

Economic Evaluation of Sodium-Glucose Cotransporter-2 Inhibitors in Patients with Heart Failure with Preserved or Mildly Reduced Ejection Fraction: A Systematic Review

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Abstract

Background: Heart Failure (HF) is a complex and life-threatening syndrome with substantial morbidity, mortality, diminished function, and high healthcare costs. Several studies have demonstrated that sodium-glucose co-transporter 2 inhibitors (SGLT2i) are very promising for improving HF outcomes in patients with preserved ejection fraction (HFpEF) or mild reduction in ejection fraction (HFmrEF). A review of the cost-effectiveness of SGLT2 inhibitors for the treatment of HFpEF is essential to help clinicians and decision-makers identify the most cost-effective treatment option for HF. The purpose of this study was to review economic studies on the addition of SGLT-2i to HFpEF or HFmrEF.

Methods: In this systematic review, searches were conducted across PubMed, Scopus, Web of Science, and EMBASE databases from January 2020 to March 2025. Full economic evaluations of adding SGLT-2i in HF with HFpEF or HFmrEF were included for data extraction. Articles were screened at the title, abstract, and full-text levels. The data were extracted into an Excel table, and the narrative synthesis was performed. The quality of the studies was assessed using the CHEERS 2022 criteria.

Results: A total of 421 references were screened after removing duplicates. Twenty-one studies were identified that examined full economic evaluations of adding SGLT-2i in HFpEF or HFmrEF. Most studies were from China and the USA. The highest and lowest incremental costs per quality-adjusted life year for empagliflozin were in China (\$10961.971) and the United States (\$48,527.33) (healthcare system perspective). In most countries except Thailand, empagliflozin or dapagliflozin plus standard care (SoC) is more cost-effective than SoC alone in patients with HFpEF or HFmrEF.

Conclusion: Study results indicate that adding SGLT2i to SoC is cost-effective in patients with HFpEF or HFmrEF. Moreover, further studies comparing dapagliflozin and empagliflozin in this patient group are needed.

Keywords: Cost-effectiveness, Cost-utility, Dapagliflozin, Empagliflozin, Heart failure

Conflicts of Interest: None declared

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Introduction

Heart failure (HF) is defined by the heart's incapacity to

adequately pump blood and oxygen to meet the metabolic requirements of other organs (1). The prevalence rates of

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↑What is “already known” in this topic:

SGLT2 inhibitors have shown clinical efficacy across the full range of ejection fractions in heart failure patients.

→What this article adds:

According to this systematic review, co-transporter 2 inhibitors are cost-effective in patients with HFpEF or HFmrEF.

HF in the adult population range from 1% to 2% (2). Prior projections indicated a significant rise in HF prevalence by 2030 across all age groups, alongside increasing trends in the anticipated risk for HF development (3).

In the United States, HF is projected to cost each patient approximately \$30,000 per year, imposing a significant financial burden. In the United States, the anticipated overall cost of HF was \$31 billion in 2012. By 2030, that amount is expected to have more than doubled to \$70 billion. HF care's direct costs account for two-thirds of this total (4).

There are different types of HF, and they can be classified as HF with reduced, mildly reduced, or preserved ejection fraction (HFrEF, HFmrEF, and HFpEF) (5). Congestive HF with preserved ejection fraction (HFpEF) is caused by an increase in left ventricular (LV) filling resistance. However, there are no specific tests or guidelines for diagnosing or treating HFpEF (6).

Inhibitors of sodium-glucose cotransporter-2 (SGLT-2i) are a new class of hypoglycemic drugs that compete with SGLT-2i's glucose binding affinity (7). Studies show SGLT-2i, such as empagliflozin and dapagliflozin, are effective in managing HFpEF (8). According to the EMPEROR-Preserved trial, empagliflozin (10 mg once daily) was significantly more effective than placebo in patients with chronic high blood pressure with preserved ejection fraction (median follow-up 26 months) compared to standard care (9).

The Food and Drug Administration approved the US Empagliflozin in February 2022 to reduce cardiac death and hospitalizations in patients with HFrEF and HFpEF (10). Patients with HFmrEF or HFpEF who took Dapagliflozin had a reduced risk of worsening HF or cardiovascular death (11).

Modern medicine and sanitation have extended life expectancy. Nonetheless, the development of novel health technologies is costly, and the cost of drugs is also rising (12). The persistent rise in healthcare expenditures, coupled with advancements in evidence-based medicine and the pursuit of transparent, data-informed decision-making, has led to the widespread application of economic evaluations within the health system. Cost-effectiveness analysis (CEA), a crucial economic evaluation tool, has attained significant prominence in the pharmaceutical policy-making process. The primary objective of CEA is to facilitate decision-making on the distribution of scarce health resources to optimize health outcomes or social welfare. This analysis evaluates the costs and outcomes of novel interventions, such as innovative pharmaceuticals or medical technologies, compared with a comparator intervention, and determines whether the new intervention has the requisite economic value for reimbursement and insurance coverage. The premise of cost-effectiveness analysis is that only economically viable therapies should qualify for payment and financial assistance from insurance systems or the government. This method facilitates the optimal utilization of scarce resources and fosters efficiency and equity within the healthcare system (13).

This study aims to systematically review the evidence for the economic evaluation of adding empagliflozin to

standard therapy in patients with HFpEF. The evidence from the present study can provide necessary information for health policy-making on the cost-effectiveness of SGLT2i added to standard treatment in patients with HFpEF or HFmrEF.

Methods

The protocol was registered with PROSPERO in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (CRD420251040231). Using the search terms in [Appendix Table 1](#), we searched PubMed, Scopus, EMBASE, and Web of Science databases in March 2025. To identify relevant economic evaluation reports, we also searched Google Scholar. Two researchers reviewed titles and abstracts. A review of the full texts of the studies meeting the eligibility criteria was conducted.

Studies examining the cost-effectiveness of adding SGLT-2i in patients with HFpEF or HFmrEF were identified based on the following inclusion criteria: a full health economic evaluation (cost-effectiveness, cost-utility, and cost-benefit analyses) was performed. Exclusion criteria were review articles, letters to the editor, editorials, comments, methodological articles, conference abstracts, and cost-per-outcome or cost-offset analyses.

Data Extraction and Synthesis

Study characteristics were collected independently by 2 investigators. They included study setting, time horizon, interventions, comparators, sources of funding, willingness-to-pay (WTP) threshold, discount rate, perspective, incremental cost-effectiveness ratios (ICERs), and main findings. We resolved the disagreements through discussion or by involving a third reviewer. Health outcomes are measured as life years gained or quality-adjusted life years (QALYs). The data were extracted into an Excel table, and the narrative synthesis was performed. All costs were adjusted using the CCEMG-EPPI-Center Cost Converter tool for inflation to 2023 US dollars, based on consumer price index data from the International Monetary Fund. The purchasing power parity rates were adjusted for the pertinent price year (14).

Quality Assessment of Studies

The CHEERS checklist 2022 was used to evaluate economic evaluation studies (15). CHEERS 2022 was divided into seven sections: title, abstract, introduction, methods, results, discussion, and other relevant information. We rated each item as "Completely fulfilled," "Not fulfilled," "Partially fulfilled," or "Inapplicable." An assessment that completely met all the criteria was rated a "1"; an evaluation that partially met the requirements was rated a "0.5"; and an assessment that did not meet the criteria was rated a "0." It was classified as excellent quality if scores exceeded 85%, very good quality if scores exceeded 70%, good quality if scores exceeded 55% to 70%, and low quality if scores exceeded 55%. A third researcher was consulted to resolve any disagreements between the two researchers who evaluated the quality of the studies independently (16).

Results

Results of Study Selection

The identification process of studies is illustrated in Figure 1. A total of 900 articles were retrieved from electronic databases and Google Scholar. In addition to removing 479 duplicate articles, we also excluded 197 that did not meet the criteria based on a review of the titles and abstracts. In addition, 203 studies were excluded by screening the full text.

Study Characteristics

Table 1 summarizes the characteristics of selected studies. These studies originated from 14 countries: China (n = 5) (17-21), United States (n = 4) (9, 22-24), the United Kingdom (n = 2) (25, 26), Thailand (n = 2) (27, 28), South Korea (n = 2) (29, 30), France (n = 2) (26, 31), Japan (n = 1) (32), Spain (n = 2) (25, 26), Finland (n = 1) (33), Germany (n = 1) (25), Philippine (n = 1) (34), Australia (n = 1) (35), and Malaysia (n = 1) (36).

Economic Evaluation Methods

The cost-utility analyses (CUA) included 20 studies that measured QALYs as health outcomes (9, 17-26, 28-36), while the cost-effectiveness analyses included 7 studies that measured life years gained as health outcomes (18,

19, 23, 26, 28, 35, 36). In most studies, cost-effectiveness was assessed using CUA and expressed as ICERs of cost per QALY and/or cost per LYG, with one study reporting cost-benefit (27) (Table 2).

Most evaluations (95%) used modeling-based approaches (9, 17-26, 28-36). Fourteen studies focused on the payer perspective (18, 23, 25, 27, 33, 34), 6 focused on the healthcare system perspective (9, 17, 19-22, 24, 26, 28-32, 35, 36), and one reported results from the collective perspective (31). A lifetime horizon was used in the majority of evaluations. Future costs and benefits were discounted at rates of 2% to 5% in studies. Uncertainty analyses have been carried out in all studies, using either deterministic or probabilistic sensitivity analyses.

Willingness-to-pay (WTP) thresholds were reported at AUS\$50,000 and AUS\$150,000 per QALY in the USA. The WTP thresholds per QALY adopted by the other studies were as follows: in Japan, \$38408; and in the Philippines, China, and Thailand, 1- or 3-times GDP per capita; in UK, £20,000; in Spain, €15000-20000; in South Korea, \$18182; in Malaysia, RM47439; in Australia, \$50,000.

Cost-Effectiveness Results of Adding Dapagliflozin to Standard of Care

Figures 2 and 3 show the incremental cost-effectiveness

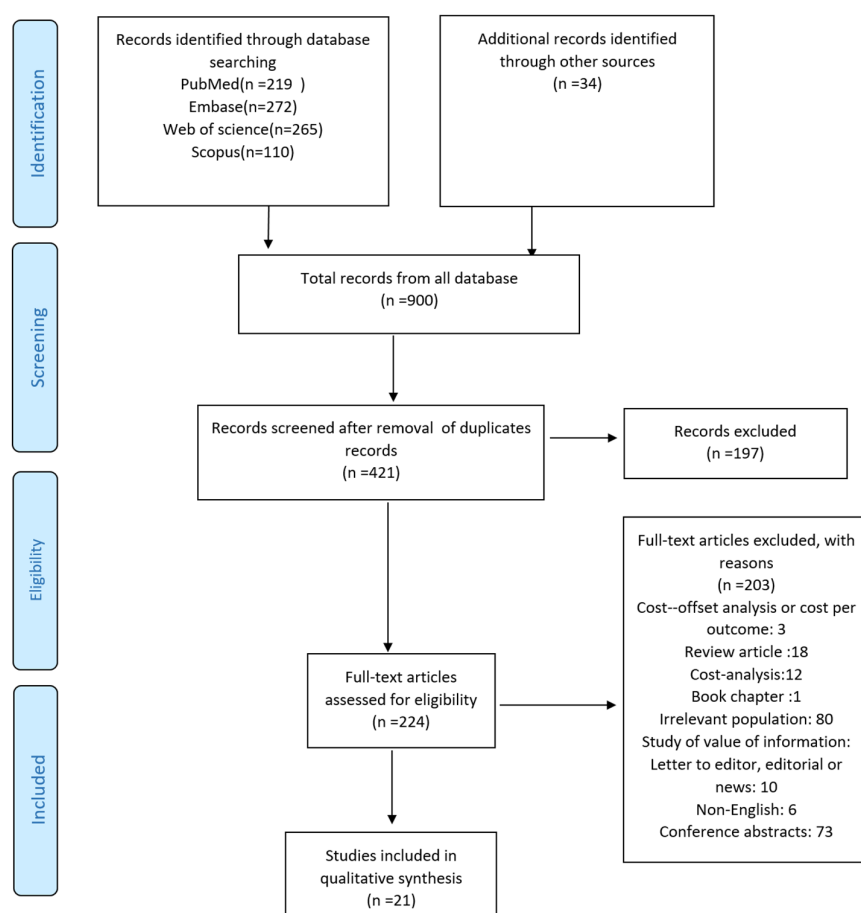


Figure 1. PRISMA flow chart for study selection

Table 1. Study design and setting overview

First author (year of publication)	Setting	Compared interventions	Population	Time horizon	Perspective	Economic evaluation analysis	Willingness to pay threshold (WTP)
Montilla, P. J. (2025)	Philip- pine	-Empagliflozin + SoC -SoC	HFpEF patients	Lifetime	Payer	CUA (Markov model)	Three times GDP per capita of Phil- ippine NR
Arunmanakul, P. (2025)	Thailand	-Dapagliflozin -Empagliflozin -SoC	HFpEF patients	5-year	Payer	CBA	
Tsutsui, H. (2024)	Japan	-Empagliflozin + SoC -SoC	HF with pre- served or mildly reduced Ejection	Lifetime	Healthcare system	CUA (Markov model)	\$38408 per QALY
Tan, Y. J. (2024)	Malaysia	-Empagliflozin + SoC -SoC	HF with pre- served or mildly reduced Ejection	Lifetime	Healthcare system	CEA and CUA (Markov model)	RM47439 per QALY
Kim, E. S. (2024)	South Korea	-Empagliflozin -SoC	HFpEF patients	Lifetime	Healthcare system	CUA (Markov model)	\$18182 per QALY
Kim, E. S. (2024)	South Korea	-Dapagliflozin + SoC -SoC	patients with EF $\geq$ 40	Lifetime	Healthcare system	CUA (Markov model)	\$18182 per QALY
Fauchier, L. (2024)	France	-Empagliflozin + SoC -SoC	HFpEF patients	Lifetime	Collective	CUA (Markov model)	Three times per capita GDP: 37663 per QALY
Dixit, N. M. (2024)	US	- Placebo - MRA - MRA+SGLT2i MRA+ARNI+SG LT2i	HF with pre- served or mildly reduced Ejection	30-year	Single- payer health care system	CEA and CUA (Markov model)	\$150,000 per QALY
Tang, Y. (2023)	China	-Dapagliflozin + SoC -SoC	HF with pre- served or mildly reduced Ejection	15-year (base-case analysis)	Public Healthcare system	CUA (Markov model)	1-3 times GDP per capita per QALY
Rane, A. (2023)	US	-Dapagliflozin -Empagliflozin	HFpEF patients	Lifetime	Healthcare system	CUA (Markov model)	150,000 per QALY
Lou, Y. (2023)	China	-Empagliflozin + SoC -SoC	HFpEF patients	Lifetime	Healthcare system	CEA and CUA (Markov model)	Three times the per capita GDP of China
Lin, L. (2023)	China	-Dapagliflozin + SoC -SoC	HF with pre- served or mildly reduced Ejection	Lifetime	Chinese national insurance (payer)	CEA and CUA (Markov model)	38256 (three times the GDP per capita)
Kolovos, S. (2023)	UK, Spain, and France	-Empagliflozin + SoC -SoC	HF with LVEF> 40%	Lifetime	Healthcare system	CEA and CUA (Markov model)	€/£20,000 Per QALY
Hallinen, T. (2023)	Finland	-Empagliflozin + SoC -SoC	HFpEF patients	Lifetime	Healthcare payer	CUA (Markov model)	€35,000 per QAY
Cohen, L. P. (2023)	US	-SoC + SGLT2-i therapy	HFpEF patients	Lifetime	Healthcare sector	CUA (Markov model)	\$50,000, \$150,000 per QALY
Booth, D. (2023)	UK, Germa- ny, and Spain	-Dapagliflozin + SoC -SoC	HF with pre- served or mildly reduced Ejection	Lifetime	Payer	CUA (Markov model)	£20,000 per QALY for UK, €25000 for Germany and €15,000 per QALY
Zhou, J. (2022)	Australia	-Empagliflozin + SoC -SoC	HFpEF patients	Lifetime	Healthcare system	CEA and CUA (Markov model)	\$50,000 per QALY

ratios per QALY for empagliflozin and dapagliflozin in comparison with standard of care alone.

The incremental costs per quality adjusted life year for empagliflozin, when compared to standard care alone, were highest in the United States at \$48,527.33 and lowest in China at \$10,961.97.

Several studies have compared the cost-effectiveness of dapagliflozin to the standard of care in South Korea, China, Germany, and the UK (18, 21, 25, 29). Kim et al's study, from the perspective of the healthcare system, demonstrated that dapagliflozin is more cost-effective than standard of care alone in patients with EF >40%

Table 1. Study design and setting overview

First author (year of publication)	Setting	Compared interventions	Population	Time horizon	Perspective	Economic evaluation analysis	Willingness to pay threshold (WTP)
Zheng, J. (2022)	US	-Empagliflozin + SoC -SoC	HFpEF patients	Lifetime	Healthcare system	CUA (Markov model)	\$50,000 per QALY, \$150,000 per QALY
Tang, Y. (2022)	China	-Empagliflozin + SoC -SoC	HFpEF patients	10-year (base-case analysis)	Healthcare system	CUA (Markov model)	1-3 times GDP per capita per QALY
Krittayaphong, R. (2022)	Thailand	-Empagliflozin + SoC -SoC	HFpEF patients	Lifetime	Healthcare system	CEA and CUA (Markov model)	Three times GDP per capita of Thailand
Jiang, Y. (2022)	China	-Empagliflozin + SoC -SoC	HFpEF patients	10-year	Healthcare system	CUA (Markov model)	1-3 times GDP per capita \$12652.5, \$378687.5

HFpEF: Heart failure with preserved ejection fraction, CEA: Cost-effectiveness analysis, CUA: Cost-utility analysis, CBA: Cost-benefit analysis, MRA: Mineralocorticoid receptor antagonists, SGLT2is: Sodium glucose co-transporter 2 inhibitors, QALY: Quality-adjusted life years, HF: Heart failure, SOC: standard of care, GDP: Gross domestic product, EF: Ejection fraction.

Table 2. Intervention cost and output results

First author (year of publication)	Comparators	Total cost (\$2023)	Mean of LYG/QALY		Main findings (\$2023)
			LYG	QALY	
Montilla, P. J. (2025)	Empagliflozin + SoC	35380.26	6.11	4.03	Incremental Cost per QALY: PHP 742,604 (\$13858.08) Incremental Cost per LYG: PHP 852,156(\$45952.15)
Arunmanakul, P. (2025)	SoC	31999.96	6.03	3.94	Dapagliflozin and empagliflozin, respectively, cost 10,178 million THB and 9,261 million THB. For dapagliflozin, 2,606 million THB were saved, and for empagliflozin, 3,524 million THB were saved. Dapagliflozin and empagliflozin saved 4,961 million THB and 6,047 million THB on HHF, respectively.
	Dapagliflozin				
Tsutsui, H. (2024)	Empagliflozin + SoC	25747.14	7.43	5.63	Incremental Cost per QALY: \$ 13241.62
Tan, Y. J. (2024)	SoC	24287.37	7.34	5.52	Incremental Cost per QALY: RM40454 (\$28537.99) Incremental Cost per LYG: RM54665 (\$38563.04)
	Empagliflozin + SoC	13076.09	5.54	4	
Kim, E. S. (2024)	SoC	10293.82	5.47	3.96	Incremental Cost per QALY: \$9300.86
	Empagliflozin	20857.73	—	8.28	
Kim, E. S. (2024)	SoC	18506.34	—	8.03	Incremental Cost per QALY: \$8691.24
	Dapagliflozin + SoC	21911.09	—	8.34	
Fauchier, L. (2024)	SoC	19160.54	—	8.03	Incremental Cost per QALY: €13980 (\$19433.93) Incremental Cost per LYG: €18597(\$25852.13)
	Empagliflozin + SoC	22857.80	7.24	6.14	
	SoC	20793.47	7.16	6.03	

MRA: Mineralocorticoid receptor antagonists, SGLT2is: Sodium glucose co-transporter 2 inhibitors, QALY: Quality-adjusted life years, LYG: life-years gained, SOC: standard of care.

(ICER: \$ 8,383 per QALY). Compared to standard of care, dapagliflozin provided an incremental QALY of 0.32 and an incremental cost of \$2653 (29). Lin et al in China also found that dapagliflozin was more cost-effective than standard care for patients with HFpEF and HFmrEF (ICERs of \$10,615.87 per QALY and \$7763.08 per QALY, respectively). According to the study, dapagliflozin had an incremental QALY of 0.15, an incremental LY of 0.2, and an incremental cost of 1551 compared to the standard of care (18). Dapagliflozin also showed cost-effectiveness compared to standard of care in another Chinese study (ICER = \$11865.33 per QALY) (20).

In a study conducted in the UK, dapagliflozin was also shown to be cost-effective compared to standard of care (ICER = £15447 per QALY). Dapagliflozin showed a probability of cost-effectiveness exceeding 50% at a WTP threshold of £20,000 per QALY in this study. Booth et al in the UK predicted increases in QALYs and life years of 0.231 and 0.354, respectively. There was an ICER of £7761(\$12462.45), €9540 (\$13556.08), and €5343 (\$9176.56) per QALY gained in the UK, Germany, and Spain, respectively. The UK, Germany, and Spain found dapagliflozin cost-effective in 91%, 89% and 92% of simulations (25).

Table 2. Intervention cost and output results

First author (year of publication)	Comparators		Total cost (\$2023)	Mean of LYG/QALY		Main findings (\$2023)
				LYG	QALY	
Dixit, N. M. (2024)	Placebo	EF: 45-52	66000	6.61	5.29	–
		EF: >52	87000	8.82	7.06	
	MRA	EF: 45-52	73000	7.38	5.96	Incremental Cost per QALY of MRA vs Placebo: 10,000 Incremental Cost per LYG of MRA vs Placebo: 9,000
		EF: >52	93000	9.50	7.67	
	MRA+SGLT2i	EF: 45-52	114000	7.77	6.32	Incremental Cost per QALY of MRA+SGLT2i vs MRA: 113,000 Incremental Cost per LYG of MRA+SGLT2i vs MRA: 106,000
		EF: >52	144000	9.86	8.02	
	MRA+ARNI+SGLT2i	EF: 45-52	159000	7.93	6.49	Incremental Cost per QALY of MRA+SGLT2i vs MRA: 138,000 Incremental Cost per LYG of MRA+SGLT2i vs MRA: 141,000 Incremental Cost per QALY of MRA+ARNI+SGLT2i vs MRA+SGLT2i: 283,000 Incremental Cost per LYG of MRA+ARNI+SGLT2i vs MRA+SGLT2i: 271,000
		EF: >52	201000	10.01	8.19	
Tang, Y. (2023)	Dapagliflozin + SoC		7512.20	–	6	Incremental Cost per QALY: \$12301.02
Rane, A. (2023)	SoC		5407.55	–	5.84	–
	Empagliflozin		167237.18	–	4.143	–
	Dapagliflozin		198232.45	–	4.953	Incremental Cost per QALY: \$38258.88
Lou, Y. (2023)	SoC		29983.73	6.18	4.67	–
	Empagliflozin + SoC		38814.54	6.32	4.80	Incremental Cost per QALY: \$10961.97 Incremental Cost per LYG: \$9411.03
Lin, L. (2023)	SoC		9159.75	8.72	6.32	–
	Dapagliflozin + SoC		10880.43	8.92	6.46	Incremental Cost per QALY: \$11006.21 Incremental Cost per LYG: \$8048.53
Kolovos, S. (2023)	UK	Empagliflozin + SoC	18464.84	6.87	4.30	Incremental Cost per QALY: \$23847.41 Incremental Cost per LYG: \$30594.89
		SoC	16205.51	6.79	4.20	–
	Spain	Empagliflozin + SoC	29047.94	7.05	5.11	Incremental Cost per QALY: \$20104.96 Incremental Cost per LYG: \$25685.09
		SoC	27076.26	6.97	5.01	–
	France	Empagliflozin + SoC	22857.80	7.24	5.42	Incremental Cost per QALY: \$ 21473.24 Incremental Cost per LYG: \$ 25852.13
		SoC	20793.47	7.16	5.32	–

Cost-Effectiveness Results of Adding Empagliflozin to Standard of Care

According to Montilla et al in the Philippines, adding empagliflozin to the standard of care increased costs and

QALYs in patients with HFpEF. Based on the results of this study, empagliflozin and standard of care alone were predicted to result in 0.55 and 0.62 hospitalizations for chronic HF, respectively. Empagliflozin had a median

Table 2. Intervention cost and output results

First author (year of publication)	Comparators		Total cost (\$2023)	Mean of LYG/QALY		Main findings (\$2023)
				LYG	QALY	
Hallinen, T. (2023)	Empagliflozin + SoC		19865.06	—	4.732	Incremental Cost per QALY: \$19917.38
Cohen, L. P. (2023)	SoC		17964.83	—	4.648	—
		SoC	174834.63	6.63	5.27	—
		SoC + SGLT2-I therapy	202114.11	6.79	5.46	Incremental Cost per QALY: \$146391.89
Booth, D. (2023)	UK	Dapagliflozin + Usual care	19368.90			Incremental Cost per QALY: £7761 (\$12462.45)
	Germany	Usual care	16486.53			Incremental Cost per QALY: —
		Dapagliflozin + Usual care	20598.43			
	Spain	Usual care	16963.58			Incremental Cost per QALY: —
		Dapagliflozin + Usual care	20809.13			
Zhou, J. (2022)	Empagliflozin + SoC	Usual care	18420.10	6.22	4.97	Incremental Cost per QALY: \$22150.70 Incremental Cost per LYG: \$34288.20
Zheng, J. (2022)	SoC		64875.44	6.06	4.81	—
	Without CV	SoC	190103.29	—	4.9	Incremental Cost per QALY: \$48527.33
		Empagliflozin	219233.89	—	5	
	With CV	SoC	187974.35	—	4.9	Incremental Cost per QALY: \$168549.68
		Empagliflozin	220973.43	—	5	
Tang, Y. (2022)	Empagliflozin + SoC		6133.74	—	4.96	Incremental Cost per QALY: \$11728.61
Krittayaphong, R. (2022)	SoC		4816.03	—	4.85	Incremental Cost per QALY: \$13100.89
	Empagliflozin + SoC		1030.85	6.25	4.52	Incremental Cost per LYG: \$10255.58
Jiang, Y. (2022)	SoC		340.26	6.18	.47	Incremental Cost per QALY: \$11707.27
	Empagliflozin + SoC		6134.05		4.81	
		SoC	4816.03		4.70	

survival of 6.11 years, and standard of care had a median survival of 6.30 years. The standard of care group had a higher rate of cardiac clinical events, including hospitalizations, heart deaths, and acute renal failure, while the empagliflozin group had a higher rate of noncardiovascular death, urinary tract infections, and HF caused by cholestyramine and mild hypotension (34).

In Finland, Hallinen et al examined the long-term cost-effectiveness of the mentioned drugs in patients with HFrEF and HFpEF using Markov models. The study was conducted from the payer's perspective. Empagliflozin added to standard of care resulted in 0.15 more QALYs and EUR 1594 more than standard of care alone, according to this study. For patients with HFpEF, the ICER was estimated at EUR 19,211 (33).

Based on the Japanese health system's perspective, Tsutsi et al found empagliflozin to be superior to standard of care alone. Empagliflozin was found to be cost-effective with a probability of 0.64. An essential factor in cost-

effectiveness results was the effectiveness of the treatment in reducing HF hospitalizations (32).

In three studies conducted in China, empagliflozin was cost-effective compared with standard of care alone in patients with HFpEF (17, 19, 20). Compared treatments resulted in a QALY incremental of 0.11 (20). Another study in China found that both the empagliflozin and standard-of-care groups had mean QALYs of 4.8 and 4.67, respectively, and the costs of empagliflozin and standard of care were \$5423 and \$4189, respectively. According to the results of this study, empagliflozin was cost-effective in patients with HFpEF (19).

In Thailand, Krittayaphong et al assessed the cost-utility of empagliflozin combined with standard therapy compared with standard treatment alone in patients with HFrEF and HFpEF. According to this study's results, adding empagliflozin to standard therapy resulted in 0.07 years of life saved and 0.05 QALYs gained, at a cost of US\$49,622 more than standard therapy alone. Adding

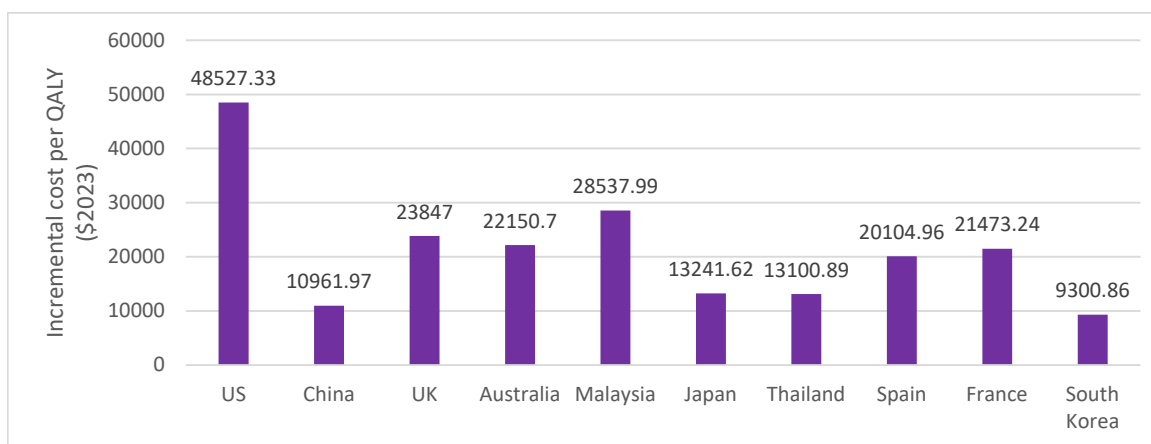


Figure 2. Incremental cost per QALY Empagliflozin vs. standard care (healthcare system perspective)

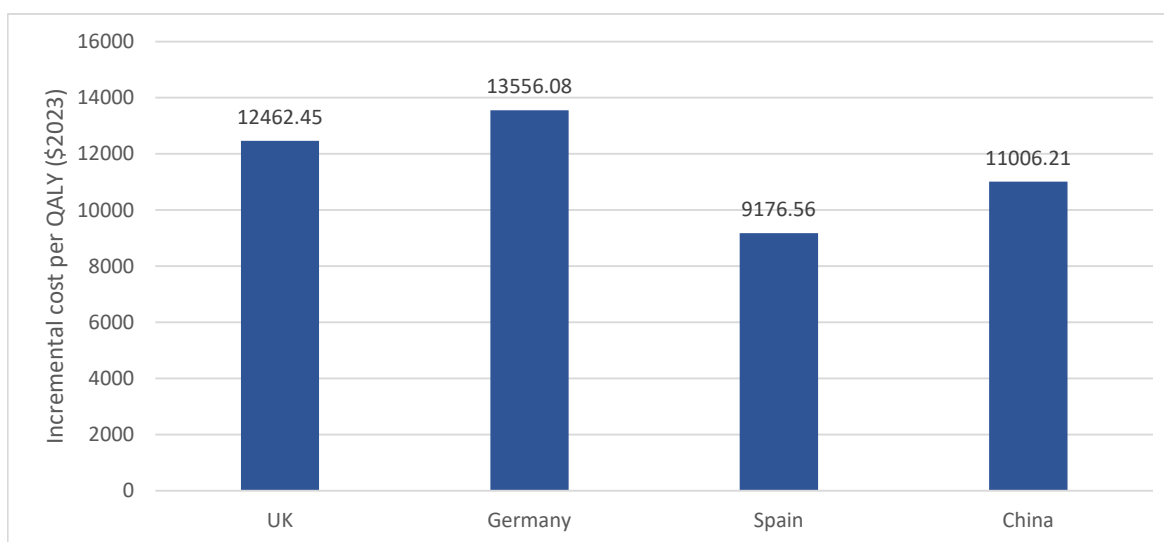


Figure 3. Incremental cost per QALY Dapagliflozin vs. standard care (payer perspective)

empagliflozin to standard treatment in patients with HFpEF in Thailand was not cost-effective (28).

Zhou et al examined the cost-effectiveness of empagliflozin in patients with HFpEF in Australia. Empagliflozin prevented 167 HF hospitalizations in this study, and the average cost of empagliflozin and standard of care was US\$63,218 and US\$58,478 per patient, respectively. Cost-effectiveness ratio per QALY was estimated at A\$29,202. Empagliflozin was cost-effective when added to standard care alone, according to the results of this study (35).

Tan et al also found that empagliflozin was cost-effective for patients with EF greater than 40% in their Malaysian study. (ICER = RM40454 (\$28537.99) per QALY). In this study, the incremental QALY between the two treatment options was 0.10, and the incremental cost was RM3941 (\$2780). In 57% of simulations, empagliflozin was cost-effective. The model results were sensitive to the treatment effect of empagliflozin on reducing hospi-

tizations and cardiovascular mortality associated with HF, as well as to the cost of empagliflozin (36).

Cost-Effectiveness Results of Empagliflozin Compared With Dapagliflozin

A Markov model was developed by Rane et al to simulate HFpEF patients treated with dapagliflozin or empagliflozin. Compared to empagliflozin, dapagliflozin had an incremental expected lifetime cost of \$29,896. This resulted in an ICER of \$36,902 per QALY. According to a value-based price threshold analysis, empagliflozin would have to be discounted by 29% to be cost-effective. Dapagliflozin would be the most cost-effective option approximately 72% of the time (24).

Thai researchers examined the budgetary and cost-benefit impacts of including dapagliflozin and empagliflozin in universal health coverage for patients with HF. It was found that including HF drugs as part of universal health coverage has a significant impact on healthcare

payer budgets, at current prices. For dapagliflozin, the budgetary impact analysis was approximately 4.96 billion Thai baht, and for empagliflozin, it was approximately 4.55 billion Thai baht in the first year of inclusion. Dapagliflozin's benefit-cost ratio in the first year was 0.396 for all HF patients, but 0.347 for patients with HFmrEF and HFpEF. Empagliflozin had a benefit-cost ratio of 0.456 and 0.443 in the first year for all HF patients and HFmrEF and HFpEF, respectively. SGLT-2i's high drug delivery costs outweigh any potential savings from

reduced hospitalization rates, which explains this increase (27).

Findings of Quality Assessment

According to the CHEERS checklist, the mean and standard deviation of study quality were 0.79 and 0.03, respectively. In Figure 4, all studies scored above 70%, indicating very high quality. According to the checklist, all studies scored zero for both criteria (health economic analysis plan, distributional effects). The source of fund-



Figure 4. Results of quality assessment of studies using CHEERS checklist

ing was not reported in two studies (18, 24) and the discount rate (27) and conflicts of interest were not reported in one study (24) (Figure 4).

Discussion

This study systematically reviewed published studies on the economic evaluation of adding SGLT2i Inhibitors in patients with HFpEF or HFmrEF. A total of 21 references were included in this systematic review (9, 17-36).

Overall, the included studies showed that adding dapagliflozin or empagliflozin to the standard of care was cost-effective in most countries (9, 17-26, 29-36), except Thailand (28). The studies were conducted from the perspectives of the payer and the health system, with a time horizon of lifetime. The studies were analysed using a Markov model. The efficiency parameters and calculations required for transition probabilities were taken from the clinical trials DELIVER for dapagliflozin and EMPEROR for empagliflozin (11, 37). In the EMPEROR-Preserved study, which included about 6000 participants and followed them for an average of 26 months, empagliflozin reduced the risk of cardiovascular death or HF hospitalization from 17.1% to 13.8%. This meant that about 30 people needed to take the drug to prevent one such event (ARR = 3.3%) (37, 38). In the DELIVER study (N = 6263; median follow-up 2.3 years), dapagliflozin reduced the risk of HF exacerbation or cardiovascular death from 19.5% to 16.4%, reflecting an absolute risk reduction (ARR) of around 3.1% and a number needed to treat (NNT) of about 32 (11). The trials demonstrate substantial internal validity and assess relevant clinical outcomes; however, they are limited by modest absolute benefits, short follow-up durations (around 2–3 years), and the requirement for economic models to forecast long-term outcomes and convert quality-of-life improvements (e.g., Kansas City Cardiomyopathy Questionnaire) into utility values, which introduces uncertainty. The absence of integrated real-world adherence and resource utilization data restricts external validity. Thus, while RCT results offer a strong methodological foundation, their use in long-term pharmacoeconomic predictions requires careful consideration.

The ICERs of adding empagliflozin to the standard of care in China were 63746, 11312.65, and 11292.06 per QALY (9, 17, 19). Empagliflozin was cost-effective in all of these studies. The incremental cost-effectiveness ratio of dapagliflozin compared to standard of care alone in China was 10615.87 per QALY. This indicates the cost-effectiveness of this medicine at a WTP threshold of 12652.5 per QALY (18). According to an economic evaluation in the United States, adding SGLT2-i to standard care has a moderate or low economic value compared with standard care in American adults with HFpEF. In this study, the ICER per QALY gained was \$141,200, with 59.1% indicating moderate value and 40.9% indicating low value. SGLT2-i costs and cardiovascular death effects were the most important factors in determining the ICER (22). The results of another cost-effectiveness study in this country also showed that dapagliflozin was more cost-effective than empagliflozin in this patient group (24). The

results of the study by Dixit et al in the United States showed that MRA had a high value in both HFmrEF and HFpEF, SGLT2i had a moderate value, and ARNI had a low value. According to this study, patients with HFmrEF/HFpEF should be encouraged to use MRA and SGLT2i therapies, and efforts should be made to reduce their costs (23). The cost-effectiveness of SGLT2 inhibitors for patients with HFpEF and HFmrEF is significantly affected by regional pricing policies. Differential pricing, external reference pricing (ERP), and national health technology assessments are policies that directly influence the costs of medication delivery. The primary determinant of incremental cost-effectiveness ratios (ICERs) in pharmacoeconomic evaluations is these costs (39). Pooled assessments of US Medicare drug pricing vs scenarios with a 50% discount indicated moderate to high cost-effectiveness values, demonstrating how sensitive the models are to assumed drug delivery costs (40).

These systematic reviews have several limitations. A majority of the studies included in this review were funded by pharmaceutical companies, which could have led to favorable cost-effectiveness ratios for SGLT2i in HFpEF or HFmrEF. Potential reporting bias could have been increased as a result. Further, there were differences across studies in parameters such as sources of information, model structures, settings, discount rates, and WTP thresholds. A WTP threshold denotes the disclosed maximum monetary value per unit of health acquired in every country, typically represented as cost per quality-adjusted life-year (QALY) (41). This serves as a standard in CEA to assess if a health intervention offers good value for money. Variability in WTP thresholds complicates global comparisons of CEAs, and findings from CEAs conducted in one country may not apply to those in others. The WTP threshold can be determined in three ways. The World Health Organization (WHO-CHOICE) recommends the per capita income-based approach, which lists interventions costing less than three times GDP per capita as cost-effective and those costing less than one time GDP per capita as extremely cost-effective. Second, techniques that use benchmarked values, such as the \$50,000 US level, emphasize health consumption. Third, the league table approach ranks interventions by Cost-Effectiveness ratio and budget to maximize health benefit and resource allocation (42-44).

Consequently, it was difficult to generalize results across settings, creating a roadblock for policymakers when determining which interventions would be most cost-effective. Few studies were conducted in low- and middle-income countries, making it difficult to generalize. The cost-effectiveness of empagliflozin compared to dapagliflozin has been studied in only 2 studies, so further research is needed to compare these 2 medicines in this patient population.

Conclusion

The present study demonstrated that, except in Thailand, patients with HFpEF or HFmrEF can benefit from adding dapagliflozin or empagliflozin to standard care. There is a need for further cost-effectiveness studies com-

paring empagliflozin and dapagliflozin in this patient group.

Authors' Contributions

The study was conceptualized or designed by A.S., M.R., and M.H. A.R., A.S., and M.R. were responsible for screening and extracting the data from the articles. A.S. carried out data analysis and interpretation, and M.R., A.S., and M.N. drafted M.T. Manuscripts. Also, M.H. A.S., M.N., and M.R. were involved in the critical revision and final approval of the manuscript.

Ethical Considerations

This research was approved by the Research Ethics Committee of Rafsanjan University of Medical Sciences (IR.RUMS.REC.1402.121).

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Conflict of Interests

The authors declare that they have no competing interests.

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Appendix

Table S1. Search strategy of databases

Database	Search strategy
PubMed	(Cost[tiab] OR "Cost analysis"[tiab] OR (cost[tiab] AND analysis[tiab]) OR "cost comparison"[tiab] OR cost-effectiveness[tiab] OR "cost effectiveness"[tiab] OR cost-utility[tiab] OR "cost utility"[tiab] OR cost-benefit[tiab] OR "cost benefit"[tiab] OR "economic evaluation"[tiab] OR "economic evaluations"[tiab] OR "health resource allocation"[tiab] OR "health economic"[tiab] OR (economic[tiab] AND medical[tiab]) OR pharmacoeconomic[tiab] OR "decision analysis"[tiab] OR decision-analytic[tiab] OR economic*[tiab]) AND ("Sodium-Glucose Transporter 2 Inhibitors"[tiab] OR "Sodium-glucose co-transporter-2 inhibitor"[tiab] OR "Sodium Glucose Transporter 2 Inhibitors"[tiab] OR "Sodium-Glucose Transporter 2 Inhibitor"[tiab] OR "Sodium Glucose Transporter 2 Inhibitor"[tiab] OR "SGLT-2 Inhibitors"[tiab] OR "Sodium-Glucose Cotransporter 2 Inhibitors"[tiab] OR "SGLT 2 Inhibitors"[tiab] OR Gliflozins[tiab] OR "SGLT2 Inhibitors"[tiab] OR Gliflozin[tiab] OR "SGLT-2 Inhibitor"[tiab] OR (Inhibitor[tiab] AND SGLT-2[tiab]) OR "SGLT 2 Inhibitor"[tiab] OR "SGLT2 Inhibitor"[tiab] OR (Inhibitor[tiab] AND SGLT2[tiab]) OR Dapagliflozin[tiab] OR Edistride[tiab] OR farxiga[tiab] OR forxiga[tiab] OR Empagliflozin[tiab] OR Jardiance[tiab]) AND ("heart failure"[tiab] OR "Heart failure with preserved ejection fraction"[tiab] OR HFpEF[tiab] OR "major adverse cardiac events"[tiab] OR "Cardiac Failure"[tiab] OR "Heart Decompensation"[tiab] OR (Decompensation[tiab] AND Heart[tiab]) OR "Myocardial Failure"[tiab] OR "Congestive Heart Failure"[tiab] OR "major adverse cardiovascular events"[tiab]) AND 2020/01/01:2025/03/19 [dp]
Web of Science	(TI=(Cost) OR TS= ("Cost analysis") OR (TS= (cost) AND TS= (analysis)) OR TS= ("cost comparison") OR TS=(cost-effectiveness) OR TS= ("cost effectiveness") OR TS=(cost-utility) OR TS= ("cost utility") OR TS=(cost-benefit) OR TS= ("cost benefit") OR TS= ("economic evaluation") OR TS= (economic evaluations) OR TS= ("health resource allocation") OR TS= ("Medical Economics") OR (TS=(economic) AND TS=(medical)) OR TS= ("health economics") OR TS=(economic*) OR TS= ("decision analysis") OR TS= (decision-analytic) OR TS= (pharmacoeconomic)) AND (TS= ('Sodium-Glucose Transporter 2 Inhibitors') OR TS= ('Sodium-glucose co-transporter-2 inhibitors') OR TS= ('Sodium Glucose Transporter 2 Inhibitors') OR TS= ('Sodium Glucose Transporter 2 Inhibitor') OR TS= ('SGLT-2 Inhibitors') OR TS= ('SGLT 2 Inhibitors') OR TS= (Gliflozins) OR TS= ('SGLT2 Inhibitors') OR TS= (Gliflozin) OR TS= ('SGLT-2 Inhibitor') OR TS= (Inhibitor) AND TS= (SGLT-2)) OR TS= ('SGLT 2 Inhibitor') OR TS= ('SGLT2 Inhibitor') OR TS= (Inhibitor) AND TS= (SGLT2) OR TS= ('Sodium-Glucose Cotransporter 2 Inhibitors') OR TS= (Dapagliflozin) OR TS= (Empagliflozin) OR TS= (Jardiance)) AND (TS= ('heart failure') OR TS= ("Heart failure with preserved ejection fraction") OR TS= (HFpEF) OR TS= ("major adverse cardiac events") OR TS= ("Cardiac Failure") OR TS= ("Heart Decompensation") OR (TS= (Decompensation) AND TS= (Heart)) OR TS= ("Myocardial Failure") OR TS= ("Congestive Heart Failure") OR TS= ('major adverse cardiac events')) AND PY=(2020-2025)
Scopus	(TITLE(Cost) OR TITLE-ABS ("Cost analysis") OR (TITLE-ABS (cost) AND TITLE-ABS (analysis)) OR TITLE-ABS ("cost comparison") OR TITLE-ABS(cost-effectiveness) OR TITLE-ABS("cost effectiveness") OR TITLE-ABS(cost-utility) OR TITLE-ABS("cost utility") OR TITLE-ABS(cost-benefit) OR TITLE-ABS("cost benefit") OR TITLE-ABS("economic evaluation") OR TITLE-ABS (economic evaluations) OR TITLE-ABS("health resource allocation") OR TITLE-ABS("Medical Economics") OR (TITLE-ABS(economic) AND TITLE-ABS(medical)) OR TITLE-ABS("health economics") OR TITLE-ABS(economic*) OR TITLE-ABS("decision analysis") OR TITLE-ABS(decision-analytic) OR TITLE-ABS(pharmacoeconomic)) AND (TITLE-ABS('Sodium-Glucose Transporter 2 Inhibitors') OR TITLE-ABS('Sodium-glucose co-transporter-2 inhibitors') OR TITLE-ABS('Sodium Glucose Transporter 2 Inhibitors') OR TITLE-ABS('Sodium-Glucose Transporter 2 Inhibitor') OR TITLE-ABS('Sodium Glucose Transporter 2 Inhibitor') OR TITLE-ABS('SGLT-2 Inhibitors') OR TITLE-ABS('SGLT 2 Inhibitors') OR TITLE-ABS(Gliflozins) OR TITLE-ABS('SGLT2 Inhibitors') OR TITLE-ABS(Gliflozin) OR TITLE-ABS('SGLT-2 Inhibitor') OR (TITLE-ABS(Inhibitor) AND TITLE-ABS(SGLT-2)) OR TITLE-ABS('SGLT 2 Inhibitor') OR TITLE-ABS('SGLT2 Inhibitor') OR TITLE-ABS(Inhibitor) AND TITLE-ABS(SGLT2) OR TITLE-ABS('Sodium-Glucose Cotransporter 2 Inhibitors') OR TITLE-ABS(Dapagliflozin) OR TITLE-ABS(Empagliflozin) OR TITLE-ABS(Jardiance)) AND (TITLE-ABS('heart failure') OR TITLE-ABS("Heart failure with preserved ejection fraction") OR TITLE-ABS(HFpEF) OR TITLE-ABS("major adverse cardiac events") OR TITLE-ABS("Cardiac Failure") OR TITLE-ABS("Heart Decompensation") OR (TITLE-ABS(Decompensation) AND TITLE-ABS(Heart)) OR TITLE-ABS("Myocardial Failure") OR TITLE-ABS("Congestive Heart Failure") OR TITLE-ABS('major adverse cardiac events')) AND (PUBYEAR > 2019 AND PUBYEAR < 2026)
Embase	(Cost:ti OR "Cost analysis":ti,ab OR (cost:ti,ab AND analysis:ti,ab) OR "cost comparison":ti,ab OR cost-effectiveness:ti,ab OR "cost effectiveness":ti,ab OR cost-utility:ti,ab OR "cost utility":ti,ab OR cost-benefit:ti,ab OR "cost benefit":ti,ab OR "economic evaluation":ti,ab OR "economic evaluations":ti,ab OR "health resource allocation":ti,ab OR "health economic":ti,ab OR (economic:ti,ab AND medical:ti,ab) OR pharmacoeconomic:ti,ab OR "decision analysis":ti,ab OR decision-analytic:ti,ab OR economic*:ti,ab) AND ("Sodium-Glucose Transporter 2 Inhibitors":ti,ab OR "Sodium-glucose co-transporter-2 inhibitor":ti,ab OR "Sodium Glucose Transporter 2 Inhibitors":ti,ab OR "Sodium-Glucose Transporter 2 Inhibitor":ti,ab OR "Sodium Glucose Transporter 2 Inhibitor":ti,ab OR "SGLT-2 Inhibitors":ti,ab OR "Sodium-Glucose Cotransporter 2 Inhibitors":ti,ab OR "SGLT 2 Inhibitors":ti,ab OR Gliflozins:ti,ab OR "SGLT2 Inhibitors":ti,ab OR Gliflozin:ti,ab OR "SGLT-2 Inhibitor":ti,ab OR (Inhibitor:ti,ab AND SGLT2:ti,ab) OR Dapagliflozin:ti,ab OR Edistride:ti,ab OR farxiga:ti,ab OR forxiga:ti,ab OR Empagliflozin:ti,ab OR Jardiance:ti,ab) AND ("heart failure":ti,ab OR "Heart failure with preserved ejection fraction":ti,ab OR HFpEF:ti,ab OR "major adverse cardiac events":ti,ab OR "Cardiac Failure":ti,ab OR "Heart Decompensation":ti,ab OR (Decompensation:ti,ab AND Heart:ti,ab) OR "Myocardial Failure":ti,ab OR "Congestive Heart Failure":ti,ab OR "major adverse cardiovascular events":ti,ab) AND [2020-2025]/PY

Table S2. Result of quality assessment of included studies

Item No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	Total
First author (year of publication)																													
Montilla, P. J. (2025)	Y	Y	Y	N	PA	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	Y	Y	0.82
Arunmanakul, P. (2025)	Y	Y	Y	N	PA	PA	Y	PA	PA	N	Y	Y	Y	Y	PA	NA	Y	Y	N	PA	PA	Y	Y	PA	PA	PA	Y	Y	0.70
Tsutsui, H. (2024)	Y	Y	Y	N	PA	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	Y	Y	0.82
Tan, Y. J. (2024)	Y	Y	Y	N	PA	PA	Y	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	Y	Y	0.8
Kim, E. S. (2024)	Y	Y	Y	N	PA	PA	Y	PA	Y	PA	Y	Y	Y	Y	PA	Y	Y	Y	N	PA	PA	Y	Y	Y	PA	PA	Y	Y	0.767
Kim, E. S. (2024)	Y	Y	Y	N	PA	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	Y	Y	0.82
Fauchier, L. (2024)	Y	Y	Y	N	PA	PA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	Y	Y	0.839
Dixit, N. M. (2024)	Y	Y	Y	N	PA	PA	Y	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	Y	Y	0.8
Tang, Y. (2023)	Y	Y	Y	N	PA	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	Y	Y	0.82
Rane, A. (2023)	Y	Y	Y	N	PA	PA	Y	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	N	N	0.73
Lou, Y. (2023)	Y	Y	Y	N	PA	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	Y	Y	0.82
Lin, L. (2023)	Y	Y	Y	N	PA	PA	Y	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	N	Y	0.767
Kolovos, S. (2023)	Y	Y	Y	N	PA	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	Y	Y	0.82
Hallinen, T. (2023)	Y	Y	Y	N	PA	PA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	Y	Y	0.839
Cohen, L. P. (2023)	Y	Y	Y	N	PA	PA	Y	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	Y	Y	0.8
Booth, D. (2023)	Y	Y	Y	N	PA	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	Y	Y	0.82
Zhou, J. (2022)	Y	Y	Y	N	PA	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	PA	PA	PA	Y	Y	0.8
Zheng, J. (2022)	Y	Y	Y	N	PA	PA	Y	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	PA	PA	PA	Y	Y	0.78
Tang, Y. (2022)	Y	Y	Y	N	PA	PA	Y	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	PA	PA	PA	Y	Y	0.78
Krittayaphong, R. (2022)	Y	Y	Y	N	PA	PA	Y	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	Y	Y	0.8
Jiang, Y. (2022)	Y	Y	Y	N	PA	PA	Y	PA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PA	Y	Y	Y	PA	PA	N	Y	0.78