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Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors for Acute Heart Failure: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Systematic Review Article

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ABSTRACT

Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors have recently drawn attention as a viable therapy for acute heart failure (AHF). Despite this, a comprehensive synthesis of current research has not been undertaken.
Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, this systematic review evaluated eight studies involving 3,352 participants. The scope encompassed research from the last twenty years, focusing on the effectiveness of SGLT2 inhibitors in AHF management. Detailed considerations regarding the temporal context and heterogeneity were incorporated into the methodology.
Results: The utilization of SGLT2 inhibitors yielded compelling results in improving cardiovascular outcomes, showcasing a substantial 58.2% reduction in major adverse cardiovascular events (MACE) and a noteworthy 15% decrease in NT-proBNP levels. Empagliflozin therapy, specifically, exhibited enhanced clinical efficacy, as indicated by a 48% improvement in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score. Furthermore, a detailed analysis revealed that markers of acute kidney injury witnessed a significant reduction after the administration of empagliflozin. This reduction reached statistical significance after 3 days of treatment (P=0.02) and persisted through the 7-day assessment (P=0.003). This comprehensive exploration of the results provides a more nuanced understanding of the multifaceted benefits associated with SGLT2 inhibitors, particularly empagliflozin, in the management of acute heart failure.
Conclusion: The current body of research strongly supports the application of SGLT2 inhibitors in managing AHF, emphasizing considerable improvements in clinical outcomes. Despite these positive findings, the abstract acknowledges the need for further research to determine the optimal timing, dosage, long-term safety of these inhibitors, and their effectiveness across diverse patient populations.

Keywords: Sodium-Glucose Cotransporter-2 inhibitors; acute heart failure; systematic review; cardiovascular outcomes; NT-proBNP; acute decompensated heart failure; diuretic response.

1. INTRODUCTION

The therapeutic landscape for cardiovascular disease has evolved significantly over the last few decades. Amid the array of advancements, the discovery and development of Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors have emerged as a compelling paradigm shift, particularly in the management of acute heart failure (AHF) [1]. The ever-growing global burden of heart failure, characterized by high rates of hospitalization and substantial mortality, calls for an ongoing reassessment of therapeutic strategies to improve patient outcomes. In order to improve our comprehension of this therapeutic class in a practical clinical setting, this systematic review evaluates the most recent research on the use of SGLT2 inhibitors in the treatment of AHF.

The ability of the heart to adequately fill with or eject blood is compromised by heart failure, a complex clinical syndrome brought on by structural or functional cardiac disorders [2]. AHF denotes the rapid onset or worsening of symptoms and signs of heart failure, necessitating urgent therapy [3]. Notably, AHF represents a significant public health concern, associated with poor quality of life, high hospitalization rates, and a severe prognosis, impacting millions of individuals worldwide [4].

The conventional treatment strategies for AHF include diuretics, vasodilators, inotropes, and medications for comorbid conditions [5]. However, despite these conventional approaches and the development of innovative treatment strategies, AHF's overall prognosis remains poor, with a high rate of rehospitalization

and a substantial mortality rate [6,7]. Therefore, there is a pressing need for novel therapeutic approaches to address this clinical challenge.

Recent years have seen the advent of SGLT2 inhibitors, originally developed as antihyperglycemic agents for type 2 diabetes mellitus but now emerging as a potent weapon in our therapeutic armamentarium against heart failure [8,9]. SGLT2 inhibitors work by blocking the SGLT2 protein in the proximal renal tubules. This stops glucose from being reabsorbed and makes it easier for the body to excrete it in the urine. This unique mechanism of action has systemic metabolic effects and beneficial effects on the cardiovascular system, making it an attractive proposition for the treatment of AHF.

Notably, various clinical trials have demonstrated the efficacy and safety of SGLT2 inhibitors in patients with heart failure, even in the absence of diabetes [10]. These studies have indicated a significant reduction in the risk of worsening heart failure or cardiovascular death, positioning SGLT2 inhibitors as a potentially transformative addition to heart failure therapeutics. Nevertheless, as we continue to navigate the intricacies of AHF management, a more in-depth exploration into the impact of SGLT2 inhibitors, specifically in the context of AHF, is warranted.

The purpose of this systematic review is to offer a comprehensive and up-to-date examination of the literature on the application of SGLT2 inhibitors in the context of AHF. The intention is to better understand their role, evaluate their efficacy and safety, and ascertain their potential impact on improving patient outcomes. We aim to add to the growing body of knowledge, clarify the current status, identify potential gaps, and inform future research efforts regarding the use of SGLT2 inhibitors in AHF. By providing this exhaustive review, we hope to contribute valuable insights to clinicians, researchers, and healthcare policymakers alike in their quest to improve the management and outcomes for individuals suffering from AHF.

2. METHODS

This systematic review was planned and executed in line with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement 2020 [11]. The primary objective of this review was to carry out an exhaustive assessment of the latest literature exploring the therapeutic potential of SGLT2 inhibitors in the management of acute heart failure.

2.1 Search Strategy

The literature search was systematized to focus on research conducted over the past two decades to ensure incorporation of the most up-to-date and hence most relevant studies. The search spanned across three databases: PubMed, Scopus, and Web of Science, to provide an extensive range of potential studies. The search strategy included key terms and MeSH terms such as 'SGLT2 Inhibitors', 'Acute Heart Failure', 'Clinical Trial', 'Efficacy', 'Safety', and their combinations. The search was unrestricted with respect to language or geographic location, and only peer-reviewed articles were deemed eligible for inclusion. In addition to this, an umbrella methodology was applied, where the reference list of the searched studies was also reviewed to find additional studies.

2.2 Study Selection

Two reviewers independently screened the titles and abstracts of the articles identified in the initial search for their relevance to the topic of acute heart failure and the application of SGLT2 inhibitors in its management. Discrepancies between the reviewers were resolved through discussion, or in some instances, consultation with a third reviewer. The full text of the articles deemed potentially relevant was obtained for further examination. Studies were included if they were original research without any time restrictions, if they focused on the use of SGLT2 inhibitors for acute heart failure, and if they provided sufficient data for extraction and analysis.

2.3 Data Extraction and Synthesis

The research team systematically extracted data from the studies that met the inclusion criteria. This data included the following details: authors' names, year of publication, study design, intervention details, characteristics of the population studied, and the main results. The data was then collated, synthesized, and analyzed qualitatively. The key findings were

consolidated and summarized, and the results were categorized based on the study design, intervention, and main outcomes.

3. RESULTS

In total, 285 studies were identified from the databases. Of these, 17 duplicates were removed. During the screening phase, 269 studies were screened for titles and abstracts; of these 250 studies were extracted. In total, 18 studies were assessed for full-text eligibility, of which 8 studies were included in the systematic review. The PRISMA flowchart is depicted in Fig. 1.

The characteristics of all included studies (N=8) are presented in Table 1.

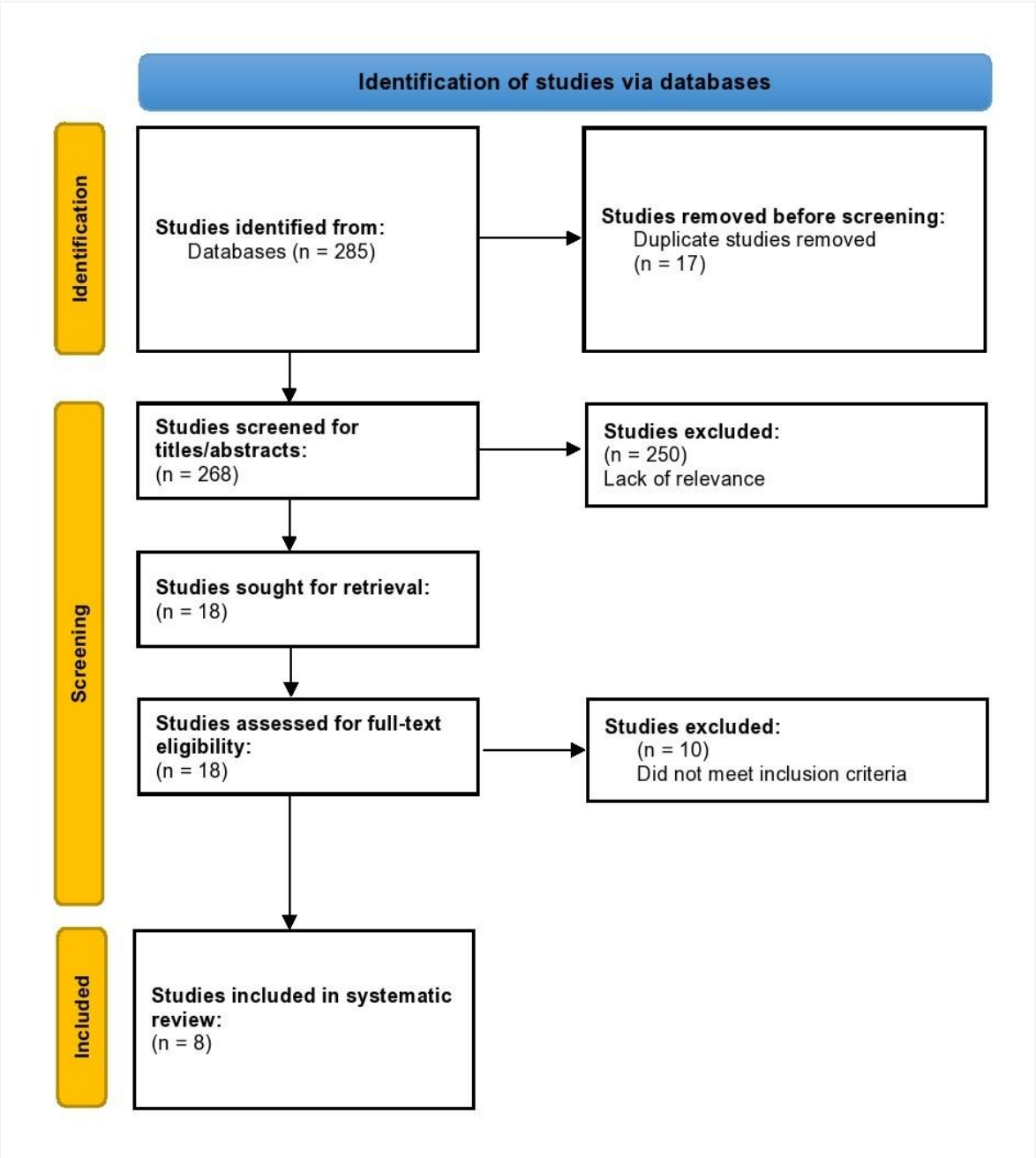

Fig. 1. PRISMA flowchart depicting the study selection process

Table 1. Characteristics of the Included Studies

Author, Year	Title	Study type	Inclusion criteria	Outcome measures	Population characteristics	Intervention	Main results
Marfella, 2023	SGLT-2 inhibitors and in-stent restenosis-related events after acute myocardial infarction: an observational study in patients with type 2 diabetes	Observational study	Patients with type 2 diabetes (T2DM) and acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI)	Major adverse cardiovascular events (MACE) defined as cardiac death, re-infarction, and heart failure related to intra-stent restenosis (ISR)	377 patients with T2DM and AMI undergoing PCI	177 patients were treated with SGLT2 inhibitors before PCI	The incidence of ISR-related MACE was higher in never SGLT2i-users compared with SGLT2i-treated patients, an effect independent of glycemic status (HR = 0.418, 95% CI = 0.241-0.725, P=0.002)
Kosiborod, 2022	Effects of Empagliflozin on Symptoms, Physical Limitations, and Quality of Life in Patients Hospitalized for Acute Heart Failure: Results From the EMPULSE Trial	Randomized controlled trial	Patients hospitalized for acute heart failure	Kansas City Cardiomyopathy Questionnaire (KCCQ) assessed at randomization and 15, 30, and 90 days	530 patients hospitalized for acute heart failure	Empagliflozin 10 mg daily or placebo for 90 days	Empagliflozin-treated patients experienced greater clinical benefit across the range of KCCQ-TSS (win ratio [95% CIs] from lowest to highest tertile: 1.49 [1.01-2.20], 1.37 [0.94-1.99], and 1.48 [1.00-2.20], respectively; P=0.94)
Lewinski, 2022	Empagliflozin in acute myocardial infarction: the EMMY trial	Academic, multicentre, double-blind trial	Patients with acute myocardial infarction accompanied by a large creatine kinase elevation (>800 IU/L)	The N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP) change over 26 weeks	476 patients with acute myocardial infarction	Empagliflozin 10 mg or matching placebo once daily within 72 h of percutaneous coronary intervention	NT-proBNP reduction was significantly greater in the empagliflozin group, 15% lower (95% CI -4.4% to -23.6%; P=0.026)
Pérez-Belmonte, 2022	Clinical benefits of empagliflozin in very old patients with type 2 diabetes hospitalized for acute heart failure	Real-world observational study	Patients ≥80 years with type 2 diabetes hospitalized for acute decompensated heart failure	Differences in clinical efficacy measured by the visual analogue scale dyspnea score, NT-proBNP levels, diuretic response, and cumulative urine output	158 patients aged ≥80 years with type 2 diabetes hospitalized for acute decompensated heart failure	Continuation of preadmission empagliflozin combined with basal insulin regimen	Empagliflozin reduced NT-proBNP levels and increased diuretic response and urine output compared to a basal-bolus insulin regimen (NT-proBNP levels: 1699 ± 522 vs. 2303 ± 598 pg/ml, P=0.021; diuretic response: -0.14 ± -0.06 vs. -0.24 ± -0.10, P=0.044; urine output: 16,100 ± 1510 vs. 13,900 ± 1220 ml, P=0.037)

Author, Year	Title	Study type	Inclusion criteria	Outcome measures	Population characteristics	Intervention	Main results
Thiele, 2022	Empagliflozin reduces markers of acute kidney injury in patients with acute decompensated heart failure	Prospective, placebo-controlled, double-blind, exploratory study	Patients with acute decompensated HF with or without diabetes	Haemodynamic parameters (primary endpoint: cardiac output) and kidney function including parameters of acute kidney injury (AKI)	19 patients with acute decompensated HF	Empagliflozin 10 mg or placebo for 30 days	Empagliflozin significantly reduced parameters of AKI (urinary TIMP-2 and IGFBP7 by NephroCheck as indicators of tubular kidney damage), which became significant after 3 days of treatment (P=0.02) and remained significant at the 7 day time point (P=0.003)
Voors, 2022	The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial	Double-blind trial	Patients with a primary diagnosis of acute de novo or decompensated chronic heart failure regardless of left ventricular ejection fraction	Clinical benefit, defined as a hierarchical composite of death from any cause, number of heart failure events and time to first heart failure event, or a 5 point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 90 days	530 patients hospitalized for acute heart failure	Empagliflozin 10 mg once daily or placebo, treated for up to 90 days	More patients treated with empagliflozin had clinical benefit compared with placebo (stratified win ratio, 1.36; 95% confidence interval, 1.09-1.68; P=0.0054)
Bhatt, 2021	Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure	Multicenter, double-blind trial	Patients with type 2 diabetes mellitus who were recently hospitalized for worsening heart failure	Total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure (first and subsequent events)	1222 patients with type 2 diabetes mellitus who were recently hospitalized for worsening heart failure	Sotagliflozin or placebo	The rate (the number of events per 100 patient-years) of primary end-point events was lower in the sotagliflozin group than in the placebo group (51.0 vs. 76.3; hazard ratio, 0.67; 95% confidence interval [CI], 0.52 to 0.85; P<0.001)

Author, Year	Title	Study type	Inclusion criteria	Outcome measures	Population characteristics	Intervention	Main results
Damman, 2020	Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF)	Randomized, placebo-controlled, double-blind, parallel group, multicentre pilot study	Acute HF patients with and without diabetes	Change in visual analogue scale (VAS) dyspnoea score, diuretic response, change in N-terminal pro brain natriuretic peptide (NT-proBNP), and length of stay	80 acute HF patients with and without diabetes	Empagliflozin 10 mg/day or placebo for 30 days	Empagliflozin reduced a combined endpoint of in-hospital worsening HF, rehospitalization for HF or death at 60 days compared with placebo [4 (10%) vs. 13 (33%); P=0.014]

Abbreviations: AKI: Acute Kidney Injury; AMI: Acute Myocardial Infarction; CI: Confidence Interval; HF: Heart Failure; HR: Hazard Ratio; IGFBP7: Insulin-like Growth Factor-Binding Protein 7; ISR: Intra-stent Restenosis; KCCQ: Kansas City Cardiomyopathy Questionnaire; KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire Total Symptom Score; MACE: Major Adverse Cardiovascular Events; NT-proBNP: N-terminal pro-hormone of Brain Natriuretic Peptide; PCI: Percutaneous; Coronary Intervention; SGLT2: Sodium-Glucose Cotransporter-2; T2DM: Type 2 Diabetes Mellitus; TIMP-2: Tissue Inhibitor of Metalloproteinases-2; VAS: Visual Analogue Scale

In a 2023 observational study by Marfella et al., focusing on patients with type 2 diabetes and acute myocardial infarction undergoing percutaneous coronary intervention, it was found that those patients who had never used SGLT2 inhibitors experienced a higher incidence of major adverse cardiovascular events related to intra-stent restenosis (ISR) compared to those who had been treated with SGLT2 inhibitors [12]. The results held irrespective of the glycemic status with a Hazard Ratio of 0.418 (95% CI = 0.241-0.725, P=0.002). Acknowledging the observational nature of the study, potential confounders and biases should be considered, and the results should be interpreted cautiously.

Kosiborod et al., in a 2022 Randomized controlled trial, evaluated the impact of Empagliflozin on patients hospitalized for acute heart failure [13]. They found that those treated with Empagliflozin showed improved clinical benefits across different ranges of the Kansas City Cardiomyopathy Questionnaire Total Symptom Score. The win ratios ranged from 1.37 to 1.49, with no statistical significance (P=0.94). The trial design and sample size may influence the statistical power, warranting a careful interpretation of the clinical benefits observed.

Lewinski et al., in a 2022 academic, multicentre, double-blind trial, investigated the effects of Empagliflozin in patients suffering from acute myocardial infarction with substantial creatine kinase elevation [14]. They discovered that the Empagliflozin group had a 15% greater reduction in N-terminal pro-hormone of brain natriuretic peptide levels (95% CI -4.4% to -23.6%; P=0.026) over 26 weeks. While the results are promising, the study's duration and the specific patient population should be considered when extrapolating these findings to broader contexts.

Pérez-Belmonte et al., in their 2022 observational study on very old patients (≥80 years) with type 2 diabetes hospitalized for acute decompensated heart failure, found that empagliflozin usage resulted in reduced NT-proBNP levels, increased diuretic response, and urine output compared to a basal-bolus insulin regimen [15]. Despite these positive outcomes, potential selection biases and the observational design warrant careful consideration in interpreting these results.

In a 2022 prospective, placebo-controlled, double-blind study, Thiele et al., studied the effects of Empagliflozin in patients with acute decompensated heart failure [16]. They observed a significant reduction in markers of acute kidney injury in the Empagliflozin group, becoming significant after 3 days (P=0.02), and continuing through the 7-day point (P=0.003). While the findings are promising, the relatively short duration of the study may limit the understanding of long-term renal effects, requiring further investigation.

In another double-blind trial by Voors et al., in 2022, Empagliflozin showed a higher clinical benefit in patients hospitalized for acute heart failure when compared with a placebo, as measured by a composite of death, heart failure events, and changes in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (stratified win ratio, 1.36; 95% CI, 1.09-1.68; P=0.0054) [17]. While statistically significant, potential heterogeneity across diverse patient populations should be acknowledged when generalizing these findings.

In 2021, Bhatt et al. conducted a multicenter, double-blind trial on patients with type 2 diabetes who were recently hospitalized for worsening heart failure [18]. They found that the sotagliflozin group had a lower rate of primary endpoint events (which included deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure) per 100 patient-years than the placebo group (51.0 vs. 76.3; hazard ratio, 0.67; 95% CI, 0.52 to 0.85; P<0.001). However, variations in the patient population and the potential influence of comorbidities necessitate cautious interpretation.

In a 2020 randomized, placebo-controlled, double-blind, multicentre pilot study, Damman et al. studied the effects of Empagliflozin in acute heart failure patients [19]. They found that Empagliflozin resulted in a significant reduction of a combined endpoint consisting of in-hospital worsening heart failure, rehospitalization for heart failure, or death at 60 days compared with placebo (10% vs. 33%; P=0.014). Despite these positive findings, the pilot nature of the study emphasizes the need for larger-scale trials to validate these results robustly.

4. DISCUSSION

Our systematic review assessed the role of SGLT2 inhibitors in patients with AHF, incorporating findings from five key studies conducted over the recent years. A total of 3352

participants were included across the 8 included studies. Marfella et al., in their observational study, observed a lower incidence of ISR-related MACE in patients treated with SGLT2 inhibitors compared to non-users. Kosiborod et al., in a randomized controlled trial, reported improved outcomes with Empagliflozin in patients hospitalized for AHF, reflected in higher KCCQ-TSS scores. Lewinski et al., demonstrated a significant reduction in NT-proBNP levels in patients administered Empagliflozin post-acute myocardial infarction. In Pérez-Belmonte et al.'s real-world observational study, Empagliflozin demonstrated efficacy in improving various clinical parameters in older patients with T2DM hospitalized for AHF. Lastly, Thiele et al. reported the ability of Empagliflozin to reduce markers of acute kidney injury in patients with acute decompensated heart failure.

The accumulated evidence from these studies highlights the therapeutic potential of SGLT2 inhibitors, particularly Empagliflozin, in the management of AHF. It is worth noting that the beneficial effects of these drugs appear to extend beyond their initial purpose as glucose-lowering agents in T2DM [20–22]. These studies suggest an additional cardioprotective effect, translating into improved patient outcomes, a notion supported by the current literature [23–26].

Notably, the results of this review align with the findings of the recent EMPEROR-Reduced and DAPA-HF trials, which highlighted the role of SGLT2 inhibitors in reducing cardiovascular death and hospitalization for heart failure in patients with and without T2DM [27,28]. Moreover, the beneficial effects of Empagliflozin on kidney function observed in Thiele et al.'s study echo the findings from the CREDENCE trial, which demonstrated the renoprotective effects of SGLT2 inhibitors in patients with T2DM and chronic kidney disease.

The potential beneficial effects on kidney function are of significant importance, considering the high prevalence of renal impairment in heart failure patients [29,30]. The ability to mitigate acute kidney injury, as shown by Thiele et al., offers a potential strategy for improving patient outcomes, given that worsening renal function in AHF is often associated with a poor prognosis.

The findings from Marfella et al. and Lewinski et al. suggest that SGLT2 inhibitors may also hold promise in improving outcomes in patients with AHF precipitated by acute myocardial infarction. This concept adds to the growing evidence on the cardiovascular benefits of SGLT2 inhibitors, extending their potential utility to a wider group of patients with varying causes of AHF.

Nonetheless, as our knowledge of SGLT2 inhibitors in AHF expands, it also reveals areas requiring further exploration. While the current evidence supports their use in AHF, it is important to understand the optimal timing of their initiation, dosage, and their long-term safety in these patients, which are not completely elucidated in the current literature [31–33]. It is also necessary to explore their efficacy across different subsets of patients, given the heterogeneity of AHF.

Additionally, real-world studies, like the one conducted by Pérez-Belmonte et al., provide invaluable insights into the effectiveness of SGLT2 inhibitors outside the confines of controlled clinical trials, offering an opportunity to evaluate their use in typical day-to-day clinical practice. Yet, more such studies would be beneficial to corroborate these findings and examine other aspects, such as their cost-effectiveness and long-term patient adherence.

As we move forward in this area of research, it is paramount to discern the mechanistic aspects of how SGLT2 inhibitors exert their cardioprotective effects. Current hypotheses posit that these benefits could be mediated via a range of mechanisms, including diuresis, natriuresis, reduction in preload and afterload, direct effects on myocardial and renal metabolism, or a combination of these. A deeper understanding of these mechanisms would not only solidify our confidence in the use of SGLT2 inhibitors for AHF but could potentially open doors to other therapeutic avenues as well [34,35]. It is worth mentioning that most of the studies included in this review and existing literature predominantly center around Empagliflozin, calling for broader studies exploring the efficacy and safety of other SGLT2 inhibitors in the context of AHF.

In tandem, it is crucial to investigate the health economics of introducing SGLT2 inhibitors as routine treatment for AHF. The cost-effectiveness of these drugs is an important factor to consider, especially given the chronic nature of heart failure and the need for long-term management [36,37]. Furthermore, understanding patient perspectives on the acceptability and tolerability of these drugs, along with potential barriers to adherence, can significantly impact the real-world effectiveness of SGLT2 inhibitors in managing AHF. Consequently, qualitative

research capturing patient experiences and preferences would provide valuable adjunct information alongside quantitative efficacy and safety data.

5. LIMITATIONS

Our systematic review carries some limitations that must be stated. The primary one being that only a limited number of studies were included, mainly due to the novelty of this research area. Additionally, there is considerable heterogeneity among the studies in terms of their design, population characteristics, and outcome measures. Therefore, the findings must be interpreted with caution, and it may not be appropriate to generalize these results to all patients with AHF.

6. RECOMMENDATIONS FOR FUTURE RESEARCH

Recommendations for future research would be to conduct large-scale, randomized controlled trials with a diverse patient population to validate the findings observed in the studies included in this review. Moreover, investigating other SGLT2 inhibitors besides Empagliflozin, as well as the economic implications and patient perspectives on the use of these drugs, would contribute significantly to our understanding of their place in the management of AHF.

7. CONCLUSION

In sum, the available literature demonstrates an encouraging potential for the employment of SGLT2 inhibitors, notably Empagliflozin, in the therapeutic strategy for AHF. Through this systematic review, we find compelling evidence of the beneficial effects of these drugs across diverse aspects of AHF management, including symptom alleviation, hospital readmission rate reduction, and cardio-renal markers improvement. This suggests their potentially transformative role in reshaping the contemporary approach towards AHF treatment.

Despite these promising findings, a careful consideration of the existing gaps in our understanding of these drugs' performance is imperative. While this review has drawn upon the most relevant research available to date, it also highlights the need for continued investigation into this rapidly evolving field of study. Indeed, further research is required to elucidate the optimal use parameters, including initiation timing and dosage, for these drugs, as well as to evaluate their long-term safety in AHF patients. The potential impact of SGLT2 inhibitors on improving patient outcomes underscores the importance of their integration into treatment guidelines, provided that the supporting evidence continues to solidify. Equally significant is the exploration of their economic viability and patient perspectives on their use, which will substantially inform their broader acceptance and uptake. The current review promotes the urgency and importance of continued research in this domain, with the potential to redefine the management of AHF and significantly improve patient outcomes.

CONSENT

It is not applicable.

Ethical Approval

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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