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Effect of SGLT2 inhibitors on the quantitative slowdown of estimated glomerular filtration rate slope in patients with heart failure with preserved ejection fraction: A systematic review and meta-analysis

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Abstract
Background: Sodium-glucose transport protein 2 inhibitors are beneficial in treating patients with heart failure with preserved ejection fraction, who commonly experience deteriorating kidney function. Sodium-glucose transport protein 2 inhibitors have been found to have a beneficiary effect in reducing the decline in kidney function, as evaluated by the estimated glomerular filtration rate slope. This meta-analysis aimed to determine sodium-glucose transport protein 2 inhibitor treatment-mediated quantitative reduction in the estimated glomerular filtration rate slope in patients with heart failure with preserved ejection fraction.
Methods: A systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines to identify randomised controlled trials comparing treatment with an sodium-glucose transport protein 2 inhibitor with that of a placebo in evaluating the tendency of decreased kidney function with the estimated glomerular filtration rate slope using PubMed, EBSCOhost, ProQuest, Google Scholar, and Web of Science databases. We performed a random-effects inverse-variance-weighted meta-analysis of the estimated glomerular filtration rate slope outcome.
Results: A total of two studies involving 12250 patients of 585 initially identified studies were included in the final analysis. Reduction in estimated glomerular filtration rate slope was significantly different between patients treated with sodium-glucose transport protein 2 inhibitors and those administered placebo (Mean difference = 0.94, 95% Confidence Interval = 0.09-1.80, P = 0.03, I^2 = 92%, Low Quality).
Conclusion: A substantial reduction was observed in the estimated glomerular filtration rate slope in sodium-glucose transport protein 2-treated patients by 0.94 ml/min per 1.73 m^2, which was almost the same as that found in the normal population. Further research is needed to improve study quality and better evaluate the effect of sodium-glucose transport protein 2 inhibitors treatment on improved kidney function in patients with heart failure with preserved ejection fraction.

Keywords: Sodium-glucose transporter 2 inhibitors, heart failure, diastolic, glomerular filtration rate, kidney glomerulus, cardiovascular diseases

Introduction
Heart failure with preserved ejection fraction (HFpEF) is a heart failure marked by impaired heart relaxation and filling during diastole [1]. Its pathophysiology involves systemic inflammation, endothelial dysfunction, ventricular stiffness, and impaired ventricular-vascular coupling, leading to elevated filling pressures and symptoms such as dyspnoea, exercise intolerance, and fluid retention. Managing HFpEF is challenging owing to limited therapeutic options and incomplete understanding of its mechanisms [2].
Traditional treatments, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and beta-blockers, have shown inconsistent benefits in HFpEF, underscoring the need for novel therapies. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, originally developed for type 2 diabetes, have shown promise for cardiovascular and renal benefits, including natriuresis, blood pressure reduction, and improved cardiac

remodelling [3]. Clinical trials, such as EMPEROR-Preserved and DELIVER, suggest that SGLT2 inhibitors can reduce hospitalisations and enhance quality of life in patients with HFpEF [4].

Renal function preservation is critical in HFpEF, as many patients have chronic kidney disease or are at risk of renal decline. Although SGLT2 inhibitors have demonstrated renoprotective effects by slowing eGFR decline and reducing adverse renal outcomes, their specific impact on HFpEF populations remains under study [4-6]. SGLT2 inhibitors improve kidney function by reducing glucose and sodium reabsorption in the proximal tubule, leading to glucosuria and natriuresis. This mechanism lowers intraglomerular pressure via enhanced tubuloglomerular feedback, mitigates hyperglycaemia-induced renal damage, and reduces inflammation and oxidative stress. These effects collectively slow chronic kidney disease progression and improve renal outcomes [7].

This systematic review and meta-analysis evaluated the effect of SGLT2 inhibitors on the quantitative slowdown of the eGFR slope in patients with HFpEF using data from multiple trials.

Materials and Methods

Study Design

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [8]. This study has been registered in the PROSPERO database (ID:CRD42025642514). Inclusion criteria included the following: (1) HFpEF with ejection fraction (EF) >40%, (2) treatment using any SGLT2 inhibitor and compared to that using a placebo, and (3) the evaluated outcome was the rate of decline in eGFR in the patients. We excluded studies with (1) patients aged below 18 years, (2) non-human subjects or *in vitro* studies, (3) a combination with other therapies, (4) data that could not be reliably extracted, and (5) duplicate or overlapping data. Abstract-only papers as preceding papers, conference papers, editorials, author responses, theses, books, case reports and series, non-English written studies, and systematic review articles were also excluded.

We searched PubMed, EBSCOhost, ProQuest, Google Scholar, Web of Science databases using the following keywords: ((HFpEF) OR (Heart Failure Preserved Ejection Fraction)) AND ((SGLT2 Inhibitor) OR (SGLT2) OR (Dapagliflozin) OR (Empagliflozin)) AND ((Renal) OR (Kidney) OR (Glomerular Filtration Rate) OR (Estimated Glomerular Filtration Rate) OR (eGFR)).

Ethical Statement

As the patient data were extracted as anonymised data, informed consent was not required.

Outcomes

The primary outcome was the eGFR slope of patients with HFpEF treated with SGLT2 inhibitors compared to that with the placebo. The eGFR slopes are obtained by calculating the difference in eGFR values of the patients each year during the span of the study. The change in eGFR is an important aspect to evaluate in patients with heart failure, especially in those with HFpEF, because over 50% of patients with HFpEF are found to have renal impairment [9]. Recently, SGLT2 inhibitors have proven to be beneficial for patients with heart failure and may be useful in improving kidney function. The quantitative degree of the improvement in kidney function can be evaluated from the eGFR values.

Data Extraction

Two investigators (KW and NB) extracted data from all studies that met the inclusion criteria, including author, trial name, SGLT2 inhibitor drugs, sample size, follow-up duration, and eGFR slope. The data were compiled in a dedicated Excel spreadsheet. The primary endpoint was to determine the difference in eGFR slope between SGLT2 inhibitor and placebo treatments in patients with HFpEF. All collected data were analysed according to the Cochrane Handbook guidelines.

The studies were then assessed for risk of bias by the two investigators using the Cochrane Risk of Bias 2 (RoB 2) tool. Study quality was also evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment guidelines by Cochrane.

Data Analysis

We conducted a meta-analysis using the mean differences in eGFR slope. We performed random effects and inverse variance weighting using the Review Manager (RevMan Web) software version 8.5.2. Between-study heterogeneity was evaluated using I^2 statistics.

Results

Search Results and Quality Assessment

We conducted the search on 7 February, 2025 and retrieved a total of 266 studies from PubMed, 217 from EBSCOhost, 100 from ProQuest, 190 from Google Scholar, and 294 from Web of Science databases. After removing 482 duplicate studies, 562 more were excluded during the screening phase: 485 based on titles and 77 based on abstracts. Of the 23 full-text studies retrieved from the analysis, 9 had incomplete data, 7 had unavailable full-text study, and 5 met the exclusion criteria (Fig. 1).

Two studies were finally included in this meta-analysis. Data from these studies were compiled into an Excel spreadsheet, including information on the author, trial name, SGLT2 inhibitor drugs, sample size, follow-up duration, and eGFR slope (Table 1).

Methodological Quality Assessment

The included studies underwent a risk of bias assessment using the Cochrane RoB 2 tool. The risk of bias assessment performed by the two investigators (KW and NB) revealed that all studies had a low risk of bias across all domains, resulting in an overall low risk of bias (Table 2).

The quality of the studies was assessed by the two investigators using GRADE assessment (Table 3). We started the assessment with high quality and downgraded the rating based on concerns related to the risk of bias, inconsistency, indirectness, imprecision, or publication bias. After considering all the factors, the study quality was deemed low. Severe inconsistencies were identified, leading to a two-point downgrade owing to the high heterogeneity of the data, reflected in an I^2 of 92%.

eGFR Slope

A random-effects analysis showed a significant change in the eGFR slope with P = 0.03, a mean difference (MD) of 0.94, and 95% Confidence Interval (CI) of 0.90-1.80. The individual results from the included studies showed a

significant difference between the experimental and control groups with MD values of 0.5 (95% CI 0.11-0.89) [10] and 1.37 (95% CI 1.07-1.67), respectively [11]. Heterogeneity analysis indicated significant heterogeneity with P = 0.0006 and I^2 = 92% (Fig. 2).

Discussion

Heart failure has become one of the most prevalent conditions associated with impaired heart function. Several types of heart failure are based on the EF of the heart: heart failure with reduced EF (≤ 40%), heart failure with mid-range EF (41-49%), and HFpEF (EF ≥ 50%) [12-14].

HFpEF results from not just a cardiovascular disorder but rather a multi-organ disorder including kidney function and metabolic disorder. HFpEF is significantly correlated with kidney disorder, mainly because the risk factors in both are similar. Patients with kidney disorders have been reported to usually develop cardiovascular disorders, which includes HFpEF, and vice versa [15]. Among the several aspects used to evaluate kidney function, eGFR reduction is one. Normally, kidney function naturally deteriorates with age. The normal average rate of decline in eGFR is reported to be 0.82 ml/min per 1.73 m^2 [16]. Heart failure is strongly correlated with decreased kidney function, highlighting the need for suitable treatments to improve the condition of patients with both heart and kidney failures [17].

Recent studies and trials of appropriate treatments for heart failure, particularly HFpEF, have expanded remarkably. Among the promising treatments are SGLT2 inhibitors. Recent studies have shown that SGLT2 inhibitors, which are primarily used to treat diabetes, have several beneficial effects on patients with heart failure, including HFpEF. SGLT2 inhibitors were found to reduce major adverse cardiovascular events, including cardiovascular mortality, nonfatal stroke, and nonfatal myocardial infarction. SGLT2 inhibitors were also effective in the reduction of the cardiovascular-related death and heart failure-related hospitalisation [18, 19]. In addition to being beneficial in cardiovascular aspects, SGLT2 inhibitors have also shown a positive impact on improving renal function [20-23]. The CREDENCE trial found that the risk of kidney failure was significantly reduced in patients treated with SGLT2 inhibitors than in those treated with the placebo [24]. SGLT2 inhibitors also reduced the progression in kidney disease, which could be observed from the reduced eGFR decline in patients with type 2 diabetes [25]. While existing research indicates that SGLT2 inhibitors exert a beneficial effect on renal function in patients with HFpEF, the precise magnitude of their impact in reducing the decline in eGFR within this patient population has not yet been studied. Building on these findings, our study aimed to analyse the amount of reduction in the eGFR slope when using SGLT2 inhibitor treatment compared to that using the placebo in patients with HFpEF.

Our meta-analysis included two studies that compared dapagliflozin and empagliflozin treatment with that of a placebo. We found a significant overall reduction in the eGFR decline in patients treated with SGLT2 inhibitors compared with that in patients receiving the placebo (MD = 0.94). With a reduction in the overall eGFR slope of almost 1 ml/min per 1.73 m^2, this data underscores the potential of SGLT2 inhibitors to improve kidney function in patients with HFpEF. Although previous studies reported the role of SGLT2 inhibitors in improving kidney function, no studies have evaluated the magnitude of the treatment effect on kidney function, especially in patients with HFpEF. Our study results provide significant insight into the extent to which SGLT2 inhibitors can decrease the average eGFR decline, similar to that observed under normal conditions. Therefore, our study demonstrated that SGLT2 inhibitor treatment in patients with HFpEF reduced the kidney function decline, as measured by the eGFR slope, to levels comparable to the normal eGFR decline in healthy populations.

However, the quality of the studies was rated low based on the GRADE assessment owing to a remarkable heterogeneity in the data, which may be attributed to differences in the ages of participants across the studies. Although the included studies used different drugs dapagliflozin 10 mg [10] and empagliflozin 10 mg [11] we believe these variations did not substantially affect the overall data, given the similar mechanisms of action of the drug [26]. The small number of included studies also contributed to the high heterogeneity and had significant impact on the reliability of the analysis. Despite the limited number of studies available for inclusion in the analysis, which may significantly compromise the study's overall quality, the substantial number of participants involved suggests the potential for meaningful findings.

Our meta-analysis had a few limitations. First, we found only two studies from five databases that were suitable and met the criteria of our analysis, which contributed significantly to the high heterogeneity of the data, thus lowering the overall quality of the analysis. Second, as the number of studies that analysed SGLT2 inhibitor effects on the eGFR in patients with HFpEF was still very low, we were unable to perform a subgroup analysis to determine the cause of the high heterogeneity found in our study. Future studies may build upon the findings of the current meta-analysis by analysing data from SGLT2 inhibitor treatment of patients with HFpEF.

Conclusion

Our meta-analysis found that SGLT2 inhibitors substantially reduced the eGFR slope in patients with HFpEF by 0.94 ml/min per 1.73 m^2, which is almost the same extent of eGFR reduction found in the normal population. The GRADE assessment indicated that the included studies had a low risk of bias but were of a low overall quality mainly because of the small number of included studies. Future studies may aim to increase the overall study quality by reducing heterogeneity and conducting subgroup analysis by including additional studies.

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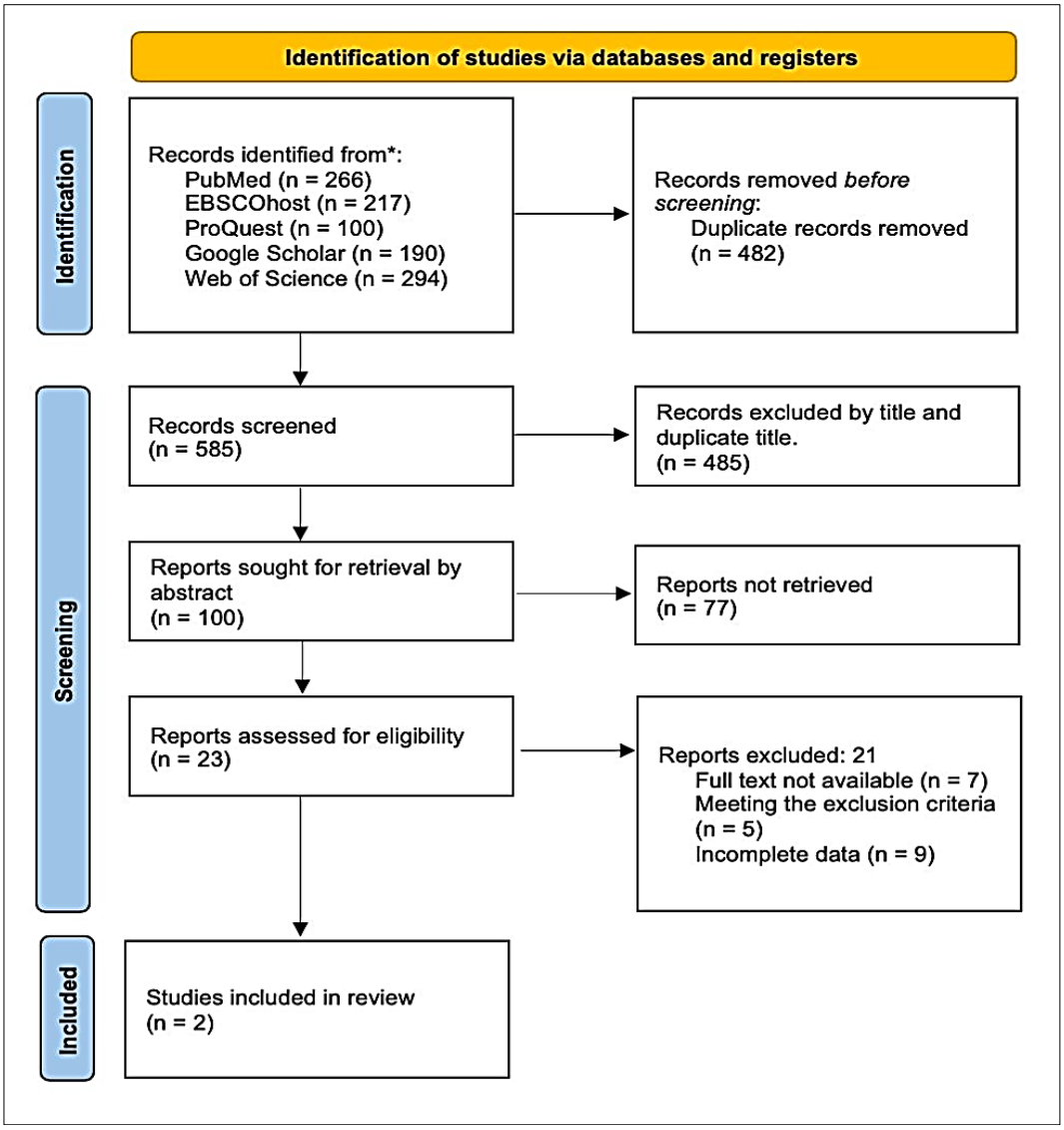

Fig 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart diagram of the study selection process. This figure depicts the systematic process of study design, including the removal of 262 duplicate studies, exclusion of 283 studies during the screening phase (246 based on titles and 37 based on abstracts), and retrieval of 12 full-text studies. Of these, six studies were excluded owing to incomplete data, and four met the exclusion criteria, leading to the final two studies included in the meta-analysis

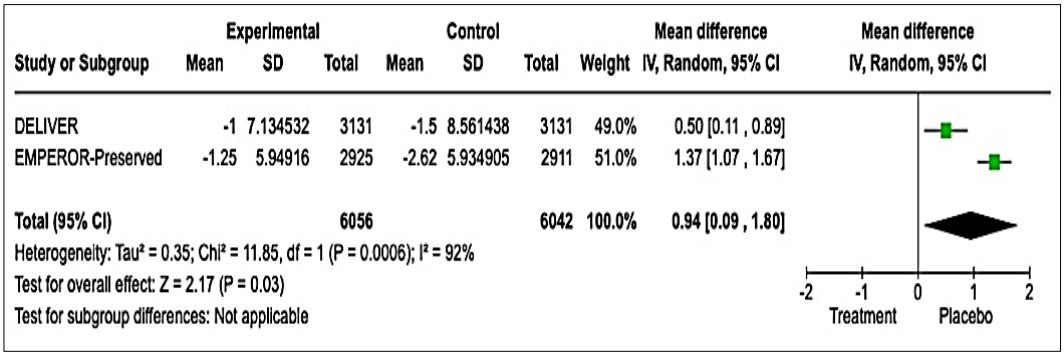

Fig: 2 Meta-analysis of the effect of SGLT2 inhibitors on the eGFR slope in patients with heart failure with preserved ejection fraction. The forest plot compares the mean difference in eGFR slope between patients treated with SGLT2 inhibitors (experimental) and those administered a placebo (control) across two studies: DELIVER and EMPEROR-Preserved. The plot shows the weighted mean difference (IV, Random, 95% CI) for each study, along with the total effect size. Heterogeneity statistics are included: $Tau^2 = 0.35$, $Chi^2 = 11.85$, df = 1, P = 0.0006, $I^2 = 92\%$. The overall effect test indicates a statistically significant improvement in the eGFR slope for the treatment group (Z = 2.17, P = 0.03). eGFR: estimated glomerular filtration rate; SGLT2: sodium-glucose transport protein 2

Table 1: Summary of the characteristics and data extracted from the two studies included in the meta-analysis

Study Characteristics				Results			Trial
				Follow-up			
Author, Year	SGLT2 Inhibitor Type[a]	Sample Size[b]	Follow-up Duration[c]	Treatment	Control	Diff	
Stefan, 2021	Empagliflozin 10 mg	5988	26 months	−1.25 ± SE 0.11	−2.62 ± SE 0.11	1.36 (1.06-1.66)	EMPEROR-Preserved
Mc Causland, 2022	Dapagliflozin 10 mg	6262	36 months	−1.0 (−1.3 to −0.8)	−1.5 (−1.8 to −1.2)	0.5 (0.1-0.9)	DELIVER

SGLT2: sodium-glucose transport protein 2
[a] Type of SGLT2 inhibitor used includes dapagliflozin and empagliflozin
[b] Sample size represents the number of patients included in each study
[c] Duration of follow-up is the length of time patients were monitored in each study

Table 2: Risk of bias assessment for included studies using the Cochrane RoB2 tool. The table presents the assessment of bias risk across five key domains (D1: Randomisation process, D2: Deviations from intended interventions, D3: Missing outcome data, D4: Measurement of the outcome, D5: Selection of the reported result) for the EMPEROR-Preserved and DELIVER trials. Each domain is categorised as indicating low risk, some concerns, or high risk, as evaluated by two investigators (KW and NB). The overall risk of bias is derived from the individual domain assessments for each study.

Study ID	D1	D2	D3	D4	D5	Overall
EMPEROR-Preserved	+	+	+	+	+	+
DELIVER	+	+	+	+	+	+
	D1	Randomisation process			+	Low risk[a]
	D2	Deviations from the intended interventions			!	Some concerns[b]
	D3	Missing outcome data			–	High risk[c]
	D4	Measurement of the outcome				
	D5	Selection of the reported result				

[a] indicates low risk, [b] indicates some concerns, [c] indicates high risk

Table 3: GRADE assessment of eGFR slope outcome in the included studies. This table presents the GRADE evaluation of the eGFR slope outcome based on five criteria: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall quality rating is 'low', with severe inconsistency noted

Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Grade
eGFR Slope	No	Severe	No	No	No	Low

eGFR: estimated glomerular filtration rate; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations

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