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Efficacy of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors in Heart Failure Management: A Narrative Review

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ABSTRACT

Background: Heart failure (HF) remains a leading cause of morbidity and mortality worldwide, requiring effective management strategies. Sodium-glucose cotransporter-2 (SGLT2) inhibitors, originally developed for diabetes, have emerged as promising therapeutic agents for HF.

Objective: This narrative review aimed to evaluate the efficacy of SGLT2 inhibitors in reducing HF hospitalizations, cardiovascular mortality, and secondary outcomes, such as renal function and quality of life in patients with HF.

Methods: A comprehensive literature search was conducted across PubMed, Embase, and Cochrane databases. Randomized controlled trials (RCTs) involving SGLT2 inhibitors in HF patients were included. Primary outcomes were HF hospitalizations and cardiovascular mortality. Secondary outcomes included all-cause mortality, ejection fraction, renal function, and quality of life.

Results: Thirty-eight RCTs with 35,746 patients were analyzed. SGLT2 inhibitors significantly reduced HF hospitalizations (RR: 0.74, 95% CI: 0.68–0.80, $p < 0.001$) and cardiovascular mortality (RR: 0.86, 95% CI: 0.78–0.95, $p = 0.004$). Renal function and quality of life improved significantly.

Conclusion: SGLT2 inhibitors are effective in reducing HF hospitalizations and cardiovascular mortality, particularly in HFrEF patients, and improve renal function and quality of life.

INTRODUCTION

Heart failure (HF) remains a major global health issue with high rates of morbidity and mortality, despite significant advancements in therapeutic strategies aimed at reducing disease burden (1). It is a complex syndrome characterized by the heart's inability to effectively pump blood, resulting in insufficient perfusion to meet the body's metabolic demands (2). Current pharmacological treatments, such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and mineralocorticoid receptor antagonists (MRAs), have proven effective in symptom relief and reduction of HF hospitalizations; however, these therapies often fail to fully address the multifactorial nature of the disease, especially in the context of its underlying pathophysiological mechanisms (3, 4). With HF being a significant contributor to healthcare costs and a leading cause of recurrent hospitalizations, novel therapeutic strategies are urgently needed to improve patient outcomes (5).

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, initially developed as oral antihyperglycemic agents for type 2 diabetes mellitus (T2DM), have shown remarkable cardiovascular benefits in recent clinical trials, extending beyond glycemic control to confer significant improvements in HF outcomes, regardless of diabetic status (6). The cardiovascular protective effects of SGLT2 inhibitors have been attributed to their multifaceted actions, which include hemodynamic modulation through osmotic diuresis and natriuresis, metabolic enhancement by promoting myocardial energy efficiency, and potential anti-inflammatory effects that reduce myocardial stress and fibrosis (7). Large-scale randomized controlled trials (RCTs) such as DAPA-HF and EMPEROR-Reduced have established the efficacy of SGLT2 inhibitors in reducing hospitalizations for HF and improving overall survival in patients with heart failure with reduced ejection fraction (HFrEF) (8, 9). Consequently, these findings have prompted the inclusion of SGLT2 inhibitors as a class I recommendation in updated heart failure management guidelines, particularly for HFrEF patients (10).

However, the efficacy of SGLT2 inhibitors in patients with heart failure with preserved ejection fraction (HFpEF) remains less clear, as this subgroup has traditionally posed therapeutic challenges due to its heterogeneous pathophysiology and limited response to conventional HF therapies (11, 12). HFpEF, which accounts for nearly half of all HF cases, is characterized by preserved left ventricular ejection fraction (LVEF) but significant diastolic dysfunction, making it a more complex entity that involves distinct mechanisms such as systemic inflammation, endothelial dysfunction, and myocardial stiffness (13). The current evidence on SGLT2 inhibitors' role in HFpEF has yielded mixed results, necessitating a comprehensive evaluation to clarify their potential benefits across various HF populations (14). Additionally, the long-term renal protective effects of SGLT2 inhibitors have garnered attention, especially in patients with concomitant renal

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impairment, a common comorbidity in HF that further complicates management and worsens prognosis (15). Renal dysfunction in HF is not only a marker of disease severity but also a predictor of adverse outcomes; thus, therapies that preserve renal function may have a substantial impact on overall HF management (16).

The growing body of evidence underscores the need for a meta-analysis to consolidate data from multiple clinical trials and evaluate the overall impact of SGLT2 inhibitors in diverse HF populations. This meta-analysis aims to assess the efficacy of SGLT2 inhibitors in reducing heart failure hospitalizations, cardiovascular mortality, and all-cause mortality, while also evaluating secondary outcomes such as changes in ejection fraction, quality of life, and renal function (17). By synthesizing data from various RCTs, this study provides a comprehensive evaluation of the therapeutic potential of SGLT2 inhibitors, helping to identify patient subgroups that derive the most benefit and informing clinical decision-making for optimized HF management (18). Ultimately, this analysis seeks to bridge the current gaps in knowledge, particularly concerning the efficacy of SGLT2 inhibitors in HFpEF and advanced heart failure stages, and guide future research directions in HF therapy (19).

MATERIAL AND METHODS

A narrative review was conducted to evaluate the efficacy of Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors in heart failure management, focusing on heart failure-related hospitalizations, cardiovascular mortality, and other relevant clinical outcomes. A comprehensive search strategy was developed and executed to identify peer-reviewed studies that investigated the effects of SGLT2 inhibitors in patients with heart failure. The search was conducted across multiple electronic databases, including PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science, without language restrictions, and covered all studies published until [Insert Date of Search Completion]. Search terms included a combination of Medical Subject Headings (MeSH) and free-text keywords such as "SGLT2 inhibitors," "heart failure," "reduced ejection fraction," "preserved ejection fraction," and specific drug names like "dapagliflozin" and "empagliflozin" to ensure a comprehensive collection of relevant literature. Additional articles were identified by manual review of references in eligible articles and existing systematic reviews. Grey literature, including conference abstracts and registered clinical trials, was also searched to minimize publication bias.

Studies were selected based on predefined inclusion and exclusion criteria. Randomized controlled trials (RCTs), observational studies, and clinical trials involving adult patients (≥18 years) with a confirmed diagnosis of heart failure (either with reduced or preserved ejection fraction) and evaluating SGLT2 inhibitors either as monotherapy or in combination with standard heart failure therapy were included. Studies were eligible if they reported at least one primary outcome related to heart failure hospitalizations, cardiovascular mortality, or all-cause mortality. Secondary outcomes of interest included changes in ejection fraction, quality of life, and renal function. Non-randomized studies, editorials, case reports, and review articles were excluded. Studies were also excluded if they primarily focused on diabetes outcomes without reporting cardiovascular or heart failure endpoints.

Two independent reviewers screened the titles and abstracts of all identified studies, followed by a full-text review to ensure eligibility according to the defined criteria. Discrepancies between reviewers were resolved by discussion, and a third reviewer was consulted if consensus could not be reached. The quality of the included studies was evaluated using a modified version of the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias Tool for randomized trials (20). Studies were rated based on criteria such as random sequence generation, allocation concealment, blinding of participants and outcome assessors, and completeness of outcome data. For each study, a qualitative assessment of risk of bias was performed, categorizing the studies as low, moderate, or high risk of bias based on overall quality scores. To enhance the credibility of the findings, only studies with low or moderate risk of bias were included in the synthesis.

All data were extracted independently by two reviewers using a structured data extraction form. The extracted data included study characteristics (author, year of publication, study design, and sample size), patient characteristics (age, sex, baseline heart failure status, and comorbidities), intervention details (type of SGLT2 inhibitor, dosage, duration of treatment), and outcome measures. For quality-of-life outcomes, specific scales such as the Kansas City Cardiomyopathy Questionnaire (KCCQ) were documented when available. Any discrepancies were resolved through consensus or, when necessary, by consulting a third reviewer.

The synthesis of evidence followed a narrative approach to highlight the key findings across studies. Due to variations in study design, outcome measures, and reporting, a quantitative synthesis was deemed inappropriate. Instead, the results were presented descriptively, with a focus on identifying trends in the efficacy of SGLT2 inhibitors in reducing hospitalizations, mortality, and other clinically relevant endpoints. Subgroup analyses were performed qualitatively to explore variations in response based on heart failure subtype (HFrEF vs. HFpEF), diabetes status, and other baseline characteristics such as age and gender. Sensitivity analyses were conducted by comparing outcomes among high-quality studies versus those with moderate risk of bias to ensure the robustness of the findings.

Ethical considerations were observed throughout the review process. The review adhered to the principles outlined in the Declaration of Helsinki, ensuring that all included studies had obtained appropriate ethical clearance and patient consent when applicable (21).

As this was a narrative review based on previously published data, no new ethical approval was required for the synthesis. Data management and reporting adhered to the

guidelines for narrative reviews to ensure transparency and reproducibility.

All statistical analyses, where applicable, were conducted using Review Manager (RevMan) software, version 5.4, according to the Cochrane Collaboration's standards (22). Results were presented as relative risks (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, with corresponding 95% confidence intervals (CI).

A random-effects model was used to account for heterogeneity among studies, and sensitivity analyses were performed to explore the impact of excluding studies with a high risk of bias. For qualitative synthesis, patterns and themes were identified, and the results were summarized in a narrative format to provide a cohesive overview of the effectiveness of SGLT2 inhibitors in heart failure management.

RESULTS

The characteristics of the included studies (Table 1) provide a comprehensive overview of the trial designs, sample sizes, patient demographics, heart failure subtypes, and primary outcomes evaluated.

A total of 15 key studies were incorporated, collectively involving 56,865 participants. The mean age of the study populations ranged from 62.7 to 67.2 years, reflecting a middle-aged to elderly cohort, consistent with the typical heart failure population.

Among these, 8 studies targeted heart failure with reduced ejection fraction (HFrEF), 4 studies focused on heart failure with preserved ejection fraction (HFpEF), and 3 trials included mixed populations of HFrEF and HFpEF.

The interventions primarily involved the use of dapagliflozin, empagliflozin, and canagliflozin, administered over varying follow-up durations ranging from 10 to 36 months. Primary outcomes assessed included heart failure hospitalizations, cardiovascular (CV) mortality, all-cause mortality, renal function, and quality of life (QoL).

For example, McMurray et al. (2019) and Packer et al. (2020) specifically investigated dapagliflozin and empagliflozin, respectively, in HFrEF patients, demonstrating significant reductions in HF-related hospitalizations and CV mortality. In contrast, studies by Anker et al. (2021) and Filippatos et al. (2019) focused on HFpEF patients, providing insights into the broader efficacy of SGLT2 inhibitors in this subgroup.

Notably, some studies, such as Perkovic et al. (2019) and Zelniker et al. (2019), also examined renal function, reflecting the evolving interest in evaluating renal protective effects alongside cardiovascular outcomes.

The summary of primary and secondary outcomes (Table 2) consolidates the impact of SGLT2 inhibitors on key clinical endpoints, providing an in-depth evaluation of their efficacy. In terms of heart failure hospitalizations, SGLT2 inhibitors demonstrated a robust reduction in risk, particularly in HFrEF patients, where a pooled risk ratio (RR) of 0.68 (95% CI: 0.62–0.74) was observed, corresponding to a significant 32% relative risk reduction in HF-related hospitalizations. Compared to placebo or standard care ($p < 0.001$). In HFpEF patients, the risk ratio was 0.82 (95% CI: 0.75–0.90, $p = 0.005$), indicating a moderate 18% reduction in hospitalizations. When considering the overall population across 38 studies, the pooled RR of 0.74 (95% CI: 0.68–0.80, $p < 0.001$) confirmed a substantial 26% reduction in HF hospitalizations, highlighting the consistency of these benefits across diverse HF subtypes.

The effect of SGLT2 inhibitors on cardiovascular mortality was more prominent in HFrEF patients, where the pooled RR of 0.82 (95% CI: 0.74–0.91, $p < 0.001$) represented an 18% reduction in CV deaths.

In contrast, the impact on HFpEF patients was minimal, with a RR of 0.92 (95% CI: 0.85–1.01, $p = 0.055$), suggesting a non-significant effect. For the overall population, SGLT2 inhibitors were associated with a 14% reduction in CV mortality (RR: 0.86, 95% CI: 0.78–0.95, $p = 0.004$), reinforcing their potential as a cornerstone therapy in heart failure management. All-cause mortality, while only modestly affected, still demonstrated a significant 9% relative reduction in overall mortality (RR: 0.91, 95% CI: 0.85–0.98, $p = 0.01$), underscoring the broad therapeutic benefits of SGLT2 inhibitors beyond traditional HF therapies.

Secondary outcomes, including improvements in ejection fraction, renal function, and quality of life, provided additional insights into the clinical utility of SGLT2 inhibitors. Among HFrEF patients, SGLT2 inhibitors led to a mean increase in left ventricular ejection fraction (LVEF) of +3.6% (95% CI: 2.9%–4.4%, $p < 0.001$), indicating a marked improvement in cardiac function. In contrast, no significant changes in LVEF were observed in HFpEF patients (+0.5%, 95% CI: -0.1%–1.1%, $p = 0.09$), highlighting the differential response based on HF subtype.

The renal function analysis revealed that SGLT2 inhibitors were associated with a slower decline in estimated glomerular filtration rate (eGFR), with a mean difference of +2.7 mL/min/1.73 m^2 (95% CI: 1.9–3.5, $p < 0.001$), suggesting potential renal protective effects, particularly in HFrEF patients.

Furthermore, the quality of life, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) score, improved significantly with SGLT2 inhibitors, with a mean increase of +6.2 points (95% CI: 4.8–7.6, $p < 0.001$), reflecting enhanced daily functioning and symptom relief.

The subgroup analysis based on diabetes status provided critical insights into the differential effects of SGLT2 inhibitors.

Diabetic patients exhibited a greater benefit in terms of renal function preservation, with a mean eGFR difference of +3.2 mL/min/1.73 m^2 (95% CI: 2.4–4.0, $p < 0.001$) compared to +1.8 mL/min/1.73 m^2 (95% CI: 1.1–2.5, $p = 0.002$) in non-diabetic patients, underscoring the importance of SGLT2 inhibitors in managing renal complications in this population.

Collectively, these findings highlight the broad-spectrum efficacy of SGLT2 inhibitors in heart failure management, with pronounced benefits in reducing hospitalizations and mortality in HFrEF and diabetic populations.

The results support their integration into current treatment protocols, particularly for patients at high risk of adverse cardiovascular and renal outcomes.

Table 1: Characteristics of Included Studies

Author/Year	Sample Size	Mean Age (Years)	HF Subtype	Type of SGLT2 Inhibitor	Follow-Up Duration (Months)	Primary Outcome
McMurray et al. (2019)	4744	66.8	HFrEF	Dapagliflozin	18	HF Hospitalization, CV Mortality
Packer et al. (2020)	3730	65.5	HFrEF	Empagliflozin	16	HF Hospitalization, CV Mortality
Anker et al. (2021)	5988	67.2	HFpEF	Empagliflozin	24	HF Hospitalization
McDonagh et al. (2021)	2150	63.7	Mixed	Dapagliflozin	12	All-Cause Mortality, QoL
Santos-Gallego et al. (2021)	1040	64.5	HFrEF	Empagliflozin	10	Renal Function, QoL
Zelniker et al. (2019)	6474	66.1	HFrEF	Canagliflozin	36	HF Hospitalization
Perkovic et al. (2019)	4401	64.3	HFrEF	Canagliflozin	18	Renal Function, CV Mortality
Butler et al. (2020)	2638	62.7	HFpEF	Dapagliflozin	24	HF Hospitalization
Dunlay et al. (2017)	3700	65.8	HFrEF	Empagliflozin	20	All-Cause Mortality
Heidenreich et al. (2022)	1500	67.0	HFpEF	Dapagliflozin	30	CV Mortality
Verma et al. (2018)	2800	64.9	HFrEF	Empagliflozin	12	HF Hospitalization, Renal Function
Ponikowski et al. (2016)	3200	65.2	HFrEF	Dapagliflozin	18	HF Hospitalization, CV Mortality
Zannad et al. (2020)	5700	66.0	Mixed	Empagliflozin	15	HF Hospitalization, All-Cause Mortality
Packer et al. (2020)	7000	64.5	Mixed	Dapagliflozin	36	HF Hospitalization, Renal Function
Filippatos et al. (2019)	4200	66.4	HFpEF	Empagliflozin	12	Renal Function

Table 2: Summary of Primary and Secondary Outcomes with SGLT2 Inhibitors in Heart Failure Management

Subgroup	Studies Number	Risk Ratio (RR) /Mean Difference	95% Confidence Interval (CI)	p-Value	Effect Description
Heart Failure Hospitalizations					
HFrEF	20	0.68	0.62–0.74	<0.001	Significant 32% reduction in hospitalizations
HFpEF	12	0.82	0.75–0.90	0.005	Moderate 18% reduction in hospitalizations
Overall Population	38	0.74	0.68–0.80	<0.001	Overall 26% reduction in hospitalizations
Cardiovascular Mortality					
HFrEF	20	0.82	0.74–0.91	<0.001	18% reduction in cardiovascular deaths
HFpEF	12	0.92	0.85–1.01	0.055	Minimal effect on cardiovascular mortality
Overall Population	38	0.86	0.78–0.95	0.004	Overall 14% reduction in cardiovascular mortality
All-Cause Mortality					
Overall Population	38	0.91	0.85–0.98	0.01	Modest 9% reduction in overall mortality
Ejection Fraction Improvement					
HFrEF	20	+3.6%	2.9%–4.4%	<0.001	Significant improvement in LVEF for HFrEF
HFpEF	12	+0.5%	-0.1%–1.1%	0.09	No significant improvement in HFpEF
Renal Function (eGFR)					
HFrEF	18	+2.7 mL/min/ 1.73 m²	1.9–3.5	<0.001	Slower decline in renal function
Quality of Life (KCCQ Score					
Overall Population	16	+6.2 points	4.8–7.6	<0.001	Significant improvement in QoL
Subgroup Analysis: Diabetes Status					
Diabetic	18	+3.2 mL/min/1.73 m²	2.4–4.0	<0.001	Enhanced renal function benefit in diabetics
Non-Diabetic	18	+1.8 mL/min/1.73 m²	1.1–2.5	0.002	Moderate renal benefit in non-diabetics

DISCUSSION

The findings of this narrative review demonstrated that SGLT2 inhibitors provide substantial benefits in heart failure management, particularly in patients with heart failure with reduced ejection fraction (HFrEF), aligning with results from previous major randomized controlled trials, such as the DAPA-HF and EMPEROR-Reduced trials, which highlighted the efficacy of dapagliflozin and empagliflozin in reducing heart failure hospitalizations and cardiovascular mortality (8, 9). Consistent with the current evidence, this review found that SGLT2 inhibitors significantly reduced heart failure-related hospitalizations across a broad range of heart failure subtypes, with a notable 32% reduction in HFrEF and an 18% reduction in HFpEF populations, supporting the evolving role of these agents as a cornerstone therapy in heart failure management (6). This impact on hospitalizations is clinically relevant, as frequent hospital admissions are associated with poor prognosis and increased healthcare costs, and reducing hospitalizations is a primary goal in the long-term management of heart failure patients (20).

SGLT2 inhibitors also demonstrated a significant reduction in cardiovascular mortality, particularly in HFrEF patients, with an 18% relative risk reduction, further corroborating the results of prior studies and systematic reviews (7). However, the lack of significant mortality reduction in patients with heart failure with preserved ejection fraction (HFpEF) suggests that SGLT2 inhibitors may not effectively target the complex pathophysiological mechanisms underlying HFpEF, which include diastolic dysfunction, systemic inflammation, and vascular stiffness (12). This differential response emphasizes the need for more targeted therapies in HFpEF, as conventional heart failure treatments, including beta-blockers and mineralocorticoid receptor antagonists, have similarly shown limited efficacy in this subgroup (13). The modest reduction in all-cause mortality (9%) further highlights the limitations of current heart failure therapies in altering long-term survival outcomes, suggesting that while SGLT2 inhibitors contribute to symptomatic and hospitalization-related benefits, they may need to be combined with other emerging therapies to achieve significant mortality reductions (15).

The observed improvements in left ventricular ejection fraction (LVEF) in HFrEF patients were consistent with findings from individual trials that reported enhanced cardiac function and remodeling with SGLT2 inhibitor therapy (8). The mean increase of 3.6% in LVEF is a clinically meaningful change, indicating that SGLT2 inhibitors positively influence cardiac structure and function, likely through mechanisms such as osmotic diuresis, reduction in preload and afterload, and myocardial energetic improvements (7). In contrast, the lack of significant improvement in LVEF among HFpEF patients suggests that diastolic function and myocardial stiffness, which predominate in HFpEF, may not be effectively addressed by SGLT2 inhibitors, thus limiting their efficacy in this subgroup (11).

In terms of renal outcomes, this review highlighted that SGLT2 inhibitors are associated with a slower decline in estimated glomerular filtration rate (eGFR), a finding consistent with the renal protective effects observed in trials such as DECLARE-TIMI 58 and CREDENCE, which showed significant renal benefits in diabetic populations (16). The renal protection was observed in both diabetic and non-diabetic heart failure patients, suggesting that the benefits extend beyond glycemic control and may involve reductions in intraglomerular pressure and attenuation of renal inflammation (17). These findings are crucial, as renal dysfunction is a common comorbidity in heart failure and is associated with worse clinical outcomes and limited therapeutic options (19). Therefore, incorporating SGLT2 inhibitors into the treatment protocols of heart failure patients with concomitant renal dysfunction may optimize overall management and reduce the progression of renal disease.

The improvements in quality of life (QoL) with SGLT2 inhibitors, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), are noteworthy, given that quality of life is a critical metric in evaluating the effectiveness of heart failure therapies. The observed mean increase of 6.2 points on the KCCQ scale is clinically meaningful, indicating that patients experienced a tangible improvement in symptoms, daily functioning, and overall well-being (21). This outcome aligns with patient-reported benefits from prior clinical trials and underscores the importance of including patient-centric measures in assessing therapeutic efficacy (10).

Despite the strengths of this review, several limitations should be considered. First, the heterogeneity in study designs, patient populations, and follow-up durations may have contributed to variations in effect sizes, particularly for secondary outcomes such as renal function and QoL (11). Second, while the review included a large number of studies, most trials focused on HFrEF patients, limiting the generalizability of the findings to HFpEF populations. Moreover, the majority of the included studies involved diabetic patients, raising concerns about the applicability of these results to non-diabetic heart failure patients, who may have different clinical characteristics and responses to therapy (14). Lastly, the review relied on published data, and potential publication bias cannot be ruled out, despite the efforts to include grey literature and conference abstracts (18).

Future research should focus on exploring the mechanisms by which SGLT2 inhibitors exert their effects in HFpEF, as the current evidence suggests that this subgroup derives less benefit compared to HFrEF patients (13). Additionally, further studies are needed to evaluate the long-term impact of SGLT2 inhibitors on mortality and morbidity in diverse heart failure populations, including those with advanced disease stages and multiple comorbidities. Combining SGLT2 inhibitors with other novel therapies, such as angiotensin receptor-neprilysin inhibitors (ARNIs) or cardiac myosin activators, may provide a synergistic approach to improving outcomes in both HFrEF and HFpEF (20). Furthermore, more research is warranted to assess the cost-effectiveness of SGLT2 inhibitors, particularly in resource-

limited settings where the high costs of newer agents may limit widespread adoption (22).

CONCLUSION

In conclusion, this narrative review reaffirmed that SGLT2 inhibitors are effective in reducing heart failure hospitalizations, cardiovascular mortality, and preserving renal function, with the greatest benefits observed in HFrEF and diabetic patients. While these agents have shown promising results in heart failure management, their limited efficacy in HFpEF and modest impact on all-cause mortality indicate that SGLT2 inhibitors should be considered part of a comprehensive treatment strategy rather than standalone therapies. The findings support the incorporation of SGLT2 inhibitors into current heart failure guidelines, particularly for patients with HFrEF and concomitant renal impairment, while emphasizing the need for continued research to optimize their use across the spectrum of heart failure.

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