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QUALITY OF LIFE IN HEART FAILURE PATIENTS RECEIVING SODIUM GLUCOSE -2 (SGLT2) INHIBITORS: A LITERATURE REVIEW

Kualitas Hidup Pasien Gagal Jantung yang Menerima Penghambat Natrium Glukosa Co-Transporter-2 (SGLT2): Literature Review

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ABSTRAK

Gagal jantung merupakan kondisi klinis progresif yang berdampak signifikan terhadap kualitas hidup pasien. Penghambat Natrium Glukosa Co-transporter-2 (SGLT2), yang awalnya dikembangkan untuk terapi diabetes melitus tipe 2, telah menunjukkan manfaat kardiovaskular. Studi ini bertujuan mengevaluasi dampak penggunaan penghambat SGLT2, terhadap kualitas hidup pasien gagal jantung melalui tinjauan sistematis literatur. Penelusuran dilakukan di database PubMed dan EBSCOhost untuk menemukan uji klinis terkontrol secara acak yang melaporkan perubahan kualitas hidup menggunakan instrumen valid seperti Kansas City Cardiomyopathy Questionnaire (KCCQ) dan EuroQol 5-Dimension (EQ-5D). Dari 398 artikel yang diidentifikasi, sebanyak 20 studi memenuhi kriteria inklusi dan dianalisis secara kualitatif. Hasil menunjukkan bahwa terapi penghambat SGLT2 secara konsisten meningkatkan skor KCCQ dan EQ-5D secara bermakna dibandingkan plasebo, mencerminkan perbaikan pada aspek fisik, gejala klinis, dan kesejahteraan emosional. Efektivitas ini tercatat konsisten pada berbagai subpopulasi, terlepas dari status diabetes dan tipe fraksi ejeksi dan mendukung peran SGLT2 inhibitor sebagai terapi komprehensif dalam meningkatkan kualitas hidup pasien gagal jantung.

Kata kunci*: empagliflozin, dapagliflozin, gagal jantung, kualitas hidup, SGLT2 inhibitor*

ABSTRACT

Heart failure is a progressive clinical condition that significantly impacts the quality of life of patients. Sodium-Glucose Co-transporter-2 (SGLT2) inhibitors, originally developed for the treatment of type 2 diabetes mellitus, have shown cardiovascular benefits. This study aims to evaluate the impact of SGLT2 inhibitors, on the quality of life of patients with heart failure through a systematic review of the literature. A search was conducted in the PubMed and EBSCOhost databases to find randomized controlled clinical trials that reported changes in quality of life using valid instruments such as the Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQol 5-Dimension (EQ-5D). Of the 398 articles identified, 20 studies met the inclusion criteria and were analyzed qualitatively. The results showed that SGLT2 inhibitor therapy consistently improved KCCQ and EQ-5D scores significantly compared to placebo, reflecting improvements in physical aspects, clinical symptoms, and emotional well-being. The efficacy was consistently noted across subpopulations, regardless of diabetes status and ejection fraction type and support the role of SGLT2 inhibitors as a comprehensive therapy in improving the quality of life of heart failure patients.

Keywords*:* dapagliflozin, empagliflozin, heart failure, quality of life, SGLT2 inhibitors

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INTRODUCTION

Heart failure is a leading cause of morbidity and mortality worldwide, with prevalence continuing to increase as the population ages [1],[2]. According to the Global Burden of Disease data released in 2022, more than 64 million people worldwide are living with a diagnosis of heart failure, and that number is expected to continue to rise [1],[3]. The condition of heart failure itself is a complex clinical syndrome, with symptoms and signs that appear due to structural or functional disorders in the filling or ejection of blood in the ventricles [4]. This not only reduces the patient's functional capacity, but also significantly affects their quality of life [1].

Patients with heart failure often experience symptoms such as dyspnea (shortness of breath), extreme fatigue, edema (swelling), and decreased tolerance to physical activity [5],[23],[6]. This condition results in limitations in carrying out daily activities, which has an impact on reducing the quality of life in the physical, psychological, and social aspects of the patient's life [7],[8],[9]. Therefore, improving the quality of life of heart failure patients has become a major focus in the management of this disease [10].

Sodium-Glucose Co-transporter-2 (SGLT2) inhibitors are a group of drugs that were originally developed to treat type 2 diabetes mellitus [11]. The main mechanism of action of this drug is to inhibit glucose reabsorption in the renal tubules by inhibiting the SGLT2 cotransporter, thereby reducing blood glucose levels [11],[12],[13]. However, as research progressed, it was found that SGLT2 inhibitors had additional benefits in patients with heart failure, regardless of their diabetes status [14]. These findings mark a paradigm shift in heart failure therapy, where the focus is no longer solely on symptom control and mortality, but also on improving patients' quality of life [10].

Several large randomized clinical trials (RCTs) have evaluated the effects of SGLT2 inhibitors in heart failure patients [15]. One of the most significant trials, DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), showed that dapagliflozin, an SGLT2 inhibitor, significantly reduced risk of worsening heart failure or death from cardiovascular causes, hospitalizations for heart failure, and emergency visits for heart failure compared to placebo in patients with heart failure with reduced ejection fraction (HFrEF) [16],[17],[18],[19]. Other studies, such as EMPEROR-Reduced and EMPEROR-Preserved, also support the finding that empagliflozin, an SGLT2 inhibitor, showed a lower risk of cardiovascular death or hospitalization due to heart failure than those in the placebo group, including in those with preserved ejection fraction (HFpEF) [19],[20],[21].

SGLT2 also provides significant improvements in quality of life in heart failure patients [22]. Commonly used instruments to measure quality of life in heart failure patients in these studies include the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EuroQol 5-Dimension (EQ-5D). The KCCQ is a widely validated assessment tool specifically designed to evaluate quality of life in patients with heart disease [23],[24]. This instrument covers various domains such as physical limitations, symptoms, quality of life and self-efficacy [24]. Meanwhile, the EQ-5D is a tool that measures general health, covering five main dimensions: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression [25],[26]. This questionnaire has two parts: a descriptive 5-level 5-dimension (EQ-5D-5L) section that defines health status, and a Visual Analog Scale (VAS) index score section that captures self-assessment of health status [26].

This article aims to review the available literature on the impact of SGLT2 inhibitors on quality of life in heart failure patients. Focusing on randomized clinical trials using validated quality-of-life assessment tools, this review will provide a comprehensive overview of how these therapies affect the physical and emotional well-being of heart failure patients.

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METHODS

Literature Search Strategy

This article uses a literature review method to search scientific journals and official websites for information on quality of life in heart failure patients undergoing therapy with sodium glucose co-transporter-2 (SGLT-2) inhibitors. The information obtained was then classified based on relevant questions and conclusions were drawn. A systematic literature search was conducted in June 2024, with publication years between 2012 and 2024, using two major databases: PubMed and EBSCOhost. The search process was designed to identify studies evaluating the effects of Sodium-Glucose Co-transporter-2 (SGLT2) inhibitors on quality of life in heart failure patients. Diagram prism the literature search is shown in Figure 1.

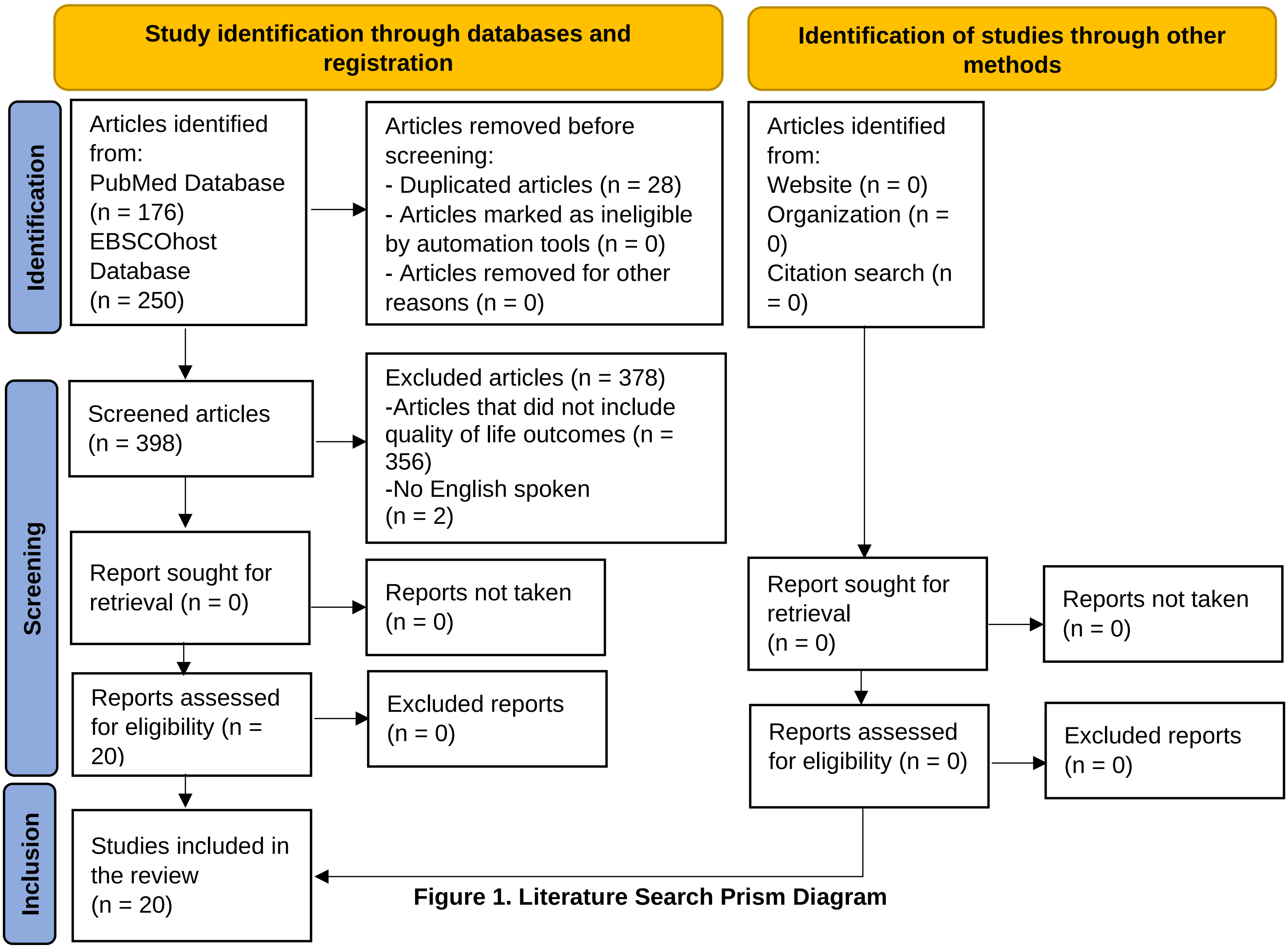

Figure 1. Literature Search Prism Diagram

Inclusion criteria

The selected articles are articles with publication years between 2012-2024 that included heart failure patients with varying ejection fractions. Studies should involve the use of an SGLT2 inhibitor (e.g., dapagliflozin, empagliflozin) as the primary intervention and report quality of life as one of the primary outcomes using a validated instrument. Selected articles using randomized controlled trials (RCTs) published in English.

Exclusion criteria

Articles that were case reports, systematic reviews, trial protocols, and irrelevant topics/outcomes were excluded. Studies that did not measure quality of life or used

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unvalidated instruments, or studies involving populations other than heart failure patients or lacking a control group were excluded.

Keywords Used

To ensure all relevant studies were found, various keyword combinations were used during the literature search. Keywords from each group were combined using "AND" in each search. The following is a list of keywords used for the search:

1. Keywords related to heart failure (HF): “heart failure” OR “HF” OR “cardiac failure” OR “cardiac insufficiency” OR “cardiomyopathy”
2. SGLT2 Inhibitor related keywords: “SGLT2 inhibitor” OR “sodium-glucose co-transporter-2 inhibitor” OR “SGLT2i” OR “gliflozins” OR “dapagliflozin” OR “empagliflozin” OR “canagliflozin” OR “sotagliflozin”
3. Key words related to quality of life: “quality of life” OR “health-related quality of life” OR “QoL” OR “HRQoL” OR “patient-reported outcome” OR “PRO”
4. Study type keywords: “randomized controlled trial” OR “RCT” OR “clinical trial” OR “randomized study”.

Data Collection Procedures

After conducting a literature search, articles found in databases were screened to eliminate duplication. Independent reviewers conducted an initial selection based on titles and abstracts to ensure that articles met the inclusion criteria. Articles that pass the initial selection are then reviewed in full text by independent reviewers. From each selected study, data were systematically extracted, including key information such as author names, year of publication, and study title; patient population characteristics, including ejection fraction and diabetes status; the type of intervention administered, including the type and dose of SGLT2 inhibitor; and instruments used to assess quality of life, such as the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EuroQol 5-Dimension (EQ-5D). The data also included the primary outcome reported regarding changes in quality-of-life scores based on these instruments. This approach aimed to ensure consistency and rigor in the selection process and analysis of data from the relevant literature.Results from the extracted studies were synthesized qualitatively and quantitatively. Analysis was performed based on the instrument used to measure quality of life (specific or generic) and stratified into subgroups based on ejection fraction (HFrEF vs. HFpEF) and diabetes status. After screening the articles, 398 relevant articles were identified, and after removing duplicates and articles that met the inclusion and exclusion criteria, 20 studies were included in this review.

RESULT

A search of the EBSCO host database yielded 250 articles published between 2012 and 2024, while the PubMed database yielded 176 articles published between 2012 and 2024. Twenty-eight duplicate articles were identified, and then selected and filtered based on inclusion and exclusion criteria. The literature search process is shown in Figure 1. Articles were selected from 2012 because the use of SGLT2 drugs began in 2012.

Table 1 lists 20 articles, with publication years 2020-2024, that met the inclusion criteria regarding the quality of life of heart failure patients receiving sodium-glucose co-transporter-2 (SGLT-2) inhibitors. All studies used valid instruments to measure quality of life, namely the Kansas City Cardiomyopathy Questionnaire (KCCQ), Minnesota Living with Heart Failure Questionnaire (MLHFQ), EuroQol 5-Dimension (EQ-5D) and EuroQol Visual Analog Scale (VAS). Most studies involved patients with heart failure with reduced ejection fraction (HFrEF), which is defined as heart failure with an ejection fraction ≤40%, although there were some studies that also included patients with preserved ejection fraction (HFpEF) where the ejection fraction is ≥50%. The patient population involved in the studies varied between patients with and without diabetes,

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suggesting that Sodium-Glucose Co-transporter-2 (SGLT2) inhibitors provide benefits regardless of their diabetes status. In this study, patients' quality of life was measured using generic and specific questionnaires. The generic questionnaires used included: EQ-5D-3L questionnaire, kEQ-5D-5L questionnaire and Visual Analog Scale (VAS). The specific questionnaires used were the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

The study was conducted using standard care interventions compared with standard care plus SGLT-2 therapy, and compared SGLT-2 therapy with other therapies. The standard dose for both dapagliflozin and empagliflozin was 10 mg, although some studies used 25 mg. [27].There are also studies using canagliflozin 100 mg and sitagliptin 100 mg[28]. A description of the intervention, treatment duration, main clinical parameters, clinical outcomes and quality-of-life outcomes in each article is shown in Table 2.

Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is the most widely used instrument to assess quality of life in heart failure patients, which covers several domains such as physical limitations, symptoms, and overall quality of life.[23], [24]. From the various studies analyzed, SGLT2 inhibitors showed significant improvements in various domains of KCCQ. In the dapagliflozin group, there was an increase in the KCCQ score indicating an improvement in quality of life in accordance with studies conducted by Syedah Fauzia Fatima Gilani, et al (2024); Mingming Yang, et al (2024); Toru Kondo, et al (2024); Michael E. Nassif, et al (2023); Ankeet S. Bhatt, et al (2023); Kieran F. Docherty, et al (2022); Jawad H. Butt, et al (2022); Pooja Dewan, et al (2021); Michael E. Nassif, et al (2021); and Mikhail N. Kosiborod, et al (2020)[26], [29], [30], [31], [32], [33], [34], [35], [36], [37]. In the empagliflozin group, there was an increase in the KCCQ score indicating an improvement in quality of life in accordance with studies conducted by Jasper Tromp, et al (2024); Moritz J. Hundertmark, et al (2023); and Mikhail N. Kosiborod, et al (2022).[38], [39], [40] Meanwhile, studies conducted by Carlos G. Santos-Gallego et al. (2021); Michael E. Nassif et al. (2021); and Jesper Jensen, MD, et al. (2020) showed no significant difference in the administration of empagliflozin.[41], [42], [43].

EuroQol 5-Dimension (EQ-5D) and Visual Analog Scale (VAS)

The EQ-5D instrument is used to assess a patient's general health status in five dimensions: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression.[25], [26]. Results from several studies have shown significant improvements in EQ-5D and VAS scores in patients receiving treatment with SGLT2 inhibitors.[29], [30]. Mingming Yang et al. (2024) reported that dapagliflozin significantly improved the EQ-5D index as well as the Visual Analog Scale (VAS), reflecting an improvement in the general health and well-being of patients given dapagliflozin compared to placebo, which is in line with the results of the study by Toru Kondo et al. (2024).[29], [30].

However, several studies such as those conducted by Liang Xie, et al (2024); P. Christian Schulze, et al (2022); and Fahmida Ilyas, et al (2021) showed that although there was an improvement in quality of life in patients receiving SGLT2inhibitor, the results did not reach statistical significance [27], [44], [45].

Minnesota Living with Heart Failure Questionnaire (MLHFQ)

Research conducted by Liang Xie, et al (2024) on patients receiving dapagliflozin 10 mg per day and heart failure therapy compared with those only receiving heart failure therapy showed no significant difference between initial and final MLHFQ scores [44]. In contrast to the research conducted by Salvatore Carbone, et al (2020) which compared the group receiving 100 mg of sitagliptin per day compared to the group given 100 mg of canagliflozin per day showed a decrease in MLHFQ scores (which indicates an increase

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in quality of life) in the canagliflozin group and an increase in scores in the sitagliptin group[28].

Table 1. List of Articles Meeting the Inclusion Criteria

Number Article	Writer, Publication Year, Country	Number of Patients and Sampling Techniques	Participants	Research Instruments
1	Syedah Fatima, et al, 2024, Pakistan [29]	150 patients non-probability	• Patients who have a left ventricular ejection fraction (LVEF) <40%	• KCCQ
2	Mingming Yang, et al, 2024, 20 Countries*[26]	11,007 patients probability sampling	• Patients who have a left ventricular ejection fraction (LVEF) ≤40% or >40%	• EQ-5D-5L • EQ-VAS • KCCQ
3	Liang Xie, et al, 2024, China [44]	120 patients probability sampling	• Patients who have a left ventricular ejection fraction (LVEF) ≤40%	• MLHFQ • EQ-5D-3L
4	Toru Kondo, et al, 2024, 20 Countries*[30]	4744 patients probability sampling	• Patients who have a left ventricular ejection fraction (LVEF) ≤40%	• KCCQ • EQ-VAS
5	Jasper Tromp, et al, 2024, 15 Countries*[38]	530 patients probability sampling	• Patients with systolic blood pressure ≥100 mmHg, and NT-proBNP** ≥1600 / BNP ≥400 pg/ml.	• KCCQ
6	Michael E. Nassif, et al, 2023, America[31]	587 patients probability sampling	• Patients with NT-proBNP** elevated ≥400 pg/ml or BNP ≥100 pg/ml	• KCCQ
7	Ankeet S. Bhatt, et al, 2023, 20 Countries*[32]	11,007 patients probability sampling	• Patients who have a left ventricular ejection fraction (LVEF) ≤40%	• KCCQ
8	Moritz J. Hundertmark, et al, 2023, English[39]	72 patients probability sampling	• Patients who have a left ventricular ejection fraction <40% or ≥50%	• KCCQ
9	Kieran Docherty, et al, 2022, 20 Countries*[33]	4744 patients probability sampling	• Patients who have a left ventricular ejection fraction (LVEF) ≤40%	• KCCQ
10	P. Christian Schulze, et al, 2022, German[27]	60 patients probability sampling	• Patients with NT-proBNP** >300 pg/mL or BNP >100 pg/mL	• EQ-5D
11	Jawad H. Butt, et al, 2022, 20 Countries*[34]	6263 patients probability sampling	• Patients who have a left ventricular ejection fraction (LVEF) >40%	• KCCQ
12	Mikhail N. Kosiborod, et al, 2022, 15 Countries*[40]	530 patients probability sampling	• Patients with systolic blood pressure ≥100 mmHg,NT-proBNP** ≥1600 pg/ml or BNP ≥400 pg/ml.	• KCCQ
13	Fahmida Ilyas, et al, 2021, Australia[45]	19 patients probability sampling	• Patient type two diabetes with decompensated heart failure	• EQ-5D-5L • EQ-VAS
14	Pooja Dewan, et al, 2021, 20 Countries*[35]	4744 patients probability sampling	• Patients who have a left ventricular ejection fraction (LVEF) ≤40%	• KCCQ
15	Michael E. Nassif, et al, 2021, America[36]	324 patients probability sampling	• Patients with NT-proBNP** elevated ≥225 pg/ml or BNP ≥75 pg/ml for patients with sinus rhythm	• KCCQ
16	Carlos G. Santos, et al, 2021, Egypt[41]	84 patients probability sampling	• Patients who have a left ventricular ejection fraction (LVEF) <50%	• KCCQ
17	Michael E. Nassif, et al, 2021, 20 Countries*[42]	65 patients probability sampling	• Patients who have a left ventricular ejection fraction (LVEF) ≤40%	• KCCQ
18	Jesper Jensen, MD, et al, 2020, Denmark[43]	190 patients probability sampling	• Patients who have a left ventricular ejection fraction (LVEF) ≤40%	• KCCQ
19	Salvatore Carbone, et al, 2020, America[28]	36 patients probability sampling	• Patients who have a left ventricular ejection fraction (LVEF) ≤40%	• MLHFQ
20	Mikhail N. K, et al, 2020, 20 Countries*[37]	4744 patients probability sampling	• Patients who have a left ventricular ejection fraction (LVEF) ≤40%	• KCCQ

*20 Countries: United States, United Kingdom, Germany, Brazil, Canada, Sweden, South Korea, China, Japan, Taiwan, Argentina, Australia, Mexico, France, Spain, Italy, India, Russia, Poland, Turkey
*15 Countries: United States, Germany, France, United Kingdom, Spain, Italy, Canada, Japan, China, Brazil, South Korea, Australia, Russia, Mexico, Netherlands

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*8 Countries: United States, Germany, France, Italy, Spain, Netherlands, Canada, Japan
** NT-proBNP: N-terminal pro-B-type natriuretic peptide *** KCCQ: Kansas City Cardiomyopathy Questionnaire; EQ-5D: EuroQol-5 Dimention; EQ-VAS: EQ Visual Analog Scale; MLHFQ: Minnesota Living with Heart Failure Questionnaire

Table 2. Population, Intervention, Control and Outcome (PICO)

No.	Interventions and Duration of Treatment	Clinical Outcome	Outcome (Quality of Life)
1	Trial (n=75) dapagliflozin 10 mg per day and conventional therapy*. Controls (n=75) received only conventional therapy*. 12 weeks	KCCQ scores improved post-intervention compared to baseline (p<0.001) in both groups. The test group showed a relatively greater improvement in NYHA health status compared to the control group.	The dapagliflozin group showed a relatively greater improvement in health status compared to the placebo group.
2	DAPA-HF: Trial (n=2373) received dapagliflozin 10 mg per day**. Controls (n=2371) received placebo. DELIVER: Trial (n=3131) received dapagliflozin 10 mg per day. Controls (n=3132) received placebo** 8 months	VAS scores were generally similar between men and women. Median baseline VAS scores for HFrEF and HFmrEF/HFpEF were 70 (57–80) and 70 (54–80), respectively (p=0.014), while median index scores were 0.88 (0.77–0.95) and 0.87 (0.74–0.95) (p<0.001). Mean baseline VAS scores were 68.1 ± 17.4 (HFrEF) and 67.1 ± 17.1 (HFmrEF/HFpEF) (p=0.005).	EQ-5D index and VAS scores strongly correlated with health status, symptom burden, worsening heart failure events, and mortality. These scores were sensitive to dapagliflozin treatment, showing improvements compared with placebo across all ejection fraction categories. Higher VAS and index scores were associated with better KCCQ scores, and improved NYHA class.
3	Trial (n=60) received optimized heart failure therapy***dapagliflozin 10 mg daily. Controls (n=60) received only optimized heart failure therapy***. 12 weeks	After 12 weeks of Dapagliflozin treatment, AHI decreased significantly from baseline (25.62±6.10 to 17.58±5.18, P<0.001), indicating improvement in the severity of sleep-disordered breathing. Hypopnea Index also decreased significantly (P=0.025)	No significant differences between initial and final MLHFQ scores and EQ-5D-3L scores were observed.
4	DAPA-HF: Trial (n=2373) received dapagliflozin 10 mg per day**. Controls (n=2371) received placebo** 12 months	At 360 days, dapagliflozin had fewer lost days compared with placebo (110.6 ± 1.6 days [30.7%] vs. 116.9 ± 1.6 days [32.5%]; difference: –6.3 days [95% CI –10.8 to –1.7]; P = 0.007), representing a relative reduction of 5.4%. After adjustment for EQ-5D VAS score or NYHA functional class, dapagliflozin consistently resulted in fewer lost days compared with placebo.	At day 120, dapagliflozin patients reported higher KCCQ-OSS scores, reflecting better physical symptoms, activity limitations, and overall quality of life, with these benefits persisting through days 240 and 360, compared with placebo. EQ-5D VAS scores indicated significant improvements in self-reported health status, suggesting both physical and emotional well-being improved.
5.	EMPULSE: Trial (n=265) empagliflozin 10 mg per day**. Controls (n=265) placebo**. 3 months.	Empagliflozin nonsignificantly reduced cardiovascular death or first HFE versus placebo in the first 90 days, regardless of baseline LVEF.	Empagliflozin improved KCCQ scores more than placebo over 90 days across all ejection fraction categories.
6.	DEFINE-HF: Trial (n=131) dapagliflozin 10mg per day****. Controls (n=132) received placebo**** PRESERVED-HF: Trial (n=162) dapagliflozin 10 mg per day****. Controls (n=162) received placebo**** 12 weeks.	Dapagliflozin improved KCCQ-CSS at 12 weeks versus placebo (adjusted difference: +5.0 points [95% CI 2.6–7.5]; P<0.001), consistent across EF subgroups: ≤40% (+4.6), >40–60% (+4.9), and >60% (+6.8). Patients with EF ≥65% had a +7.5 point improvement (P=0.04). Other KCCQ domains also improved: TSS (+5.0), Physical Limitations (+5.0), and OSS (+3.7).	Dapagliflozin significantly improved KCCQ-CSS, TSS, Physical Limitations, and OSS at 12 weeks compared with placebo, with consistent benefits across all EF categories, including higher EF.
7.	DAPA-HF:Trial (n=2373) dapagliflozin10mg/day** Control(n=2371)placebo **. DELIVER: A (n=3131)	Dapagliflozin significantly improved mean KCCQ-TSS at 4 months (+1.8; 95% CI +1.4 to +2.4) and 8 months (+2.5; 95% CI +1.8 to +3.2).	Dapagliflozin improved health status across all KCCQ domains consistently across ejection fraction categories. Fewer patients on dapagliflozin had ≥5-

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	dapagliflozin10mg/day** B (n=3132) placebo** 8 months.	Improvements were greater in patients with type 2 diabetes (+3.4) than in those without (+1.8; P-interaction = 0.026).	point deterioration (21% vs. 29%), and more achieved ≥15-point improvement (28% vs. 25%) compared with placebo.
8.	EMPA-VISION: Trial (n=35) received empagliflozin 10 mg per day**. Controls (n=37) received placebo** 12 weeks.	At 12 weeks, no significant differences in PCr/ATP changes were observed between empagliflozin and placebo. In HFrEF, the adjusted mean difference was -0.25 (95% CI, -0.60 to 0.10; P=0.14). In HFpEF, changes were also not significantly different between them.	Empagliflozin showed a trend toward greater improvement in KCCQ overall summary score (mean change 9.81±1.27) compared with placebo (4.24±1.39).
9.	DAPA-HF: Trial (n=2373) received dapagliflozin 10 mg per day**. Controls (n=2371) received placebo** 8 months.	Black patients had a higher risk of worsening heart failure or cardiovascular death than white patients (HR 1.37; 95% CI 1.02–1.84), mainly due to more heart failure events (HR 1.65; 95% CI 1.17–2.33). The risk of all-cause death was similar between groups. Dapagliflozin reduced the risk of worsening heart failure or cardiovascular death similarly in black (HR 0.62; 95% CI 0.37–1.03) and white patients (HR 0.68; 95% CI 0.52–0.90).	A greater proportion of patients achieved a ≥5-point improvement in KCCQ-TSS with dapagliflozin versus placebo, consistently across races (Black OR 1.20; 95% CI 0.89–1.61; White OR 1.13; 95% CI 1.10–1.28; P-interaction = 0.76). Similarly, fewer patients experienced a ≥5-point decrease in KCCQ-TSS with dapagliflozin versus placebo, in both Black (OR 0.76; 95% CI 0.55–1.05) and White patients (OR 0.86; 95% CI 0.76–0.99; P-interaction = 0.53).
10.	EMPAG-HF: Trial (n=30) received empagliflozin 25 mg per day**. Controls (n=30) received placebo** 5 days.	Cumulative urine output over 5 days was higher with empagliflozin compared to placebo (median 10,775 mL vs 8,650 mL; group difference 2,125 mL; 95% CI 840–3,550 mL). This represented a 25% increase in urine output over 5 days for empagliflozin versus placebo (P=0.003).	Patients in the empagliflozin group experienced greater absolute improvements in NYHA class from baseline to day 5 and hospital discharge. Improvements in EQ-5D index and EQ VAS were numerically greater with empagliflozin versus placebo but did not reach significance.
11.	DELIVER: Trial (n=3131) received dapagliflozin 10 mg per day**. Controls (n=3132) received placebo** 8 months.	Compared with placebo, dapagliflozin reduced the risk of worsening heart failure or cardiovascular death across FI (Frailty Index) classes, with HRs of 0.85 (95% CI 0.68–1.06), 0.89 (95% CI 0.74–1.08), and 0.74 (95% CI 0.61–0.91) from lowest to highest FI class.	The effect of dapagliflozin on KCCQ score improvement was influenced by FI class, with greater improvements observed at 4 and 8 months among patients with higher FI compared to placebo.
12.	EMPULSE: Trial (n=265) received empagliflozin 10 mg per day**. Controls (n=265) received placebo** 90 days.	Patients treated with empagliflozin experienced greater clinical benefit across the entire KCCQ-TSS range, with no evidence of heterogeneity of treatment effect (confidence ratios from lowest to highest tertile: 1.49 [95% CI 1.01–2.20], 1.37 [95% CI 0.94–1.99], and 1.48 [95% CI 1.00–2.20]; P for interaction=0.94).	Both groups improved KCCQ-TSS substantially over 90 days. Empagliflozin led to a greater mean improvement in KCCQ-TSS (+36.2 points; 95% CI 33.3–39.1) versus placebo (+31.7 points; 95% CI 28.8–34.7). Empagliflozin showed greater improvements in all KCCQ domains (PLS, QoL, CSS, OSS) and consistent across prespecified clinical and demographic subgroups.
13	Subjects were given dapagliflozin 10 mg per day in a double-blind manner or matching placebo**. 2 weeks	Dapagliflozin did not change the 6-MWT distance after 2 weeks [338 (281, 397) m] vs. placebo [327 (208, 389) m, P = 0.118].	Dapagliflozin had no significant effect on clinical, functional, or quality of life parameters except for body weight, which decreased slightly [90 (73, 111) vs. 89 (73, 110) kg, P < 0.05].
14.	DAPA-HF: Trial (n=2373) received dapagliflozin 10 mg per day**. Controls (n=2371) received placebo**	Patients with COPD had significantly worse KCCQ scores in all but one domain compared to those without COPD. Health status was lower in COPD patients than in those with other	The effect of dapagliflozin on the primary outcome was consistent in patients with COPD (HR 0.67; 95% CI 0.48–0.93) and without (HR 0.76; 95% CI 0.65–0.87; P-interaction= 0.47). Improvements in

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	12 months.	common comorbidities, with every KCCQ score being worse in the COPD group.	KCCQ-TSS, as well as exploratory KCCQ-CSS and KCCQ-OSS analyses, were similar between both group.
15.	PRESERVED-HF: Trial (n=162) received dapagliflozin 10 mg per day****. Controls (n=162) received placebo**** 6 months.	At 12 weeks, dapagliflozin improved KCCQ-CS by 5.8 points (95% CI 2.3–9.2), improvements in symptoms (KCCQ-TS: +5.8 points; 95% CI 2.0–9.6; P=0.003) and physical limitations (KCCQ-PL: +5.3 points; 95% CI 0.7–10.0; P=0.026). These effects were consistent at patients with and without T2D and those with EF >60% or <60%.	More patients treated with dapagliflozin achieved a ≥5-point improvement in KCCQ-CS (49.4% vs 38.2%; adjusted OR 1.64; 95% CI 0.98–2.75; P=0.06) and KCCQ-OS (45.4% vs 34.9%; adjusted OR 1.73; 95% CI 1.05–2.85; P=0.03). The mean KCCQ-OS was also higher with dapagliflozin (adjusted difference 4.5 points; 95% CI 1.1–7.8; P=0.009).
16.	EMPA-TROPISM: Trial (n=42) received empagliflozin 10 mg per day**. Controls (n=42) received placebo** 6 months	From baseline to 6 months, empagliflozin significantly reduced LVEDV compared with placebo (−25.1 mL vs −1.5 mL; P<0.001) and also reduced LVESV more than placebo (−26.6 mL vs −0.5 mL; P<0.001).	From baseline to 6 months, the empagliflozin group showed greater improvement in overall quality of life compared with placebo, despite no significant differences at baseline.
17.	EMBRACE-HF: Trial (n=33) received empagliflozin 10 mg per day****. Controls (n=32) received placebo**** 12 weeks.	Empagliflozin significantly reduced mean pulmonary artery (PA) diastolic pressure between weeks 8 and 12 compared with placebo. Between weeks 8 and 12, PA diastolic pressure was 1.5 mmHg lower with empagliflozin (95% CI 0.2–2.8; P=0.02), and at week 12 it was 1.7 mmHg lower (95% CI 0.3–3.2; P=0.02).	There was no significant difference in the proportion of patients achieving a ≥5-point improvement in KCCQ-OS (34% vs 33%; P=0.72) or KCCQ-CS (38% vs 17%; P=0.12) at 12 weeks. Adjusted KCCQ-OS (64.2 vs 61.7; P=0.55) and KCCQ-CS (65.8 vs 60.2; P=0.18) scores were not significantly different. Significant improvement was KCCQ total symptom score (72.0 vs 61.8; P=0.04).
18	Trial (n=95) received empagliflozin 10mg per day. Controls (n=95) received placebo 12 weeks.	There was no significant between-group difference in NT-proBNP change from baseline to 12 weeks (empagliflozin: 582→478 pg/mL; placebo: 605→520 pg/mL; adjusted change ratio 0.98; 95% CI 0.82–1.11; P=0.7). NT-proBNP did not change significantly over time in either the empagliflozin (P=0.1) or placebo (P=0.2) groups.	The between-group difference in KCCQ-OSS was not significant (empagliflozin: 75.6→77.6; placebo: 74.9→76.8; adjusted mean difference 0.8; 95% CI −2.3 to 3.9; P=0.6). Similar nonsignificant results were observed for KCCQ-CSS and KCCQ-TSS.
19.	Sitagliptin (n=19) received sitagliptin 100 mg per day. Canagliflozin (n=17) received canagliflozin 100 mg per day 12 weeks.	There were no statistically significant improvements in the peak VO_2 and VE/VCO_2 slope in either group, and no differences between canagliflozin and sitagliptin. Canagliflozin significantly increased peak lean VO_2 compared with sitagliptin and showed significant improvements in VAT to sitagliptin.	Canagliflozin reduced MLHFQ scores more than sitagliptin, indicating improved quality of life (mean difference between groups: −12.1, P=0.018). Within-group changes were from 49.2 ± 26.8 to 41.3 ± 28.6 for canagliflozin (P=0.073) and from 38.4 ± 26.6 to 42.6 ± 29.5 for sitagliptin (P=0.14).
20.	Trial (n=2373) received dapagliflozin 10 mg per day**. Controls (n=2371) received placebo** 12 months	Patients treated with dapagliflozin showed significant improvements in KCCQ scores compared to placebo. At 4 months, the mean differences were +1.9 (TSS), +1.8 (CSS), and +1.7 (OSS) points (P<0.0001 for all), increasing at 8 months to +2.8, +2.5, and +2.3 points, respectively (P<0.0001 for all).	Dapagliflozin reduced the proportion of patients with clinically significant deterioration (25.3% vs 32.9%; OR 0.84, 95% CI 0.78–0.90; P<0.0001) and increased the likelihood of improvement. Minor, moderate, and major improvements were higher in the dapagliflozin group (58.3%, 54.5%, and 54.0% vs 50.9%, 47.6%, and 48.2% with placebo; ORs ~1.14–1.15; all P<0.0001).

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*Conventional therapy includes medical care according to recommended clinical guidelines, and primary initiation of loop diuretics
**Other treatments include: (i) angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), or sacubitril/valsartan, and (ii) beta-blockers, unless contraindicated/not tolerated, (iii) mineralocorticoid receptor antagonists (MRAs).
***Optimized drug therapy consists of a combination of beta blockers, ACEi, ARBs, ARNIs, and MRAs at optimal doses.
****Other medications include: ACEi, ARBs, ARNIs, beta-blockers, MRAs, diuretics, lipid-lowering agents, anticoagulants

Comparison Between Patient Groups

Some studies also evaluate the differences in the impact of SGLT2 inhibitors on various different patient subpopulations. The study conducted Ankeet S. Bhatt, et al (2023) reported that patients with type 2 diabetes experienced greater improvements in scores KCCQ-TSS compared to patients without diabetes when treated with dapagliflozin [32]. Meanwhile, Docherty et al. (2022) found that dapagliflozin improved scores KCCQ-TSS in both black and white patients, with a greater proportion of patients experiencing significant improvement in quality of life compared to placebo [33]. Another research by Pooja Dewan, et al (2021) reported that patients with chronic obstructive pulmonary disease (COPD) had significantly worse scores on the KCCQ score, compared with those without [39]. Improvement in KCCQ-TSS scores with dapagliflozin, compared with placebo, was similar in patients with and without COPD [35]. These findings indicate that dapagliflozin provides consistent benefits in improving quality of life across different patient groups, despite differences in clinical characteristics.

DISCUSSION

Based on the results of various studies analyzed in this systematic review, SGLT2 inhibitors have been shown to provide significant benefits to the quality of life of patients with heart failure, both in patients with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF).[29], [31], [32], [38] Several quality-of-life assessment instruments, such as the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EuroQol 5-Dimension (EQ-5D), were used in this study to provide a more comprehensive picture of the impact of this therapy on patient well-being. Consistent results indicate that SGLT2 inhibitors, particularly dapagliflozin and empagliflozin, play a significant role in improving quality of life, reducing symptoms, and increasing functional capacity in heart failure patients [26], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40].

Consistent Improvement in Quality of Life

The included studies demonstrated consistent improvements in KCCQ and EQ-5D scores across a diverse patient population. In the DAPA-HF study, dapagliflozin significantly improved the KCCQ Overall Summary Score (OSS) after 120 days of therapy, with improvements seen in physical symptoms, disease stability, and overall quality of life.[32], [33], [35], [37]. Reduction of symptoms such as shortness of breath and fatigue also contributes to increased functional capacity, which ultimately improves patient participation in daily activities [32], [33], [35], [37]. Several studies such as EMPULSE, EMPA-VISION, EMPAG-HF, and also EMBRACE-HF showed similar benefits with the use of empagliflozin [27], [38], [39], [40], [42] that patients receiving empagliflozin experienced significant improvements in the KCCQ Total Symptom Score (TSS) and KCCQ Physical Limitation Score, [27], [38], [39], [40], [42]. This improvement affect either in patients HFrEF and HFpEF [38]. In these studies, patients receiving empagliflozin experienced significant improvements in the KCCQ Total Symptom Score (TSS) and KCCQ Physical Limitation Score, indicating significant improvements in physical limitations and symptom burden compared to the placebo group [27], [38], [39], [40], [42]. This improvement in quality of life was not limited to patients with reduced ejection fraction, but was also seen in patients with preserved ejection fraction [38].

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Benefits Regardless of Diabetes Status

One important finding of this review is that the benefits of SGLT2 inhibitors on quality of life appear to be independent of the patient's diabetes status. Studies including patients with and without diabetes showed that both groups experienced significant improvements in quality of life after treatment with SGLT2 inhibitors [16], [32]. For example, Yang et al. (2024) reported similar improvements in EQ-5D and KCCQ in patients with type 2 diabetes and non-diabetic patients, suggesting that SGLT2 inhibitors may be broadly applicable in the heterogeneous heart failure population [29]. This finding is in line with previous research findings that confirmed that SGLT2 inhibitors have cardioprotective effects beyond glycemic control [46], [47]. In addition to reducing blood glucose levels in diabetic patients, SGLT2 inhibitors can also improve heart function and reduce stress on the kidneys through other mechanisms, such as lowering blood pressure and reducing plasma volume [47], [48].

Reduction in the Risk of Hospitalization and Mortality

In addition to improved quality of life, the review also highlighted the finding that patients receiving SGLT2 inhibitors had a lower risk of heart failure-related hospitalization and cardiovascular death compared to patients receiving placebo [29], [30]. In the DAPA-HF study, patients receiving dapagliflozin experienced a 30% reduction in the risk of hospitalization compared to placebo, as did patients receiving empagliflozin [49], [50]. This risk reduction is likely due to several interrelated mechanisms, namely a reduction in systolic and diastolic blood pressure, improved endothelial function, reduced arterial stiffness, diuretic effects, reduced preload and afterload, and prospective impacts on myocardial energy metabolism so can reduce serious clinical events [51], [52] [51],[52].

Study Limitations

Although these results support the use of SGLT2 inhibitors to improve the quality of life in heart failure patients, there are several limitations to the studies analyzed. Many studies had only short-term follow-up (3 to 12 months), so the long-term effects of these therapies on quality of life are not yet fully understood. Furthermore, although the KCCQ and EQ-5D are validated instruments, variations in measurement methods and definitions of quality-of-life improvement may influence the interpretation of results across studies. Most of the included studies used patient populations with relatively good access to healthcare. This may limit the generalizability of the results to patient populations with limited access to healthcare facilities, such as those in developing countries. Further studies that include more demographically and geographically diverse populations are needed.

Recommendations for Future Research

Future research should focus on assessing the long-term effects of SGLT2 inhibitors on quality of life in heart failure patients. Furthermore, studies exploring the effects of SGLT2 inhibitors in underrepresented subpopulations and populations with limited access to care, are needed. Further research assessing the relationship between improved quality of life and reduced clinical events would also provide deeper insight into the holistic benefits of SGLT2 inhibitors.

Clinical Implications

Based on available evidence, SGLT2 inhibitors such as dapagliflozin and empagliflozin should be considered an integral part of heart failure management, especially for patients who prioritize improving their quality of life. The use of SGLT2 inhibitors not only improves physical capacity and emotional well-being, but also significantly reduces the risk of serious clinical events, such as hospitalization and cardiovascular death.

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CONCLUSION

Sodium-Glucose Co-transporter-2 (SGLT2) inhibitors have been consistently shown to improve the quality of life of heart failure patients, both with HFrEF and HFpEF. Significant improvements in physical symptoms, functional capacity, and emotional well-being, as measured by the KCCQ and EQ-5D, demonstrate that SGLT2 inhibitors provide broad and substantial benefits. Furthermore, reduced risk of hospitalization and cardiovascular death further strengthens the role of SGLT2 inhibitors in modern heart failure management.

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