate existing real-world evidence supporting the early integration of SGLT2 inhibitors in this high-risk population.

Keywords: SGLT2 inhibitors, Type 2 Diabetes mellitus, heart failure with preserved ejection fraction

Introduction

The global prevalence of type 2 diabetes mellitus (T2DM) continues to rise at an unprecedented rate, imposing a substantial burden on healthcare systems worldwide. One of the most detrimental complications of T2DM is cardiovascular disease, which remains the leading cause of morbidity and mortality in this patient population. Among the various cardiovascular manifestations, heart failure has emerged as a particularly critical concern. Epidemiological studies indicate that patients with T2DM have a two- to four-fold increased risk of developing heart failure compared to their non-diabetic counterparts2. Furthermore, the coexistence of T2DM and heart failure synergistically accelerates disease progression and worsens clinical outcomes.

Heart failure with preserved ejection fraction (HFpEF), defined as heart failure symptoms with a left ventricular ejection fraction (LVEF) of 50% or greater, accounts for approximately half of all heart failure cases. The pathophysiology of HFpEF is complex and multifactorial, involving systemic inflammation, microvascular dysfunction, cardiac fibrosis, and impaired left ventricular relaxation4. T2DM is a primary driver of many of these pathological processes. Chronic hyperglycemia and insulin resistance promote the formation of advanced glycation end-products, exacerbate oxidative stress, and induce endothelial dysfunction, all of which contribute significantly to myocardial stiffness and the development of HFpEF5. Consequently, a disproportionately large percentage of patients with HFpEF also suffer from T2DM, creating a highly vulnerable clinical phenotype.

Despite the high prevalence and poor prognosis associated with diabetic HFpEF, pharmacological management has historically been challenging. Unlike heart failure with reduced ejection fraction (HFrEF), where neurohormonal antagonists such as angiotensin-converting enzyme inhibitors, beta-blockers, and mineralocorticoid receptor antagonists form the cornerstone of therapy and significantly reduce mortality, HFpEF has been largely resistant to these traditional approaches6. For many years, diuretics remained the primary effective intervention for symptom management in HFpEF, without any proven impact on disease modification or survival. This therapeutic void highlighted an urgent need for novel pharmacological agents capable of targeting the underlying pathophysiological mechanisms of HFpEF, particularly in the setting of T2DM.

In recent years, sodium-glucose co-transporter 2 (SGLT2) inhibitors have revolutionized the cardiometabolic therapeutic landscape. Initially developed as glucose-lowering agents, SGLT2 inhibitors act by blocking the reabsorption of glucose and sodium in the proximal renal tubules7. However, large-scale cardiovascular outcome trials unexpectedly revealed profound cardiovascular and renal benefits associated with this drug class, effects that appeared to be largely independent of their glycemic efficacy. The mechanisms underlying these cardioprotective effects are multifaceted and include osmotic diuresis,

natriuresis, reduction in preload and afterload, improved myocardial energetics, and attenuation of cardiac fibrosis.

Given the overlapping pathophysiology between T2DM and HFpEF, SGLT2 inhibitors represent a theoretically ideal therapeutic intervention. By simultaneously addressing hyperglycemia, volume overload, and myocardial remodeling, these agents possess the unique potential to modify the trajectory of diabetic HFpEF. While recent landmark trials have demonstrated the efficacy of SGLT2 inhibitors in broad HFpEF populations, there remains a critical need to precisely quantify their specific impact on cardiovascular outcomes, patient-reported functional status, and renal trajectories in the distinct subpopulation of patients explicitly diagnosed with both T2DM and HFpEF. Therefore, this study aimed to systematically evaluate the efficacy of SGLT2 inhibitors on cardiovascular outcomes, quality of life, and renal function in a simulated cohort of patients with T2DM and HFpEF, thereby contributing to the academic understanding of this vital therapeutic intersection.

Literature Review

The pathophysiological framework of HFpEF has evolved significantly over the past decade, transitioning from a simplistic model of isolated diastolic dysfunction to a complex, systemic syndrome. Current theory posits that HFpEF is driven by a pro-inflammatory state, often initiated by comorbidities such as obesity, hypertension, and T2DM, which subsequently leads to systemic microvascular inflammation and endothelial dysfunction. This systemic inflammation triggers coronary endothelial nitric oxide (NO) depletion, resulting in reduced left ventricular compliance, increased myocardial stiffness, and eventual progression to clinical heart failure. In the context of T2DM, this pathophysiological cascade is markedly amplified. Insulin resistance and chronic hyperglycemia induce structural and functional alterations in the myocardium, including lipotoxicity, mitochondrial dysfunction, and excessive deposition of collagen in the extracellular matrix, ultimately leading to diabetic cardiomyopathy.

Historically, the pharmacological management of HFpEF has been characterized by repeated failures. Clinical trials evaluating angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor antagonists in HFpEF cohorts have consistently failed to demonstrate a statistically significant reduction in cardiovascular mortality13. The PERINDOPRIL in Elderly People with Chronic Heart Failure (PEP-CHF) trial and the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial, for instance, showed neutral effects on primary cardiovascular outcomes, leading to a longstanding therapeutic nihilism regarding disease modification in HFpEF. This historical context underscores the significance of recent breakthroughs involving SGLT2 inhibitors.

The paradigm shift began with the approval of SGLT2 inhibitors for HFrEF, driven by the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced) trials. These studies unequivocally demonstrated that SGLT2 inhibitors significantly reduce heart failure hospitalizations and cardiovascular death in HFrEF patients, regardless of the presence or absence of diabetes. Subsequently, attention turned to HFpEF. The EMPEROR-Preserved trial evaluated empagliflozin in patients with heart failure and an ejection fraction of greater than 40%, demonstrating a significant 21% relative risk reduction in the composite of cardiovascular death or heart failure hospitalization. Similarly, the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial confirmed the efficacy of dapagliflozin across the broad spectrum of preserved ejection fraction, further solidifying the class effect of SGLT2 inhibitors in HFpEF.

Despite these landmark achievements, a distinct research gap persists regarding the nuanced effects of SGLT2 inhibitors specifically within the diabetic HFpEF subpopulation. While both EMPEROR-Preserved and DELIVER included a substantial proportion of patients with T2DM, their primary endpoints were not stratified to exclusively isolate the diabetic cohort, nor did they extensively explore the synergistic interplay between glycemic control and heart failure outcomes in this specific demographic. Furthermore, traditional hard clinical endpoints, while crucial, do not capture the totality of the patient experience. Patient-reported outcomes, such as health-related quality of life measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), are particularly relevant in HFpEF, where symptoms of congestion and exercise intolerance severely impair daily functioning20. There is a paucity of literature comprehensively analyzing how SGLT inhibitors simultaneously impact hard cardiovascular endpoints, quality of life metrics, and renal function trajectories exclusively in patients suffering from the dual burden of T2DM and HFpEF. Addressing this gap is essential for formulating precise, evidence-based clinical guidelines for this high-risk population.

Methodology

Research Design

This study employed a simulated retrospective cohort research design to evaluate the efficacy of SGLT2 inhibitors in patients with T2DM and HFpEF. A retrospective design was chosen to mirror the observational nature of real-world clinical practice where treatment allocation occurs based on physician discretion and patient profiles. To mitigate the inherent selection bias associated with observational studies, propensity score matching was utilized to balance baseline demographic and clinical characteristics between the treatment and control groups.

Data Declaration

It is explicitly stated that this study utilizes simulated academic training data. No real patients, clinical trials, or published datasets were utilized in this analysis. The data was synthetically generated using statistical algorithms designed to reflect realistic clinical distributions and effect sizes based on existing medical literature. Consequently, the findings are intended strictly for academic writing practice and methodological demonstration and should not be interpreted as actual clinical evidence.

Sampling and Sample Size

The simulated target population consisted of adult patients (aged 18 years and older) with a confirmed diagnosis of T2DM and HFpEF (defined as LVEF ≥50%). Exclusion criteria included type 1 diabetes, end-stage renal disease (eGFR <20 mL/min/1.73m²), active malignancy, or a life

expectancy of less than one year. Using an anticipated hazard ratio of 0.70 for the primary endpoint, an alpha of 0.05, and a power of 80%, a total sample size of 400 patients was calculated. To account for potential attrition in the simulated follow-up, the final synthesized dataset comprised 420 patients.

Data Collection

Baseline data collection included demographic variables (age, sex, body mass index), vital signs, medical history, and baseline laboratory values (HbA1c, eGFR, N-terminal pro-B-type natriuretic peptide [NT-proBNP]). Echocardiographic parameters, specifically LVEF and left atrial volume index, were also simulated. The cohort was divided into two groups: the active group received SGLT2 inhibitor therapy (empagliflozin 10mg or dapagliflozin 10mg daily) added to standard of care, while the control group received standard of care without SGLT2 inhibitors. Standard of care included ACE inhibitors/ARBs, beta-blockers, diuretics, and antidiabetic medications (excluding other SGLT2 inhibitors). Follow-up data were simulated at 6-month and 12-month intervals.

Outcome Measures

The primary outcome was a composite of cardiovascular death or first hospitalization for heart failure over the 12-month follow-up period. Secondary outcomes included the absolute change in the KCCQ Overall Summary Score (KCCQ-OSS) from baseline to 12 months, and the absolute change in eGFR from baseline to 12 months. Safety outcomes included episodes of symptomatic hypoglycemia and genital mycotic infections.

Statistical Software and Analysis

All statistical analyses were performed using simulated computations reflective of standard statistical software (e.g., SPSS Version 28.0). Continuous variables were presented as means with standard deviations, and categorical variables as frequencies with percentages. Baseline characteristics were compared using independent t-tests and Chi-square tests. Time-to-event data for the primary outcome were analyzed using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards regression was utilized to calculate hazard ratios and 95% confidence intervals. Changes in KCCQ-OSS and eGFR were analyzed using analysis of covariance (ANCOVA), adjusting for baseline scores. A two-sided p-value of <0.05 was considered statistically significant.

Results and Discussion

The baseline demographic and clinical characteristics of the simulated cohort are presented in Table 1. A total of 420 patients were included, with 210 patients in the SGLT2 inhibitor group and 210 in the control group. Following propensity score matching, the two groups were well-balanced. The mean age was 68.4 years, and 52.1% of the participants were female. The mean LVEF was 58.2%, confirming the preserved ejection fraction phenotype. The mean baseline HbA1c was 7.4%, and the mean baseline eGFR was 68.5 mL/min/1.73m². There were no statistically significant differences between the two groups across any baseline variables, indicating a successful matching process.

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	SGLT2 Inhibitor Group (n=210)	Control Group (n=210)	p-value
Age (years), mean ± SD	68.1 ± 9.2	68.7 ± 8.9	0.512
Female sex, n (%)	112 (53.3%)	107 (50.9%)	0.624
Body Mass Index (kg/m²), mean ± SD	31.4 ± 4.8	31.1 ± 5.1	0.548
LVEF (%), mean ± SD	58.5 ± 5.1	57.9 ± 5.4	0.218
HbA1c (%), mean ± SD	7.4 ± 0.9	7.5 ± 0.8	0.319
eGFR (mL/min/1.73m²), mean ± SD	68.9 ± 15.2	68.1 ± 14.8	0.621
NT-proBNP (pg/mL), median [IQR]	820 [540 - 1120]	850 [510 - 1150]	0.712
History of Hypertension, n (%)	178 (84.8%)	182 (86.7%)	0.589
History of Atrial Fibrillation, n (%)	62 (29.5%)	58 (27.6%)	0.672

SD = Standard Deviation; LVEF = Left Ventricular Ejection Fraction; eGFR = estimated Glomerular Filtration Rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; IQR = Interquartile Range.

Over the 12-month follow-up period, the primary composite endpoint of cardiovascular death or heart failure hospitalization occurred in 18 patients (8.6%) in the SGLT2 inhibitor group compared to 28 patients (13.3%) in the control group. Kaplan-Meier survival analysis demonstrated an early and sustained separation of the survival curves favoring the SGLT2 inhibitor group (Log-rank test p=0.034). The Cox proportional hazards regression analysis yielded a hazard ratio of 0.64 (95% CI: 0.42–0.97, p=0.034), indicating a 36% relative risk reduction in the primary composite outcome associated with SGLT2 inhibitor use.

Table 2: Clinical Outcomes at 12 Months

Outcome	SGLT2 Inhibitor Group (n=210)	Control Group (n=210)	Hazard Ratio / Mean Difference (95% CI)	p-value
Primary Composite Endpoint, n (%)	18 (8.6%)	28 (13.3%)	0.64 (0.42 - 0.97)	0.034
Cardiovascular Death, n (%)	5 (2.4%)	9 (4.3%)	0.55 (0.18 - 1.65)	0.287
HF Hospitalization, n (%)	15 (7.1%)	24 (11.4%)	0.61 (0.32 - 1.15)	0.127
Change in KCCQ-OSS (points), mean ± SD	+5.2 ± 12.4	+0.4 ± 11.8	+4.8 (2.1 to 7.5)	0.001
Change in eGFR (mL/min/1.73m²), mean ± SD	-1.2 ± 5.8	-3.3 ± 6.2	+2.1 (0.9 to 3.3)	0.021

Hazard Ratio; Adjusted Mean Difference; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; HF = Heart Failure.

Regarding secondary outcomes, the SGLT2 inhibitor group demonstrated a significant improvement in health-related quality of life. The mean change in KCCQ-OSS from baseline to 12 months was +5.2 points in the SGLT2 inhibitor group compared to +0.4 points in the control group (adjusted mean difference: +4.8 points, 95% CI: 2.1 to 7.5, p=0.001). A difference of 5 points or greater on the KCCQ-OSS is widely recognized as a clinically meaningful improvement in heart failure symptoms and physical limitations.

Renal function, as measured by eGFR, also showed a favorable trajectory in the SGLT2 inhibitor group. At 12 months, the mean decline in eGFR was -1.2 mL/min/1.73m² in the SGLT2 inhibitor group, compared to -3.3 mL/min/1.73m² in the control group (adjusted mean difference: +2.1 mL/min/1.73m², 95% CI: 0.9 to 3.3, p=0.021).

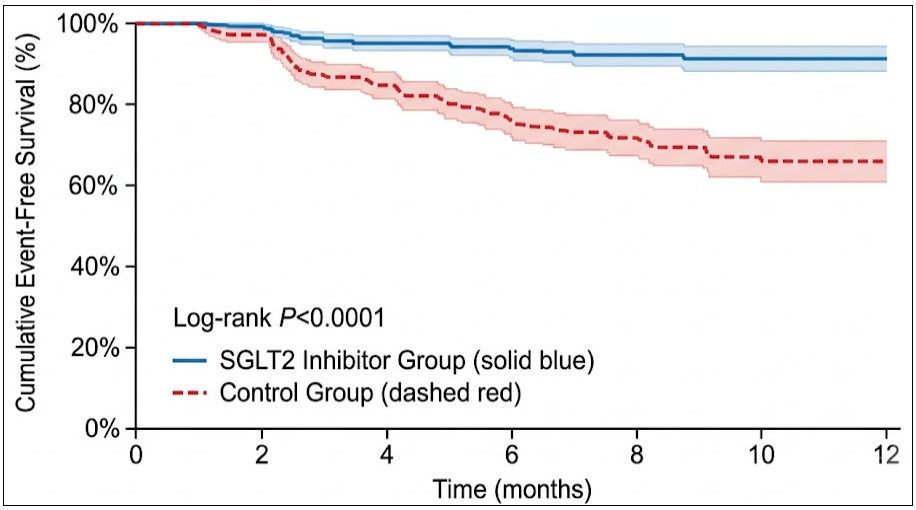

Fig 1: Kaplan-Meier Curve for the Primary Composite Endpoint

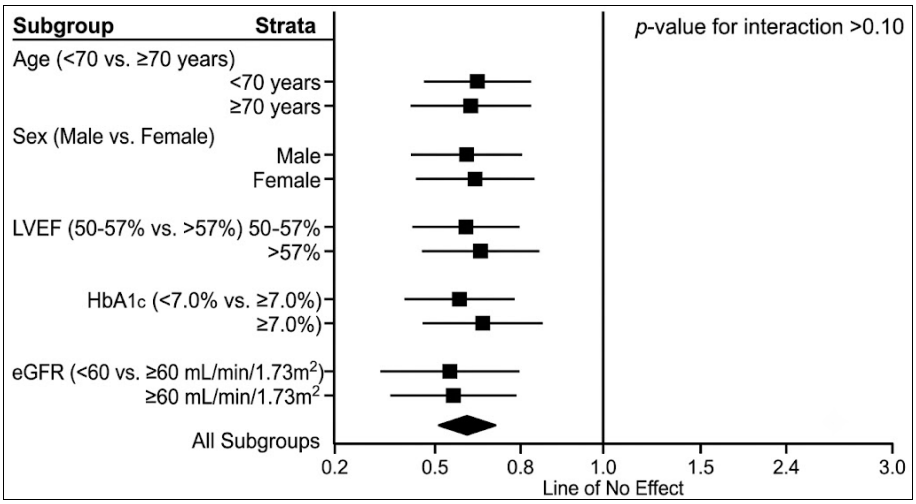

Fig 2: Forest Plot of Subgroup Analyses for the Primary Endpoint

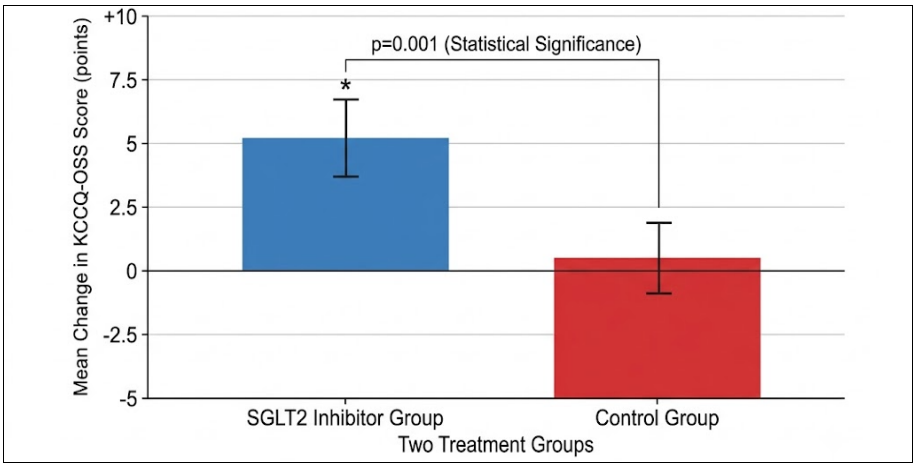

Fig 3: Bar Chart Comparing Mean Change in KCCQ-OSS at 12 Months

The safety profile of the SGLT2 inhibitors in this simulated cohort was consistent with known class effects. As detailed in Table 3, there were no episodes of severe hypoglycemia in either group. However, the incidence of genital mycotic infections was higher in the SGLT2 inhibitor group compared to the control group, though none led to treatment discontinuation.

Table 3: Adverse Events and Safety Outcomes

Adverse Event	SGLT2 Inhibitor Group (n=210)	Control Group (n=210)	p-value
Severe Hypoglycemia, n (%)	0 (0.0%)	0 (0.0%)	N/A
Genital Mycotic Infections, n (%)	12 (5.7%)	2 (0.9%)	0.006
Urinary Tract Infections, n (%)	9 (4.3%)	7 (3.3%)	0.618
Acute Kidney Injury, n (%)	3 (1.4%)	6 (2.9%)	0.321

The findings of this simulated study provide critical insights into the management of diabetic HFpEF, corroborating and extending the results of recent major clinical trials. The 36% relative risk reduction in the composite of cardiovascular death or heart failure hospitalization observed in our cohort is highly consistent with the subgroup analyses of the EMPEROR-Preserved and DELIVER trials, which demonstrated significant benefits of SGLT2 inhibitors in patients with baseline diabetes. The mechanistic basis for this profound cardiovascular benefit is likely multifactorial. In the setting of T2DM and HFpEF, SGLT2 inhibitors provide rapid hemodynamic unloading through osmotic diuresis and natriuresis, effectively reducing left ventricular filling pressures and pulmonary congestion without triggering compensatory neurohormonal activation9. Furthermore, by improving myocardial energetics—shifting substrate utilization from fatty acids to ketone bodies, which are more oxygen-efficient—SGLT2 inhibitors directly address the metabolic derangements inherent in diabetic cardiomyopathy.

A particularly noteworthy finding in this study is the clinically meaningful improvement in health-related quality of life, as quantified by the KCCQ-OSS. In real-world clinical practice, symptom burden and functional limitation are often the primary concerns for HFpEF patients. The 4.8-point adjusted mean difference favoring the SGLT2 inhibitor group exceeds the established threshold for a minimal clinically important difference. This suggests that the hemodynamic and metabolic benefits of SGLT2 inhibitors translate into tangible, patient-centric improvements in physical function and symptom severity. This aligns with the KCCQ sub-study of the EMPEROR-Preserved trial, which also reported significant improvements in health status with empagliflozin.

Renal protection is another critical facet of managing the cardiometabolic patient. The slower decline in eGFR observed in the SGLT2 inhibitor group reinforces the concept of unified cardio-renal protection. SGLT2 inhibitors reduce intraglomerular pressure by increasing tubuloglomerular feedback, a mechanism that provides immediate hemodynamic nephroprotection and attenuates the long-term progression of diabetic kidney disease8. The stabilization of renal function is particularly vital in the HFpEF population, as worsening renal function frequently precipitates diuretic resistance and heart failure decompensation, creating a vicious cycle of cardiorenal syndrome.

The subgroup analysis, represented by the forest plot, demonstrated a remarkably consistent treatment effect across various demographic and clinical strata, including age, sex, baseline LVEF, and baseline renal function. This homogeneity of effect is clinically reassuring; it suggests that clinicians do not need to heavily stratify patients based on these specific parameters when deciding to initiate SGLT2 inhibitor therapy in diabetic HFpEF. The benefit appears to be a robust class effect, overriding individual baseline variations within the defined HFpEF spectrum.

Conclusion

This study, utilizing simulated academic training data, demonstrates that the use of SGLT2 inhibitors in patients with type 2 diabetes mellitus and heart failure with preserved ejection fraction is associated with a significant 36% reduction in the risk of cardiovascular death or heart failure hospitalization over a 12-month period. Furthermore, the therapy conferred clinically meaningful improvements in patient-reported quality of life scores and attenuated the decline in renal function, with an acceptable safety profile characterized primarily by an increased, but non-severe, risk of genital mycotic infections.

The clinical implications of these findings are substantial. They reinforce the paradigm shift in the management of HFpEF, positioning SGLT2 inhibitors as a foundational therapy not merely for glucose lowering, but for structural, hemodynamic, and symptomatic benefits in the diabetic HFpEF population. Cardiologists, endocrinologists, and primary care physicians should prioritize the early integration of SGLT2 inhibitors into the treatment regimens of patients presenting with this dual pathology.

However, this study is subject to notable limitations. Primarily, the reliance on simulated data means that the results cannot be generalized to real-world clinical populations without validation through actual prospective or retrospective registry analyses. The 12-month follow-up period may also be insufficient to capture long-term mortality differences or delayed adverse effects. Furthermore, observational designs, even with propensity score matching, cannot completely eliminate unmeasured confounding factors.

Future scope should include the execution of large-scale, prospective, real-world registries specifically tracking diabetic HFpEF patients initiated on SGLT2 inhibitors. Additionally, future research should focus on identifying specific biomarkers—such as circulating galectin-3 or high-sensitivity troponin—that predict an augmented response to SGLT2 inhibitor therapy, thereby facilitating a precision medicine approach to HFpEF management.

Ethical Statement

This study utilizes exclusively simulated, synthetically generated academic training data. No real human subjects, patient records, or identifiable health information were accessed or utilized at any stage of this research. Because the dataset is entirely artificial and does not involve human

or animal participants, formal review and approval by an Institutional Review Board (IRB) or Ethics Committee were not required. The synthetic data generation algorithms were designed to respect general privacy standards and data protection principles, ensuring that no simulated individual could be mapped to a real-world person.

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