HEALTH TECHNOLOGY ASSESSMENT REPORT

ON

Cost-Effectiveness of SGLT2 inhibitors as addon treatment prior to hospital discharge among patients with Heart Failure in India

RESOURCE HUB FOR

HEALTH TECHNOLOGY ASSESSMENT IN INDIA (HTAIn)

ICMR – NATIONAL INSTITUTE OF EPIDEMIOLOGY

CHENNAI

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LIST OF ABBREVIATIONS

AE	Adverse Event
ARB	Angiotensin receptor blockers
ARNi	Angiotensin-receptor neprilysin inhibitors
BB	Beta-blocker
CE	Cost effectiveness
CEA	Cost effectiveness Analysis
CUA	Cost utility analysis
FDA	Food and Drug Administration
GDP	Gross Domestic Product
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HICs	Higher income countries
HRQL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental Cost utility ratio
INB	Incremental Net Benefit
INR	Indian Rupees
LVEF	Left ventricular ejection fraction
LICs	Low-income countries
LMICs	Low and middle-income countries
MRA	Mineralocorticoid receptor antagonists
NHA	National Health Authority
NICE	National Institute for Health and Care Excellence
NMB	Net Monetary Benefit
OADs	Oral anti-diabetic medications
PGIMER	Post Graduate Institute of Medical Education and Research
PSA	Probabilistic sensitivity analysis
QALY	Quality Adjusted Life Years
RCTs	Randomised Controlled Trials
SGLT2i	Sodium–glucose cotransporter-2 inhibitors
SC	Standard of care
SRMA	Systematic Review and Meta analysis
UICs	Upper income countries
UMICs	Upper middle-income countries
WHO	World Health Organization
WTP	Willingness to pay threshold

EXECUTIVE SUMMARY

This analysis evaluates the cost-effectiveness of SGLT2 inhibitors as an add-on to standard care for heart failure patients with reduced ejection fraction (HFrEF) in India. Using a Markov model, the study assesses the economic efficiency of add-on SGLT2 inhibitors compared to standard care alone.

Key Findings

- Addon SGLT2 inhibitors are not cost-effective compared to standard care for HFrEF patients at the current market prices of drugs and one GDP per capita willingness-to-pay (WTP) threshold in India.
- Considering the current market price, only after a 71% reduction in the average annual market price of SGLT2i drugs (from ₹12,124 to ₹3,516) the add-on SGLT2i therapy could become cost-effective for HFrEF patients. Cost-effectiveness is achieved with specific price reductions: a 67% reduction for Empagliflozin (per tablet ₹28.75 to ₹9.48; annual ₹10,494 to ₹3,463), a 61% reduction for Dapagliflozin (per tablet ₹24.09 to ₹9.44; annual ₹4,344 to ₹3,518), and an 84% reduction for Canagliflozin (per tablet ₹59 to ₹9.63; annual ₹21,535 to ₹3,446).
- **Clinical Benefits**: SGLT2 inhibitors provide significant gains in life years for HFrEF populations. The clinical benefits observed support their consideration in treatment protocols.

Conclusion: Addon SGLT2 inhibitors offer longer life years than the standard of care for patients with heart failure; however, at current market prices SGLT2 inhibitors is not a cost-effective option for HFrEF patients in India.

Recommendations

- The administration of add-on SGLT2i therapy to heart failure patients with reduced ejection fraction in India is not a cost-effective option at current market prices.

- An average price reduction of about 71% in the SGLT2i market price is necessary for it to become a cost-efficient option in the Indian context.

- To explore strategies to reduce the market price of SGLT2 inhibitors, including price negotiation with the manufacturers for its inclusion in the treatment packages.

Chapter 1- INTRODUCTION

1.1 Background

Heart Failure (HF) is a potentially life-threatening condition characterized by significant morbidity, mortality and diminished quality of life, impacting over 64 million individuals globally (1). The prevalence of HF in India ranges extensively, reported to be between 1.3 to 23 million, with an annual incidence of 0.5–1.8 million in India (2-4). Though there have been significant developments in the management of chronic heart failure, it remains a public health issue with a worse prognosis leading to several million hospitalizations (5, 6). The primary goals of HF treatment are improving a patient's clinical condition, functional capacity, and overall quality of life while avoiding hospitalisations and lowering mortality rates (7).

Heart failure with preserved ejection fraction (HFpEF) is identified as a subtype of heart failure marked by impaired relaxation of the heart muscle, where the confirmed left ventricular ejection fraction (LVEF) is equal to or greater than 50% (8). Conversely, heart failure with reduced ejection fraction (HFrEF) occurs when the LVEF is 40-50% or less, accompanied by progressive left ventricular dilatation and adverse cardiac remodelling (9). Approximately 20% of heart failure patients in India are attributed to HFpEF (10, 11). The use of beta-blockers (BB) and pharmaceuticals targeting the renin-angiotensin-aldosterone system, such as angiotensin-receptor neprilysin inhibitors (ARNi), angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists (MRA), has resulted in significant advances in HF prognosis (7, 12, 13). Sodium-glucose cotransporter-2 (SGLT2) inhibitors represent a modern class of oral anti-diabetic medications (OADs) that specifically target and reduce renal tubular glucose reabsorption (14). Empagliflozin, dapagliflozin, ertugliflozin sotagliflozin and canagliflozin are among the frequently prescribed medications belonging to the class of SGLT2 inhibitors (15). While individual SGLT2 inhibitors share similar mechanistic effects,

pharmacological differences have led to varying efficacy and safety outcomes in different clinical trials posing challenges in determining the most suitable SGLT2 inhibitor (16, 17).

In the DAPA-HF and DEFINE-HF trials, dapagliflozin significantly reduced the risk of worsening heart failure or cardiovascular death (18) and improved symptoms and functional status (19) compared to placebo. In the EMPA-REG OUTCOME trials, high-risk patients with type 2 diabetes who received empagliflozin demonstrated a reduced incidence of the primary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) compared to those receiving a placebo (20). Following the EMPA-REG OUTCOME study, it was subsequently approved for reducing the risk of cardiovascular death in patients with type II diabetes and established atherosclerotic cardiovascular disease (21). Other key trials such as EMPEROR-Preserved, EMPEROR-Reduced, and EMPULSE consistently demonstrate the clinical superiority of empagliflozin compared to conventional heart failure therapies (20, 22-24). Similarly, in the SOLOIST-WHF trial, sotagliflozin significantly reduced the risk of cardiovascular death, hospitalizations for heart failure, and urgent visits for heart failure among patients with diabetes and recent worsening heart failure, including both HFrEF and HFpEF, compared to placebo (25). Various studies emphasize the clinical efficacy of SGLT2i in improving cardiorenal outcomes, decreasing mortality, reducing heart failure-related hospitalizations, and enhancing quality of life indicators in patients with chronic heart failure across varying left ventricular ejection fractions (24, 26, 27). The list of approved SGLT2 inhibitors along with the conditions are given in Table 1.

Table 1.1 List of SGLT2 inhibitors

Drug Name	Approval Agencies	Approved Indications	Year of First Approval	Recommended Dosage
Canagliflozin (Invokana)	FDA, EMA, PMDA, DCGI	Type 2 Diabetes, Chronic Kidney Disease	2013 (FDA)	100 mg once daily, can increase to 300 mg
Dapagliflozin (Farxiga)	FDA, EMA, PMDA, DCGI, TGA, ANVISA	Type 2 Diabetes, Heart Failure, Chronic Kidney Disease	2014 (FDA, EMA)	5 mg once daily, can increase to 10 mg
Empagliflozin (Jardiance)	FDA, EMA, PMDA, DCGI, ANVISA	Type 2 Diabetes, Heart Failure, Chronic Kidney Disease	2014 (FDA, EMA)	10 mg once daily, can increase to 25 mg
Ertugliflozin (Steglatro)	FDA, EMA, PMDA	Type 2 Diabetes	2017 (FDA)	5 mg once daily, can increase to 15 mg
Ipragliflozin (Suglat)	PMDA, DCGI	Type 2 Diabetes	2014 (PMDA)	50 mg once daily, can increase to 100 mg
Luseogliflozin (Lusefi)	PMDA	Type 2 Diabetes	2014 (PMDA)	2.5 mg once daily, can increase to 5 mg
Tofogliflozin (Apleway, Suglat)	PMDA, DCGI	Type 2 Diabetes	2014 (PMDA)	20 mg once daily
Remogliflozin (Remozen, Brenzavvy)	DCGI, EMA	Type 2 Diabetes	2019 (DCGI)	100 mg twice daily
Sotagliflozin (Zynquista)	EMA	Type 1 Diabetes (approved in EU only, not approved by FDA for T1D)	2019 (EMA)	200 mg once daily, can increase to 400 mg

FDA: U.S. Food and Drug Administration; EMA: European Medicines Agency; PMDA: Pharmaceuticals and Medical Devices Agency (Japan); DCGI: Drug Controller General of India; TGA: Therapeutic Goods Administration (Australia); ANVISA: National Health Surveillance Agency (Brazil)

1.2 Review of Literature

1.2.1 Clinical effectiveness of SGLT2 inhibitors for Heart Failure

SGLT2 is a glucose and sodium transporter localized in the proximal tubule. Inhibition of SGLT2 lowers blood glucose by promoting the excretion of glucose into the urine, so SGLT2 was initially marketed as a treatment for diabetes. Subsequently, clinical studies demonstrated its efficacy in heart failure and chronic kidney disease(28-30), and the indication was expanded; however, the mechanism of efficacy of SGLT2 inhibitors remains unclear.

EMPA-REG OUTCOME study demonstrated that, in patients with T2D and high CVD risk, empagliflozin reduced adverse cardiac events by 14%, which resulted in a 38% reduction in cardiovascular (CV) mortality (20). It is the first antidiabetic agent that reduces CV events beyond glycemic control. Subsequently, the CANVAS Program also achieved comparable effects with another SGLT2 inhibitor (31). The unique action of SGLT2 inhibitors corrects several metabolic and hemodynamic abnormalities that are risk factors for CVD, by decreasing serum glucose, body weight, and blood pressure and by increasing diuresis(14). However, other underlying mechanisms to explain the cardioprotective effects of SGLT2 inhibitors are as yet unclear.

1.2.2 Cost-effectiveness of SGLT2 inhibitors for Heart Failure

A systematic search was performed to retrieve the available evidence on the cost effectiveness of different SGLT2i compared with standard of care. Isaza et al. (2021) found that adding dapagliflozin to the standard of care, at an annual cost of $4,192, would be a cost-effective therapy for patients with HFrEF, regardless of whether the treated patients have diabetes (32). Within the context of the Finnish setting, the cost-effectiveness analysis of Empagliflozin treatment for HF patients revealed favourable (33). The incremental cost-effectiveness ratio

(ICER) values obtained for the HFpEF population were comparatively higher than those observed in the HFrEF population in scenarios spanning the lifetime. (33) The cost-effectiveness comparison for treating HFrEF patients indicated an incremental expected lifetime cost of $37,684 and an ICER of $44,763 per QALY suggesting that both dapagliflozin and empagliflozin present optimal choices for favourable outcomes, emphasizing their potential cost-effectiveness subject to decision makers' thresholds. (34) Empagliflozin treatment, in conjunction with SC for HF patients, yields 0.16 more QALYs but with an incremental per-patient cost compared to SC alone. Empagliflozin, when combined with SC, represents a cost-effective utilization of resources for treating chronic HF patients, irrespective of ejection fraction with an ICER of £7,757/QALY (35).

The prevailing evidence indicates that, in the majority of studies conducted globally, SGLT2i is deemed cost-effective compared to SC, regardless of the ejection fraction among patients with or without diabetes (Table 1.2.1). However, these studies are from higher income countries (HICs), upper income countries (UICs) and upper middle-income countries (UMICs). Most of these studies were conducted from a health system perspective using the markov model. As the cost-effectiveness of interventions could be setting specific such results from HICs and UMICs may not be suitable for lower income countries (LICs) and lower middle-income countries (LMICs) like India. Further, the higher prevalence of HF cases warrants the need to generate economic evidence for cost-effectiveness for initiating SGLT2i treatment before hospital discharge in heart failure patients in India. In this context, the National Health Authority (NHA), Government of India has recommended a comprehensive evaluation of the cost-effectiveness of SGLT2 in the Indian context to determine the eligibility of different SGLT2i for inclusion in the Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (AB PM-JAY) package. Hence, we undertook an economic evaluation of SGLT2i treatment as an add-on treatment for HF patients.

1.2.3 Current Scenario of Heart Failure in India

The CVD epidemic in Indians is characterized by a higher relative risk burden, an earlier age of onset, higher case fatality and higher premature deaths (36). Indians present with CVD a decade earlier compared with western population (37). Nearly two-thirds (62%) of all cardiovascular deaths in Indian populations are premature. The mean (SD) age of first myocardial infarction among South Asians (53.0 [11.4] years) is lower compared with other countries (58.8 [12.2] years; $p < 0.001$) (37). Over the last three decades, the country has undergone a rapid epidemiological transition from communicable to non-communicable diseases (38). With advances in the field of medicine and with better availability of affordable healthcare, there is a demographic shift with an increase in the life-expectancy of the Indian population as observed from studies and Sample Registration System data (39).

The clinical and demographic data available on HF in India is limited. Table 1.2.3.1 shows the major HF registries reported in India. The available data from these registries show that HF patients in India are younger by 10-years, and the majority of the burden lies below 65years of age, as compared to the patients from high-income countries.(40) Table 1.2.3.2 shows prescription of disease modifying agents in heart failure as reported in the heart failure registries in India.

Table 1.2.2 List of published cost-utility studies with SGLT2i among patients with heart failure

Author_Year	Country	Income classification	Study perspective	Target population	Time Horizon	Intervention	Comparator	Data Pooling-Findings
Hallinen_2023(41)	Finland	High income	Healthcare	HFrEF	Lifetime	Empa+SC	SC	CE
				HFpEF	Lifetime	Empa+SC	SC	CE
Tafazzoli_2022(42)	United Kingdom	High income	Healthcare	HFrEF	Lifetime	Empa+SC	SC	CE
	Spain	High income	Healthcare	HFrEF	Lifetime	Empa+SC	SC	CE
	France	High income	Healthcare	HFrEF	Lifetime	Empa+SC	SC	CE
Abdelhamid_2022(43)	Egypt	Lower middle income	Healthcare	HFrEF	Lifetime	Dapa+SC	SC	CE
Nilsson_2023(44)	Sweden	High income	Societal	With T2D and CVD	3 Years	Empa+SC	SC	Not CE
Tsutsui_2023(45)	Japan	High income	Healthcare	HFrEF	Lifetime	Empa+SC	SC	CE
Mendoza_2021(46)	Philippines	Lower middle income	Healthcare	HFrEF	Lifetime	Dapa+SC	SC	CE
Guo_2023(47)	United States	High income	Healthcare	HFrEF	5 Years	SGLT2i+SC	SC	Not CE
Jiang_2022(48)	China	Upper middle income	Healthcare	HFpEF	10 years	Empa+SC	SC	CE
Fauchier_2023(49)	France	High income	Societal	HFpEF	Lifetime	Empa+SC	SC	CE
Zhou_2022(50)	Australia	High income	Healthcare	HFpEF	Lifetime	Empa+SC	SC	CE
Sang_2022(51)	China	Upper middle income	Healthcare	HFrEF	20 Years	Empa+SC	SC	CE
Lin_2022(52)	China	Upper middle income	Healthcare	HFrEF	15 Years	Empa+SC	SC	CE
Rojas_2021(53)	Colombia	Upper middle income	Healthcare	HFrEF	5 Years	Dapa+SC	SC	CE
Savira_2020(54)	Australia	High income	Healthcare	HFrEF	Lifetime	Dapa+SC	SC	CE
Isaza_2021(55)	United States	High income	Healthcare	HFrEF	Lifetime	Dapa+SC	SC	CE
Yao_2020(56)	China	Upper middle income	Healthcare	HFrEF	15 Years	Dapa+SC	SC	CE
McEwan_2020(57)	United Kingdom	High income	Healthcare	HFrEF	Lifetime	Dapa+SC	SC	CE
	Germany	High income	Healthcare	HFrEF	Lifetime	Dapa+SC	SC	CE
	Spain	High income	Healthcare	HFrEF	Lifetime	Dapa+SC	SC	CE
Yan_2023(58)	United States	High income	Healthcare	HFrEF	Lifetime	SGLT2i+SC	SC	CE
Zheng_2022(59)	United States	High income	Healthcare	HFrEF	Lifetime	Empa+SC	SC	CE
Kriittayaphong_2020(60)	Thailand	Upper middle income	Healthcare	HFrEF	Lifetime	Dapa+SC	SC	CE
Kolovos_2023(61)	United Kingdom	High income	Healthcare	HFpEF	Lifetime	Empa+SC	SC	CE
	Spain	High income	Healthcare	HFpEF	Lifetime	Empa+SC	SC	CE
	France	High income	Healthcare	HFpEF	Lifetime	Empa+SC	SC	CE

Author_Year	Country	Income classification	Study perspective	Target population	Time Horizon	Intervention	Comparator	Data Pooling-Findings
Ong_2023(62)	Malaysia	Upper middle income	Healthcare	HFrEF	Lifetime	Empa+SC	SC	CE
Liao_2021(63)	Thailand	Upper middle income	Healthcare	HFrEF	15 Years	Empa+SC	SC	CE
Booth_2023(64)	United Kingdom	High income	Healthcare	HFpEF	Lifetime	Dapa+SC	SC	CE
	Germany	High income	Healthcare	HFpEF	Lifetime	Dapa+SC	SC	CE
	Spain	High income	Healthcare	HFpEF	Lifetime	Dapa+SC	SC	CE
Tsutsui_2023(65)	Japan	High income	Healthcare	HFpEF	Lifetime	Empa+SC	SC	CE
Miller_2023(66)	United Kingdom	High income	Healthcare	With T2D and CVD	Lifetime	Dapa+SC	SC	CE
Reifsnider_2020(67)	United Kingdom	High income	Payers	With T2D and CVD	Lifetime	Empa+SC	SC	CE
Kolovos_2023(68)	United Kingdom	High income	Healthcare	With T2D and CVD	Lifetime	Empa+SC	SC	CE
Huang_2022(69)	China	Upper middle income	Healthcare	With T2D and CVD	30 Years	Dapa+SC	SC	CE
Lu_2023(70)	China	Upper middle income	Healthcare	HFpEF	20 Years	Empa+SC	SC	CE
						Dapa+SC	SC	CE
McEwan_2020(71)	United Kingdom	High income	Healthcare	With T2D and CVD	Lifetime	Dapa+SC	SC	CE
Yi Tang_2023(72)	China	Upper middle income	Healthcare	With T2D and CVD	Lifetime	Dapa+SC	SC	CE
Parizo_2021(73)	United States	High income	Healthcare	HFrEF	Lifetime	Dapa+SC	SC	Not CE
Jiang_2021(74)	China	Upper middle income	Healthcare	HFrEF	Lifetime	Dapa+SC	SC	CE
						Empa+SC	SC	CE
Tang_2022(75)	China	Upper middle income	Healthcare	HFrEF	Lifetime	Empa+SC	SC	CE
				HFpEF	Lifetime	Empa+SC	SC	CE
Krittayaphong_2022(76)	Thailand	Upper middle income	Healthcare	HFrEF	Lifetime	Empa+SC	SC	CE
				HFpEF	Lifetime	Empa+SC	SC	Not CE
Reifsnider_2021(77)	United States	High income	Payers	With T2D and CVD	Lifetime	Empa+SC	SC	CE

HFrEF- heart failure with reduced ejection fraction; HFpEF- heart failure with preserved ejection fraction; EMPA- empagliflozin; Dapa- dapagliflozin; SC- standard of care; CE- cost effective

Table 1.2.3.1 List of major HF registries reported in India

HF registry	Category	N	AGE	All-cause mortality rate per 100 person years	All-Cause Death (one year mortality) n/N (%)	All-Cause Death (90 day mortality) n/N (%)	Cardiovascular Death n/N (%)	HF readmision rate (%)	Source
ASIAN-HF registry South Asia (India)	Overall	1688	59.0 (12.6)		117/1570 (7.5)		64(5.7)		(78)
	HFrEF	1436	58.3 (12.5)		110/1328 (8.3)		61 (55.5)		
	HFmEF								
	HFpEF	252	63.4 (12.5)		7/242 (2.9)		3 (42.9)		
Trivandrum Heart Failure Registry THFR	Overall	1205	61.2 (13.7)	22.6(21.0, 24.3)	371 (30.8)	218 (18.1)		49	(79)
	HFrEF	752	61.8 (13.4)	24.9(22.8, 27.3)	286 (32.0)	174 (19.5)			(80)
	HFmEF	263	60.8 (13.7)	22.3(19.1, 26.0)					(81)
	HFpEF	190	59.4 (14.5)	15.5(12.6, 19.0)	85 (27.3)	44 (14.2)			(82)
Kerala HF registry (CSI-KAHFR)	Overall	7507	64 ± 12.9	11.6	-			11.4	(83)
	HFrEF	5069	63.4 (12.9)	15.5(14.4–16.8)					
	HFmEF	1319	66.0 (12.3)	12.2(10.3–14.5)					
	HFpEF	1119	66.5 (13.6)	13.1(10.9–15.7)					
INTER-CHF	Overall	858	56 (15)		(23)		13%		(84)
	HFrEF		392 (53%)						
	HFmEF								
	HFpEF								
Global Congestive Heart Failure Registry (G-CHF) LMIC & LIC	Overall	W-4,121 M-4,735	55·8 ± 17·4						(85)
	HFrEF	W-2044 M-2784							
	HFmEF	W-464 M-519							
	HFpEF	W-1170 M-771							
Medanta	Overall	5590	59.1 ± 11.8		984 (17.6%)				(86)
	HFrEF	3304							
	HFmEF								

	HFpEF								
National Heart Failure Registry (NHFR)	Overall	10 851	59.9 (13.5)			1542(14.2)		8.4	(87)
	HFrEF	7082	60.2 (13.2)			1107(15.7)			
	HFmEF	2396	59.9 (13.0)			264(11.0)			
	HFpEF	1373	58.8 (15.7)			171(12.5)			
Manipal Heart Failure Registry	Overall	1354	65.08 ± 13.6		(24.8%)			39.8	(88) (89)
	HFrEF	506							
	HFmEF								
	HFpEF	104							
PSG hospital HF registry	Overall	449	59.9±13.3				9 (2)		(90)
	HFrEF	296	59.1±13.6						
	HFmEF	90	61.2±11.7						
	HFpEF	63	61.3±13.5						

*Asian HF Registry South Asia India – Asian Heart Failure Registry South Asia India, THFR-Trivandrum Heart Failure Registry, CSI-KAHFR -Kerala Acute Heart Failure registry, INTER-CHF-International Congestive Heart Failure Registry ,G-CHF-Global Congestive Heart failure registry, Medanta- The Medicity, NHFR-National Heart Failure Registry, PSG Hospital HF registry.

HFrEF (LVEF <40%), HFmEF (LVEF 40%–49%), HFpEF (LVEF >50%)

Guideline-directed medical therapy (GDMT) for heart failure (HF). These include ARNi , angiotensin receptor neprilysin inhibitors, ACEi, ARB, MRA mineralocorticoid receptor antagonists, and beta-blockers,

THFR HFpEF EF > 45% HFrEF EF < 45% 5 YEAR followup, Medanta LVEF 30% or below

Table 1.2.3.2 Prescription of disease modifying agents in heart failure as reported in the heart failure registries in India.

HF registry	Category	N	ACEI	ARB	ACEI/ARB	β-Blocker	MRA	ARNI	Source
ASIAN-HF registry South Asia (India)	Overall	1688	639 (40.9)	517(33.1)	1134 (72.6)	990(63.3)	868(55.5)		(78)
	HFrEF	1436	616 (43.7)	459 (32.6)	1053 (74.7)	914 (64.9)	832 (59.0)		
	HFmEF								
	HFpEF	252	23 (14.9)	58 (37.7)	81 (52.6)	76 (49.4)	36 (23.4)		
Trivandrum Heart Failure Registry THFR	Overall	1205			545 (45.2)	649 (53.9)			(79) (80) (81) (82)
	HFrEF	752			422 (47.2)	500 (55.9)			
	HFmEF	263							
	HFpEF	190			123 (39.6)	149 (47.9)			
Kerala HF registry (CSI-KAHFR)	Overall	7507	-	-		-			(83)
	HFrEF	5069	1642 (32.4)	919 (18.1)		3154 (62.2)		115 (2.3)	
	HFmEF	1319	378 (28.7)	232 (17.6)		797 (60.4)		13 (0.9)	
	HFpEF	1119	174 (15.6)	181 (16.1)		530 (47.4)		3 (0.3)	
INTER-CHF	Overall	858	449 (51%)	143 (17%)	586 (68%)	495 (57%)	421 (47%)		(84)
	HFrEF								
	HFmEF								
	HFpEF								
Global Congestive Heart Failure Registry (G-CHF) LMIC & LIC	Overall	W-4,121 M-4,735			1082/1634 868/1290	1075/1634 835/1290	820/1634 617/1290		(85)
	HFrEF	W-2044 M-2784							
	HFmEF	W-464 M-519							
	HFpEF	W-1170 M-771							
Medanta- The Medicity	Overall	5590	2796 (50.0)	953 (17.0)	3680 (65.8)	4574 (81.8)			(86)
	HFrEF	3304							
	HFmEF								
	HFpEF								
National Heart Failure Registry (NHFR)	Overall	10 851			58.3	75.9	65.5	3.6	(87)
	HFrEF	7082			60	78	73	4.8	
	HFmEF	2396							

	HFpEF	1373							
Manipal Heart Failure Registry	Overall	1354	28.4%	(23.4)		39.3%			(88)
	HFrEF	506							(89)
	HFmEF								
	HFpEF	104							
PSG hospital HF registry	Overall	449							(90)
	HFrEF	296			67.9%	57.4%	80%		
	HFmEF	90							
	HFpEF	63							

1.3 Objectives

- To conduct Markov model-based cost-utility analysis on initiating SGLT2i as an addon treatment prior to hospital discharge among Heart Failure patients in India.

Chapter 2 – MODEL-BASED ECONOMIC EVALUATION

2.1 Review question

Are SGLT2 inhibitors cost-effective as an add-on therapy to standard care compared to standard care alone in heart failure patients prior to hospital discharge in India?

2.2 Methods

We conducted a cost-utility analysis (CUA) using a Markov model to calculate and compare the costs and QALY of SGLT2 inhibitors as an addon treatment prior to hospital discharge among Heart Failure patients in India. The project proposal was presented to the Technical advisory committee, DHR, HTAIn.

TAC commented that patients with HF (especially HFpEF) in India are younger, have more severe disease, and face significantly higher morbidity and mortality compared to those in Western countries. Data on mortality or hospitalizations for heart failure (HHF) specific to SGLT2 inhibitors (SGLT2i) is not available for the HFpEF population from Indian HF registries. Additionally, the mortality profile of HFpEF in the West is vastly different from that in India. In Western populations, HFpEF patients tend to be older and more likely to have comorbid conditions like CAD and advanced diabetes, making direct comparisons with the Indian population may be inappropriate. As a result, TAC advised against relying on data from the meta-analyses of international trials for HFpEF population and suggested to proceed analysis for HFrEF population in Indian setting.

2.2.1 PICO

Population: Patients with all-cause hospitalization heart failure above the age of 18 years with reduced ejection fraction (EF <40%)

Intervention: SGLT2i (Empagliflozin, Dapagliflozin, Canagliflozin) as per their standard dosages as an add-on therapy to standard of care (SC)

Comparator:

Standard of care (As per the guidelines before the introduction of SGLT2 inhibitors in the standard treatment guidelines) including, beta-blockers (BB), angiotensin-receptor neprilysin inhibitors (ARNi), angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists (MRA).

Outcome: Incremental Cost-utility Ratio (ICUR) per QALY gained or Incremental Net Benefit (INB)

Time Horizon: Lifetime horizon

Perspective: Disaggregated societal perspective

Discounting: All future costs and consequences were discounted at 3% as per WHO guidelines.

Willingness to pay (WTP) threshold: Currently, a formally recognized cost-effectiveness threshold (CET) for India is not available. One-time GDP per capita is suggested by the Indian reference case for conducting economic evaluations in health technology assessments (91). We applied India's 2024 GDP per capita of INR ₹ 2,26,765 as the cost-effectiveness threshold value per QALY gained (92, 93). ICUR of less than one GDP per capita was considered cost-effective.

Table 2.2.1 Model input parameters

Input Parameters	Mean	(CI/SE/SD)	Distribution	Reference
Transitional_Probabilities_SGLT2+SC				
TP3_SGL_HF_Hosp	0.0492	0.01183	Beta	Meta Analysis of RCT
TP3_SGL_All_cause_Death	0.057	0.01303	Beta	Meta Analysis of RCT
TP3_SGL_All_cause_Hosp	0.5114	0.00007	Beta	EMPA_REG Trail (94)
TP3_SGL_HHF_HHF	0.03719	0.001895	Beta	EMPORER Reduced (29)
Adverse Events_SGLT2+SC				
P3_SGL_AE_hypog	0.0061	0.00257	Beta	Meta Analysis of RCT
P3_SGL_AE_uti	0.0414	0.0211	Beta	Meta Analysis of RCT
P3_SGL_AE_amputa	0.0046	0.00068	Beta	Meta Analysis of RCT
P3_SGL_AE_BoneFrac	0.0162	0.0012	Beta	Meta Analysis of RCT
P3_SGL_AE_genital	0.011	0.00242	Beta	EMPA Reduced (29)
Transitional_Probabilities_SC				
TP3_SC_HF_Hosp	0.07	0.01576	Beta	Meta Analysis of RCT
TP3_SC_all_cause_Death	0.0637	0.01553	Beta	Meta Analysis of RCT
TP3_SC_All_cause_Hosp	0.52516	0.0001	Beta	EMPA_REG Trail (94)
TP3_SC_HHF_HHF	0.03719	0.00189	Beta	EMPORER Reduced (29)
Adverse Events_SC				
P3_SC_AE_hypog	0.0065	0.0027	Beta	Meta Analysis of RCT
P3_SC_AE_uti	0.039	0.01987	Beta	Meta Analysis of RCT
P3_SC_AE_amputa	0.0043	0.00066	Beta	Meta Analysis of RCT
P3_SC_AE_BoneFrac	0.0163	0.001276	Beta	Meta Analysis of RCT
P3_SC_AE_genital	0.004	0.00151		EMPA Reduced (29)
Utilities				
u_Hosp_HF	0.4992	0.0303	Beta	Grustam et al 2018(95)
u_stable_HF	0.7117	0.0094	Beta	Grustam et al 2018(95)
u_reco_HF	0.8797	0.0082	Beta	Grustam et al 2018(95)
Utilities_Adverse events				
u_hypog	0.418	0.323	Beta	Shafie et al 2018(96)
u_uti	0.76	0.0866	Beta	Neveu et al 2023(97)
u_amputa	0.954	0.0725	Beta	Chung et al 2009(98)
u_boneFrac	0.212	0.31	Beta	Nwankwo et al 2022(99)
u_genital	0.76	0.0866	Beta	Neveu et al 2023(97)
Costs				
c_SGLT2i	12124	8710.9	Gamma	Calculated
c_empa	10494	5063.5	Gamma	Market price
c_dapa	4344	4456.3	Gamma	Market price
c_cana	21535	68.8	Gamma	Market price
c_Reduced_HF	83541.0	30444.5	Gamma	Sing et al 2019(11)
c_hospi	87948.6	24057.6	Gamma	Sing et al 2019(11)
c_hypog	14351.3	1435.1	Gamma	Bagepaly et al 2022(100)
c_uti	9994.7	999.47	Gamma	Tiwari et all 2013(101)
c_amputa	16303.9	1630.3	Gamma	Kumpatla et al 2013(102)

c_boneFrac	42859.9	4285.9	Gamma	Mithal et al 2014(103)
c_Genital_AE	9994.7	999.4	Gamma	Tiwari et all 2013(101)
c_SC	17177.6	2370.8	Gamma	Calculated
c_ACEi_Enalapril	2965.6	408.8	Gamma	Market price
c_BB_Bisoprolol	7921	2144.7	Gamma	Market price
c_BB_Carvedilol	4526	1473.4	Gamma	Market price
c_BB_Metoprolol	2381.9	5.6	Gamma	Market price
c_BB_Nebivolol	12035.9	3926.7	Gamma	Market price
c_ARB_Losartan	4745	1042.4	Gamma	Market price
c_ MRA_Spironolactone	777.5	339.9	Gamma	Market price
c_OOPE_HF	36952.0	11647.8	Gamma	Sing et al 2019(11)

2.2.2 Data Collection

Transition probabilities and Proportions

Data on input parameters and transitional probabilities were systematically collected from published, peer-reviewed literature, following a hierarchy of evidence. The highest priority was given to systematic reviews and meta-analyses of randomized controlled trials (RCTs) (104, 105) followed by different SGLT2 inhibitor trials (18, 19, 24, 25, 29, 94, 106). The probability of age-specific all-cause mortality was obtained from Sample Registration System data (107).

Estimation of Costs and health outcomes

Costs

The cost analysis was undertaken from the disaggregated societal perspective in line with current HTAIn guidelines for health-economic evaluation. Direct medical costs (DMC) such as cost of drugs, monitoring and administration, common adverse drug reactions, outpatient visits, inpatient care and hospital readmission costs were included. Direct non-medical costs such as travel, food and accommodation costs and Out-of-pocket expenditure (OOPE) costs were additionally considered for the disaggregated

societal perspective. Further, all supply chain-related costs will be considered for preparing the model input parameters. The costing information was taken from India-specific primary costing studies (11, 101, 108), databases such as the National Health System Cost Database for India developed by the Post Graduate Institute of Medical Education and Research (PGIMER), Manipal heart failure registry (11), Trivandrum heart failure registry (109, 110), the Ayushman Bharat Package, and from market prices search. For the base case analysis/deterministic analysis, we used SGLT2i market prices. All the previous year's costs were adjusted and reported for the year 2024 in Indian Rupees (INR). The cost data are provided in Table 2.2.1.

Utility

The health state utility values used in the model were obtained from a systematic search of published peer-reviewed literature and from Tuff's registry (95-99). The details of utility data are provided in Table 2.2.1.

2.2.3 Model Framework

A Markov decision-analytic model was developed to evaluate the cost-effectiveness of adding SGLT2i to the SC compared to SC alone for patients with stable heart failure and HFrEF in India. The model adheres to the conventional framework, with health states accounting for the possibilities of stable HF, all-cause hospitalization including, acute decompensated HF or additional adverse effects, and death. A one-year cycle was used for the Markov model, reflecting the standard one-month duration of the acute stage in HF. The schematic representation of the model framework is provided in Figures 2.2.1 and 2.2.2.

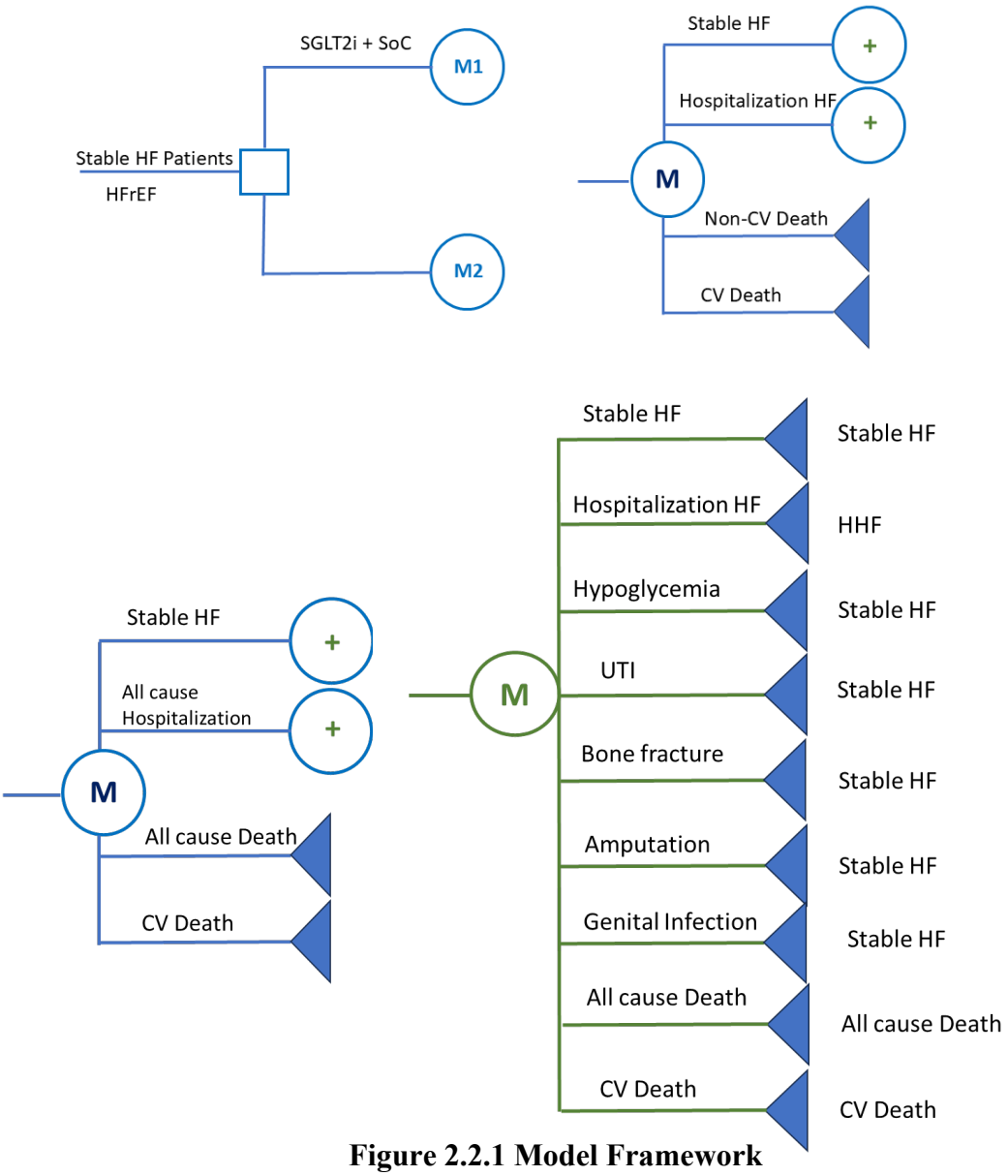


Figure 2.2.1 Model Framework

In the base-case analysis, all patients commence treatment at the age of 60 years for HFrEF (111, 112) progressing from a condition without acute events through the Markov model. They will be tracked from the onset of stable HFrEF without clinical events, progressing through various states within the markov model, until death. Initially, the patient groups receiving either SGLT2i in combination with SC or SC alone are presumed to have a stable HF condition. Patients may either maintain their stable HF status or subsequently transition to other states, either into hospitalization or

death. Death in the model can occur due to cardiovascular causes, non-cardiovascular causes, or age-specific mortality, all of which are collectively categorized as all-cause mortality. Hence, patients in a stable HF state may either remain without clinical events or progress to hospitalization or eventually result in death.

We incorporated the common adverse effects (AE) associated with SGLT2i into our model. The AEs under consideration included hypoglycaemia, urinary tract infections, bone fractures, genital infection and amputations. In the base case analysis, we utilized context-specific values as model parameters in the Indian setting to the extent feasible for HFrEF based on the literature (10, 11).

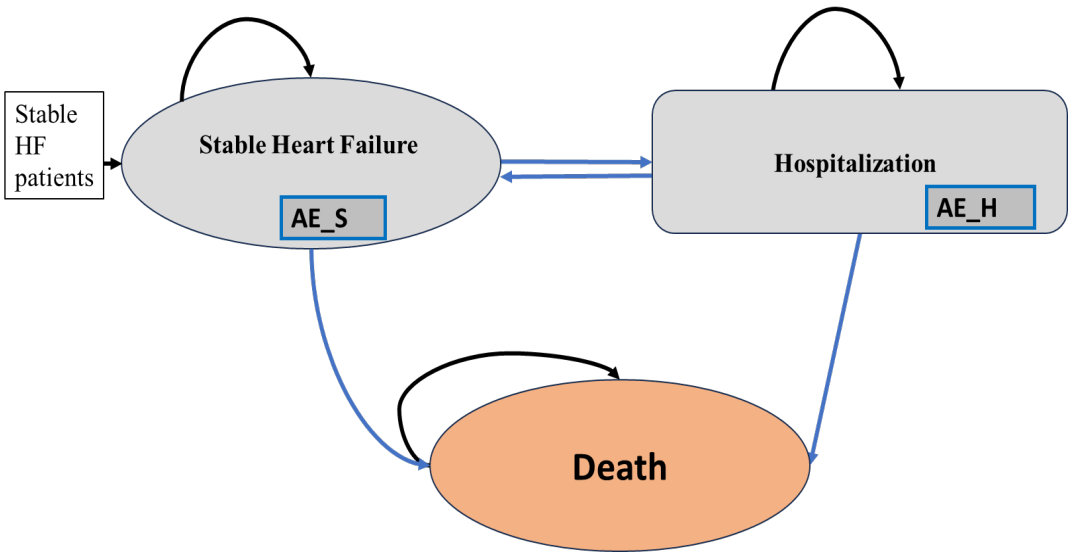


Figure 2.2.2 Schematic representation of Markov model
The model is adapted from Lio et al 2021, Tang et al 2022 (63, 113)

2.2.4 Model Assumptions

- The cost of adverse events for SC is assumed to be already included in the cost of HF hospitalization (11).

- No CVD from Stable heart failure state

- The proportions of prescriptions for disease-modifying agents in heart failure are derived from the NHFR Heart Failure (HF) Registries.

- We assumed equal proportions of prescriptions between ACE inhibitors and ARBs for heart failure management.

- For the ACE class, we specifically used Enalapril as the representative drug in the model.

- Among the beta blockers, we assumed equal proportions of prescriptions for Bisoprolol, Carvedilol, Metoprolol, and Nebivolol within the class.

- For MRAs, we assumed Spironolactone to represent the class of drugs in the model.

- We did not include ARNi (such as Valsartan) in the analysis due to their high cost, assuming they would not significantly influence prescription patterns in the population being studied.

- The average cost of Empagliflozin, Dapagliflozin, and Canagliflozin was used as the cost of SGLT2i, as current utilization data for heart failure in India is unavailable.

- The primary endpoints (effectiveness composite of cardiovascular death or hospitalization) were assumed to be a class effect rather than specific to individual drugs.

- The base case analysis assumed the market price for all drugs, with the median price being used for calculations.

2.2.5 Cost-effectiveness Analysis

Half-cycle correction was performed for the costs and QALYs. The total cost and total QALYs gained were calculated for the intervention and comparator. The total cost in each comprised the intervention or comparator cost and the cost of treating adverse events. QALYs were estimated by combining the disease-state-specific utility and adverse-event-specific utility using a multiplicative method, considering a baseline value of 1 for perfect health. The formula used to calculate QALYs is as follows:

$$QALY = \text{Life years} * \text{u\_HS} * \text{u\_AE}$$

where,

Life years represent the number of years a person remains in a particular health state.

u_HS represents the utility (quality of life) associated with the specific health state.

u_AE represents the utility associated with experiencing adverse events.

The total QALY for an intervention was estimated by summing up the QALYs of all states in the model. The ICUR represents the difference in total cost and total QALY gained between the two interventions, giving an indication of the cost-effectiveness of one intervention compared to the other.

The ICUR per QALY is calculated as follows:

$$ICUR = \frac{Cost\ of\ intervention - Cost\ of\ comparator}{QALY of\ intervention - QALY\ of\ comparator}$$

Apart from ICUR, Net Monetary Benefit (NMB) and Incremental Net benefit (INB) were also calculated using the formula given below:

$$NMB = Qaly\ of\ intervention * lambda - Cost\ of\ intervention$$

where lambda is the willingness to pay threshold (1 GDP)

$$INB = NMB\ of\ intervention - NMB\ of\ comparator$$

2.2.6 Sensitivity analysis

The robustness of the model was assessed using sensitivity analysis, including one-way sensitivity analysis and probabilistic sensitivity analysis (PSA)

One Way Sensitivity Analysis (OWSA)

In one-way sensitivity analysis, 95% CI values for utility values and 25% upper/lower values for the other model input parameters were used and reported as tornado diagrams.

Probabilistic Sensitivity Analysis (PSA)

PSA was performed with 5000 Monte Carlo simulations based on its data distribution. Transitional probabilities and utilities were simulated using beta distribution, whereas costs were simulated using Gamma distribution. Results are reported as Cost-effectiveness (CE) plane and Cost-effectiveness Acceptability Curve (CEAC).

2.2.7 Budget Impact Analysis

The budget impact analysis (BIA) was considered during the protocol phase to be conducted only if the intervention is found to be cost-effective using the method described as follows.

BIA using the standard methods was planned for a period of 5 years as per HTAIn guidelines if the intervention was cost-effective in the base case scenario. The costs were calculated from the markov model. The budget required for offering treatment will be estimated using the following formula.

B=N*(Cm)

where,

B= Budget required for offering SGLT2i to the eligible population

N= Eligible population

Cm= Unit cost of SGLT2i intervention from Markov model

No discount was applied since the budget impact is estimation of financial cost. The health budget was planned to be projected based on a 5% annual increase in the health expenditure, and the estimated budget was planned to be projected using population annual growth rate until year 2028. Further, the same method was used to estimate the state-specific budget impact for country-wide implementation.

2.2.8 Scenario and Threshold Analysis

As part of the scenario analysis, we evaluated the cost-effectiveness for each SGLT2i drug at market price. The threshold analysis considers market drug price reduction till ICUR for addon SGLT2i falls below the threshold of one GDP per capita.

2.3 Results

2.3.1 Cost-effectiveness analysis

From a disaggregated societal perspective, we assessed the cost-effectiveness of adding SGLT2i to the SC compared to SC alone for patients with HFrEF in India. SGLT2 inhibitors improve survival and quality of life in HFrEF populations, providing additional life years, QALYs, however with a negative net monetary benefit compared to standard care. The base-case/deterministic analysis results are presented in Table 2.3.1.

In the base-case analysis, for the HFrEF population, the ICUR of SGLT2i as an add-on to SC compared to SC is ₹ 6,59,043, which is higher than the WTP threshold of one-time GDP per capita for India; hence it is not cost-effective. (Table 2.3.1)

Table 2.3.1 Cost-effectiveness Analysis: Base-case HFrEF Population

	SGLT2i	**SC**
Cost	₹ 380,345	₹ 301,346
LY	5.2098	4.1161
QALY	3.2584	3.1386
NMB	₹ 358,554	₹ 410,370
Inc. Cost	₹ 78,998	
Inc. LY	1.0936	
Inc. QALY	0.1199	
ICUR per LY	₹ 72,234	
ICUR per QALY	**₹ 6,59,043**	
INB	₹ -51,816	

2.3.2 Sensitivity Analysis

One-Way Sensitivity Analysis

The most influential parameters on ICUR were found to be SGLT2i drug price, all-cause mortality and all-cause hospitalization due to heart failure. Based on OWSA the ICUR ranged from -50% to 300% for different parameters. When the probability of all-cause mortality for addon SGLT2i is reduced to the lower limit, the ICUR decreases by 55%, and it increases by 300% when the probability is increased to the upper limit. When the probability of all-cause mortality for SC is reduced to the lower limit, the ICUR decreases by 150%, and it decreases by 60% when the probability is increased to the upper limit. For addon SGLT2i versus SC in the HFrEF population, when the probability of all-cause hospitalization for the SGLT2i is reduced to the lower limit, the ICUR decreases by almost 50%, and it increases by 40% when the probability is increased to the upper limit. When the probability of all-cause hospitalization for SC is reduced to the lower limit, the ICUR increases by almost 40%, and it decreases by 40% when the probability is increased to the upper limit. When the lower limit of drug price for SGLT2i was used, the ICUR decreases by almost 70%, and increases by nearly 10%, when the upper limit is used. (Figure 2.3.1).

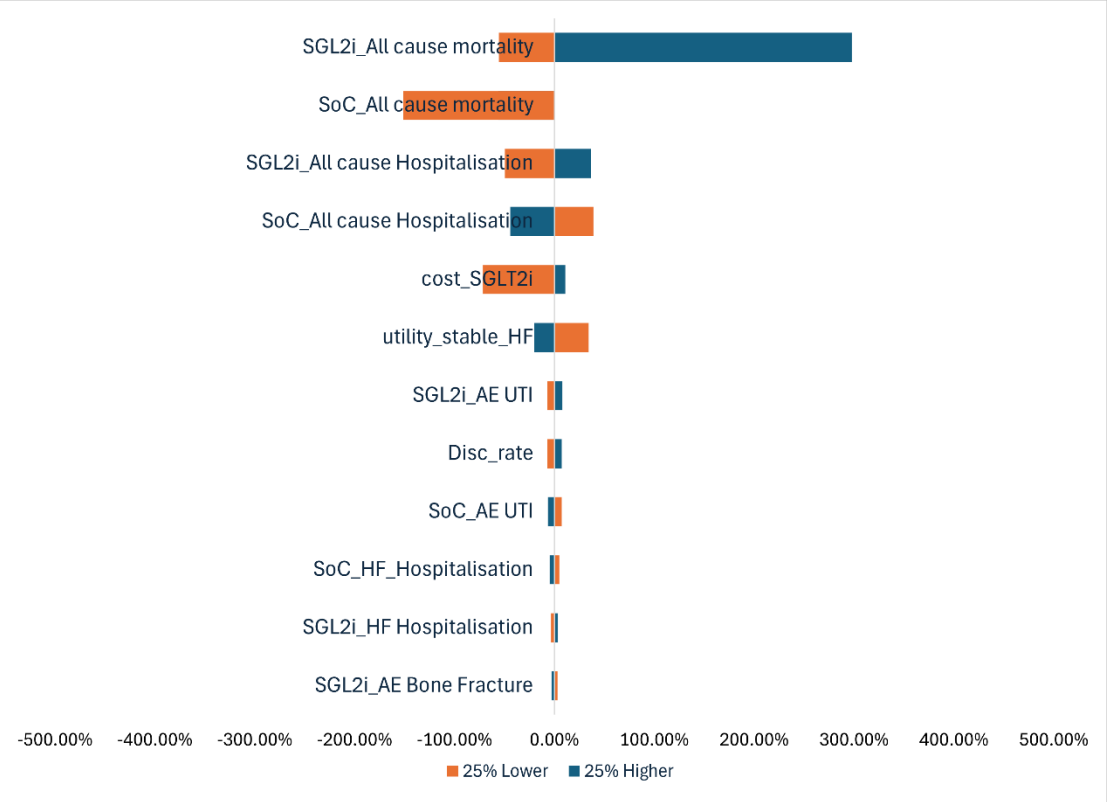


Figure 2.3.1 One-way sensitivity analysis for SGLT2i vs SC among the HFrEF population

One-way sensitivity analysis was conducted using 25% higher and lower values of all the transitional probabilities, cost, and utility values. The orange bars show the effect on the ICUR of applying the lower limit (-25%) of the specific parameter, while the dark blue bars show the effect on the ICUR of applying the upper limit (+25%) of the specific parameter.

Probabilistic Sensitivity Analysis

The PSA was performed with 5000 Monte Carlo simulations for SGLT2i compared to SC for HFrEF population. The mean stochastic ICURs were in line with the base case result for all the interventions indicating no uncertainty (Table 2.3.2).

Table 2.3.2 Probabilistic Sensitivity Analysis results for HFrEF Population

	SGLT2i	**SC**
Cost	₹ 382,639	₹ 303,172
LY	5.2325	4.1342
QALY	3.2715	3.1487
NMB	₹ 359,215	₹ 410,844
Inc.Cost	₹ 79,467	
Inc.LY	1.0983	
Inc.QALY	0.1228	
ICUR per LY	₹ 72,355	
ICUR per QALY	**₹ 6,47,321**	
INB	₹ -51,628	

For the HFrEF population, ICUR points were observed to be equally distributed in the upper right and lower left quadrants, indicating the chance of potential mixed outcomes (Figure 2.3.3). More than 50% of the ICUR points lie below the WTP threshold line, indicating the chance of SGLT2i+SC being cost-effective compared to SC alone. However, the mean stochastic ICUR is ₹ 6,47,321, which is in line with the base case result, and the INB is also negative (₹ -51,628), indicating consistency in the results.

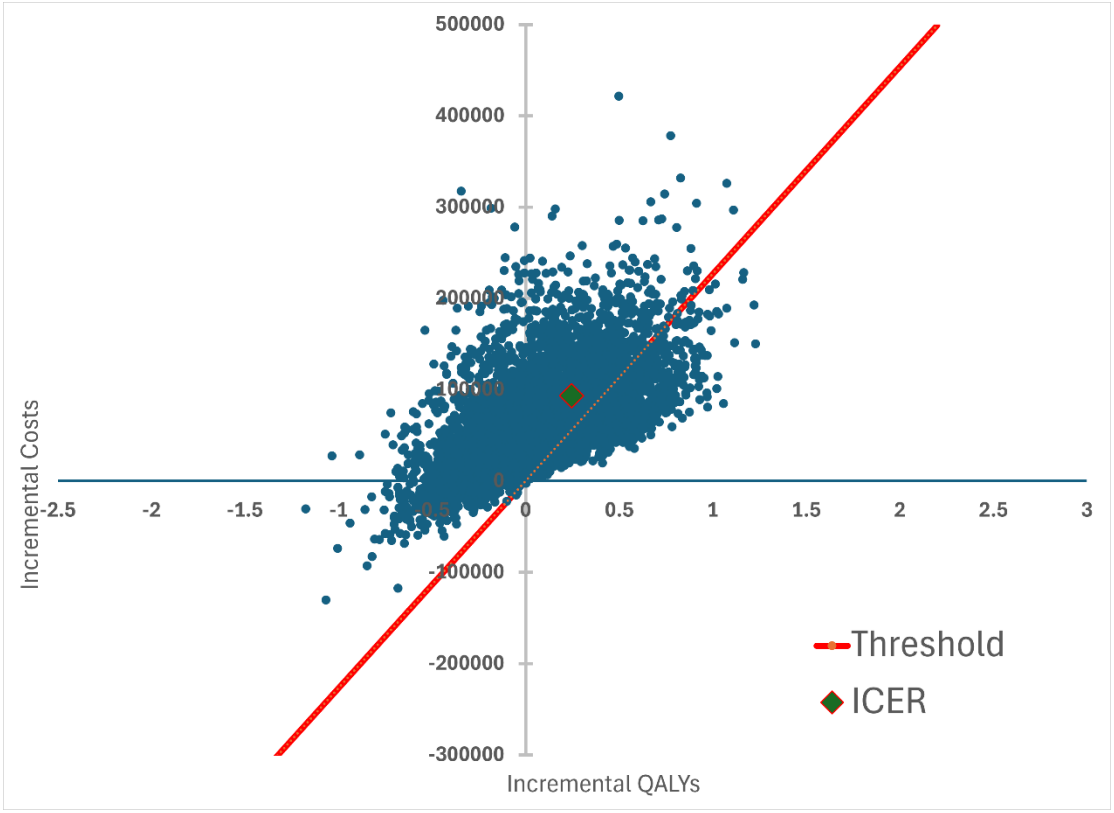


Figure 2.3.3 CE-plane for SGLT2i vs SC among the HFrEF population

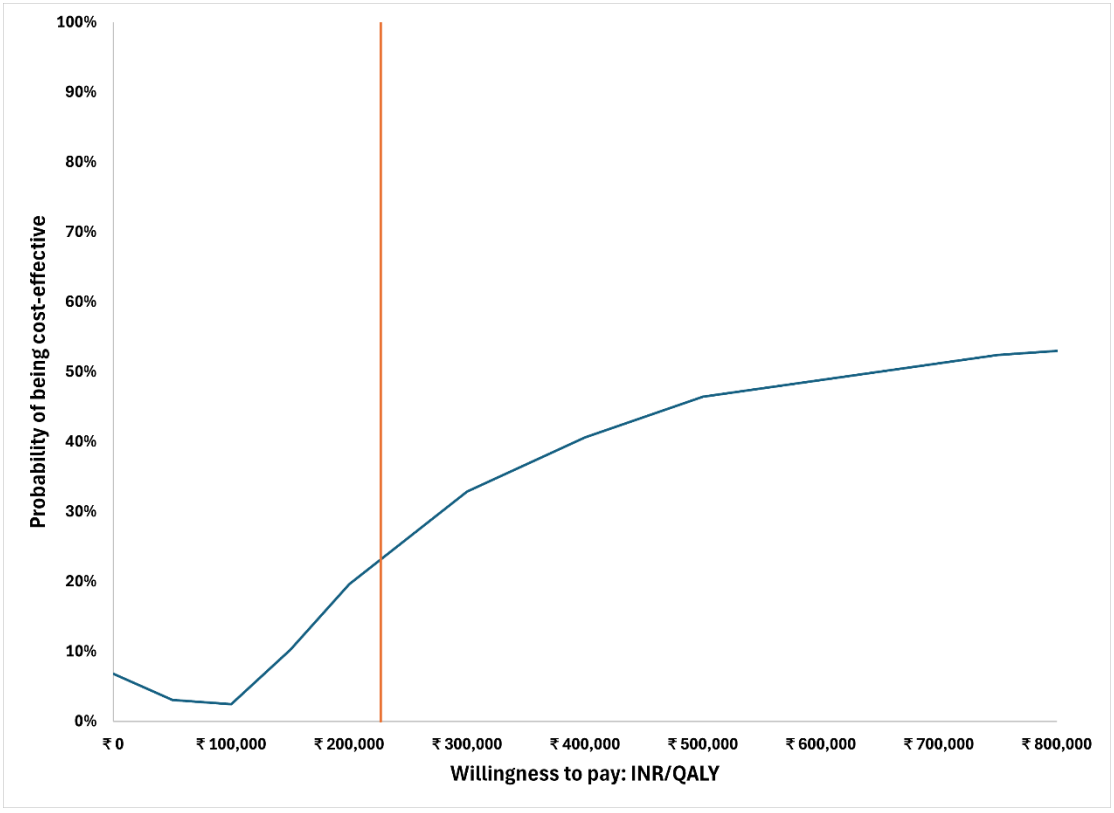


Figure 2.3.4 CEAC for SGLT2i vs SC among the HFrEF population

2.3.3 Budget Impact analysis

We did not do a budget impact analysis for add-on SGLT2i treatment for heart failure with reduced ejection fraction for India since the SGLT2i is not cost-effective at the current market price of the drugs.

2.3.4 Scenario analysis

The results of the scenario analysis using individual drug market prices for SGLT2 inhibitors are presented in Appendix 3. Addon SGLT2i with SC, such as empagliflozin, dapagliflozin, or canagliflozin, at current market prices is not cost-effective compared to standard care alone for patients with heart failure with reduced ejection fraction (HFrEF) in India.

2.3.5 Threshold analysis

For HFrEF population, addon SGLT2i was not cost-effective at the market price, hence a threshold analysis was conducted to determine the market drug price at which the addon SGLT2i would be cost-effective. With a 71% reduction in the average market drug price (annual) SGLT2i drugs (from ₹ 12,124 to ₹ 3,516), addon SGLT2i will be cost-effective for HFrEF patients.

Considering the market price of individual drugs (assuming only one drug from the SGLT2i class is used), the addition of SGLT2i therapy is cost-effective for HFpEF patients when:

- A 67% price Median Market Price reduction per tablet of Empagliflozin, from ₹28.75 to ₹9.48 (annual cost reduced from ₹10,494 to ₹3,463).

- A 61% price Median Market Price reduction per tablet of Dapagliflozin, from ₹24.09 to ₹9.44 (annual cost reduced from ₹4,344 to ₹3,518).
- A 84% price Median Market Price reduction per tablet of Canagliflozin, from ₹59.00 to ₹9.63 (annual cost reduced from ₹21,535 to ₹3,446).

2.4 Discussion

In this model-based cost-utility analysis, we aimed to assess the cost-effectiveness of SGLT2 inhibitors as an add-on treatment to standard of care prior to hospital discharge among Heart Failure patients with reduced ejection fraction in India. Our findings indicate that, at the willingness-to-pay threshold of one GDP per capita, SGLT2i as an add-on to SC is not cost-effective compared to SC for the HFrEF population at the current market price of the drugs.

Our analysis provides valuable insights into the relative cost-effectiveness of SGLT2i as an add-on to SC, aiding healthcare decision-makers in optimizing resource allocation for improving patient outcomes. In the base case analysis for HFrEF, SGLT2i demonstrated negative net benefits relative to the SC. Moreover, at current pricing, SGLT2i was found to be not cost-effective compared to SC in the Indian context. Considering the incremental gains in both QALYs and overall life years associated with SGLT2i, their adoption in clinical practice for HFrEF may be economically justified.

One-way sensitivity analysis revealed some level of uncertainty in the cost-effectiveness estimates as some of the parameters have a significant influence on the ICUR value. However, the probabilistic sensitivity analysis offered a more comprehensive perspective of the uncertainty in the results as the mean stochastic ICURs were in line with the base case results. Reducing the cost of SGLT2i further could potentially lead to more favourable cost-effectiveness profiles making them an attractive choice for all heart failure before discharge for healthcare decision-makers.

As newer and more SGLT2i have been introduced, evaluating their economic implications alongside clinical efficacy becomes crucial. By employing a Markov

model, we were able to simulate the long-term outcomes and associated costs for each intervention, considering their impact on quality-adjusted life years and life years. Our analysis revealed that SGLT2i demonstrated higher costs than SC, with the difference in QALY gain, and gain in life years.

Previous studies, from USA(55), China (48, 52, 56, 74, 75), Thailand (76), Finland (41), Spain (57), UK (67), and Australia (54) have reported SGLT2i as cost-effective in the HFrEF population. Additionally, studies from China(48, 70) and Australia(50) have found SGLT2i to be cost-effective for the HFpEF population. However, SGLT2i was not found to be cost-effective for the HFpEF population in Finland (41) and Thailand (76).

Despite the clinical benefit, reflected in higher gains in QALYs and life years for HFrEF, the ICUR for HFrEF was higher than WTP threshold when market price of drugs was used. This variability in SC drug pricing may lower the incremental cost of adding SGLT2 inhibitors, resulting in a more favorable ICUR. This is further supported by the results of the OWSA.

The economic value of SGLT2i is highly dependent on the effect of all cause hospitalization as shown by our analysis. Not surprisingly, both the absolute clinical benefit and economic value of SGLT2 inhibition vary across these diverse populations. The baseline risk differs, among HFrEF patients, the absolute risk of cardiovascular death is substantially higher than among patients with HFpEF. Moreover, among patients with HFpEF, a higher proportion of overall mortality is non-cardiovascular (114). Moreover, given the limited availability Indian data from post hoc analyses of SGLT2i trials, conducting a analysis for this population was not recommended.

Patient-level pooled analysis of the DAPA-HF and DELIVER trials, which evaluated the effects of dapagliflozin in HFrEF notes that efficacy and safety of dapagliflozin

were consistent across global regions despite geographic differences in patient characteristics, background treatment, and event rates (115). There were notable differences in the placebo event rates for major HF events across diverse regions, Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial.493 (13.2%) in Asia Other regions comprise 173 (4.6%) from India and Australia (116) A post-hoc subgroup analysis of the EMPEROR-Preserved trial (Includes 686 (11.5%) from Asia, 379 (6.3%) in “other” countries (Australia, India and South Africa), does not indicate a significant effect modifier for the primary endpoint, cardiovascular death or hospitalization for heart failure in patients with heart failure and preserved ejection fraction (HFpEF) and therefore a consistent risk reduction of empagliflozin may be postulated independent of region (117).

Integrating SGLT2i into clinical practice prior to discharge for heart failure patients can be beneficial, considering their favorable cost-effectiveness profile. Frequent non-ischemic hospitalizations and additional resource utilization lead to higher costs and lower Utility, as as evident from our model results.

When considering these findings, it is important to recognize that cost-effectiveness analyses provide valuable insight into expected long-term benefits and costs for the health system but are not intended for individual patient decision-making. Not only do they generally fail to capture the patient-level heterogeneity, but patients weigh their expected benefit against affordability, which is based on out-of-pocket costs rather than overall costs. In our model, by considering an abridged societal perspective we tried to account for this issue.

The study has some limitations that should be considered when interpreting its findings. The study is limited due to the lack of effectiveness evidence from the Indian context.

Also, it is essential to consider the limitations associated with the model and assumptions used, which could influence the results. Sensitivity analysis revealed some level of uncertainty in the cost-effectiveness estimates. The probabilistic sensitivity analysis provided a more comprehensive perspective by incorporating uncertainty into the results. The stochastic mean ICURs were very close to base-case ICURs. This highlights the importance of carefully considering the parameters and assumptions used in the model and interpreting the findings cautiously.

Indeed, despite its limitations, the study gains strength due to several key components. Most of the input parameters used in our economic model have been obtained through meta-analysis, which may increase the reliability of the data. By incorporating these components, the study strengthens its potential to provide valuable insights and guidance in Heart failure treatment despite its inherent limitations.

2.5 Conclusion

Addon SGLT2 inhibitors offer longer life years than standard of care alone for patients with heart failure. At current market prices, Addon SGLT2 inhibitors is not cost-effective treatment option for HFrEF patients in India. Threshold analysis considering current market price, addon SGLT2i would be cost-effective only after price reduction of median market price of SGLT2i (average 71% reduction); 67% price reduction per tablet of Empagliflozin from ₹28.75 to ₹9.48, a 61% price reduction per tablet of Dapagliflozin, from ₹24.09 to ₹9.44, a 84% price reduction per tablet of Canagliflozin, from ₹59 to ₹9.63. Overall, this study highlights the potential for economic efficiency of addon SGLT2 inhibitors for HFrEF, contingent upon substantial price reductions,

offering valuable guidance for healthcare decision-making in the evolving landscape of heart failure treatment.

STUDY RECOMMENDATIONS

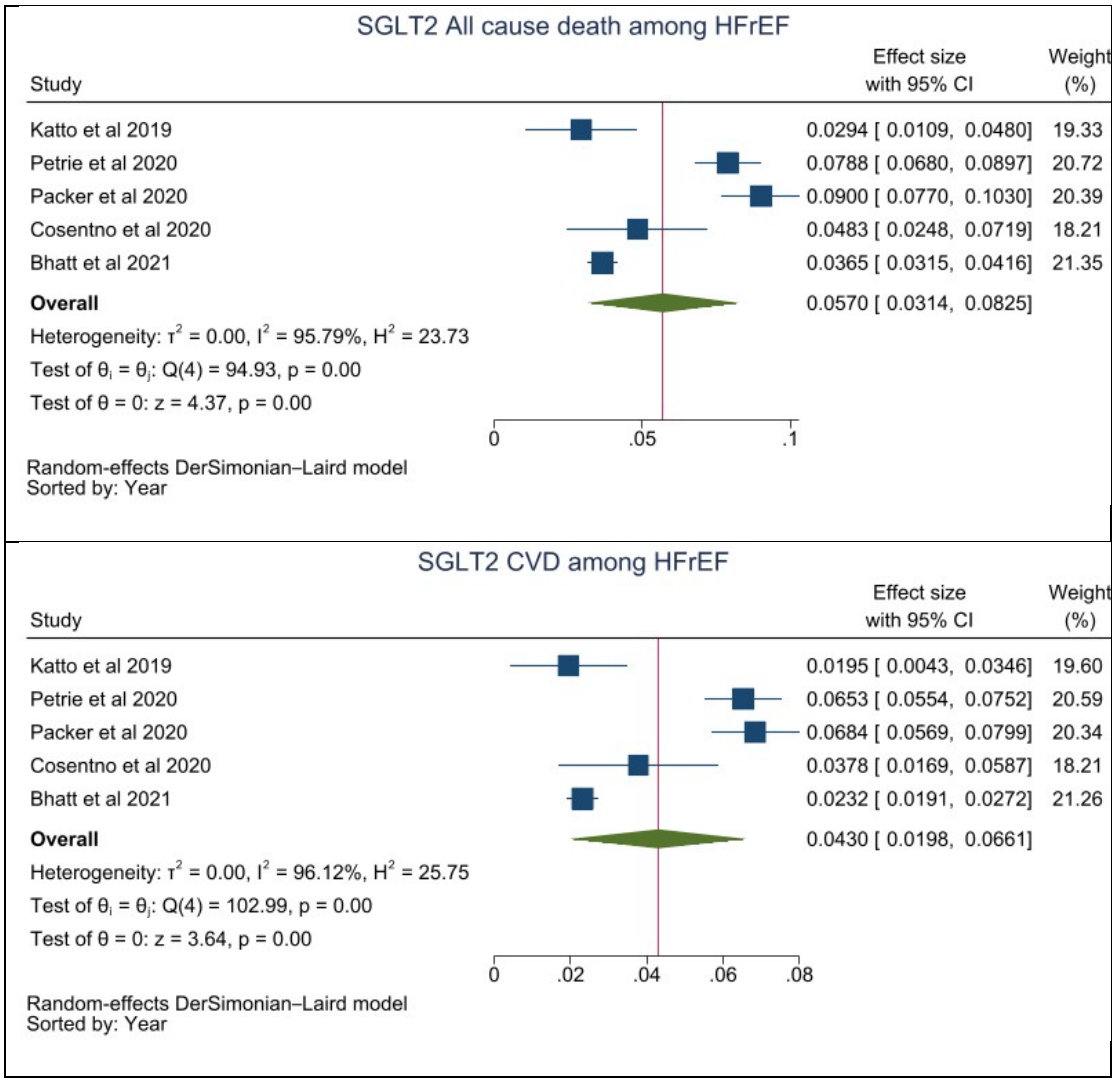
- The administration of add-on SGLT2i therapy to heart failure patients with reduced ejection fraction in India is not a cost-effective option at current market prices.

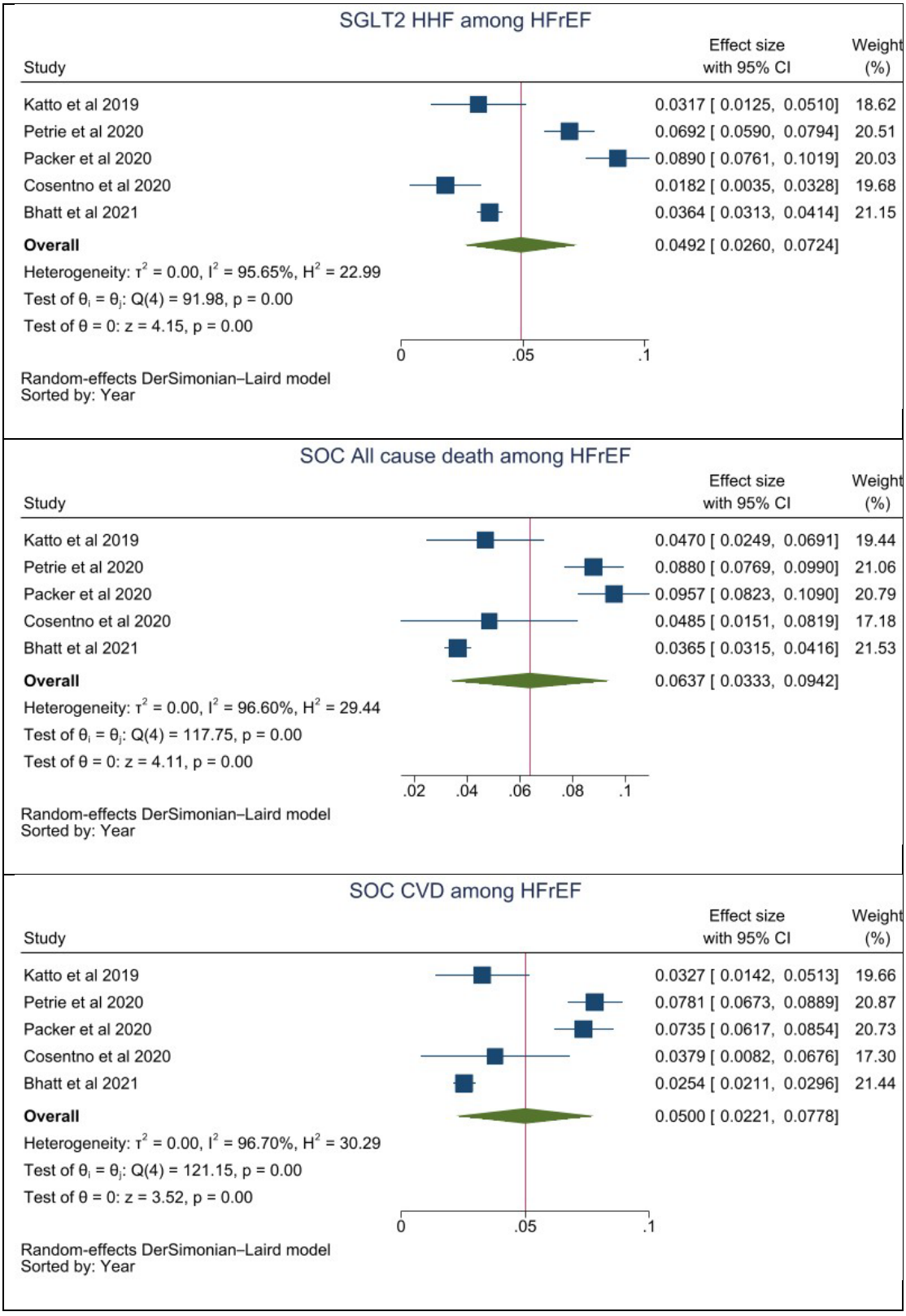
- An average price reduction of about 71% in the SGLT2i market price is necessary for it to become a cost-efficient option in the Indian context.

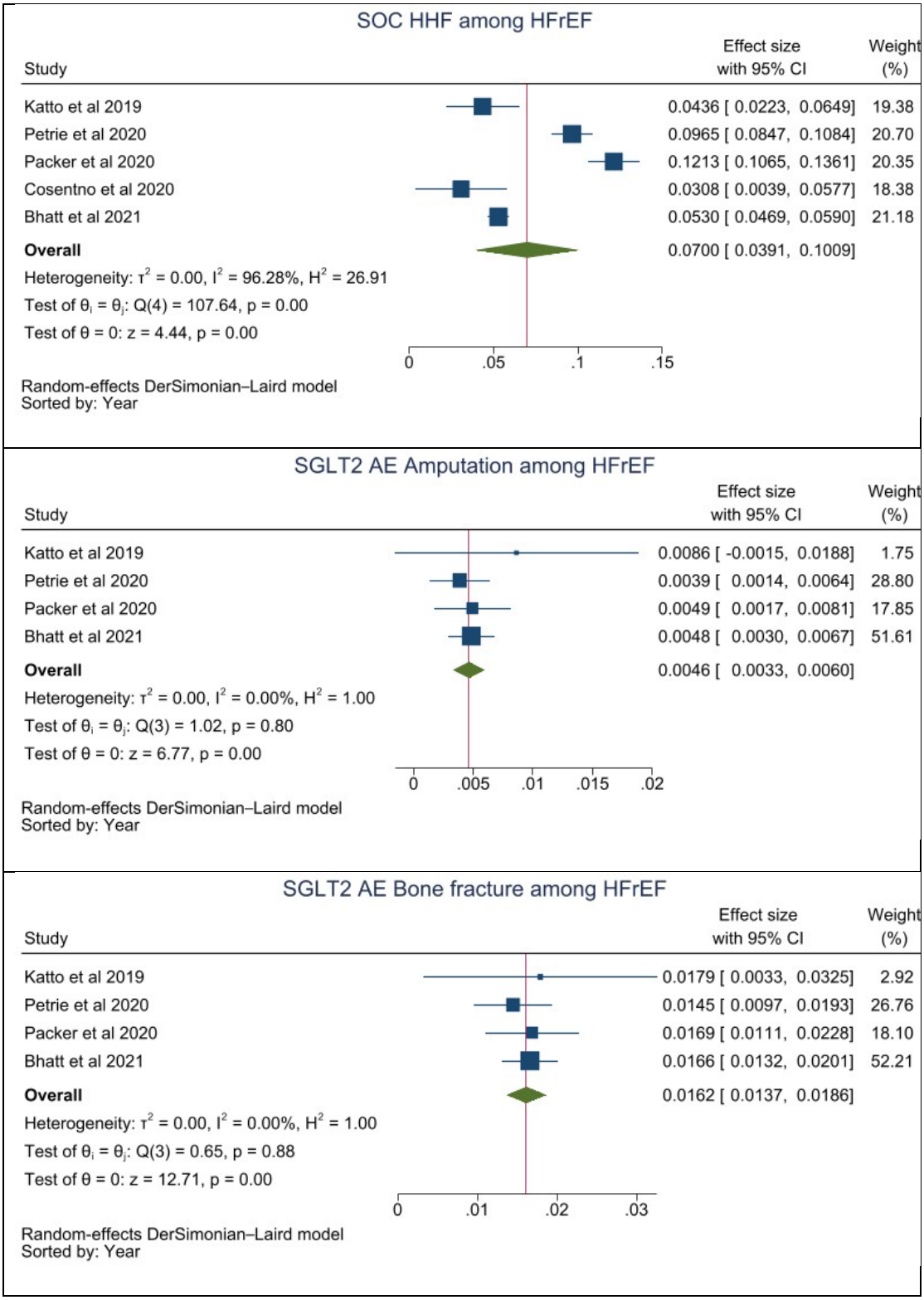
- To explore strategies to reduce the market price of SGLT2 inhibitors, including price negotiation with the manufacturers for its inclusion in the treatment packages.

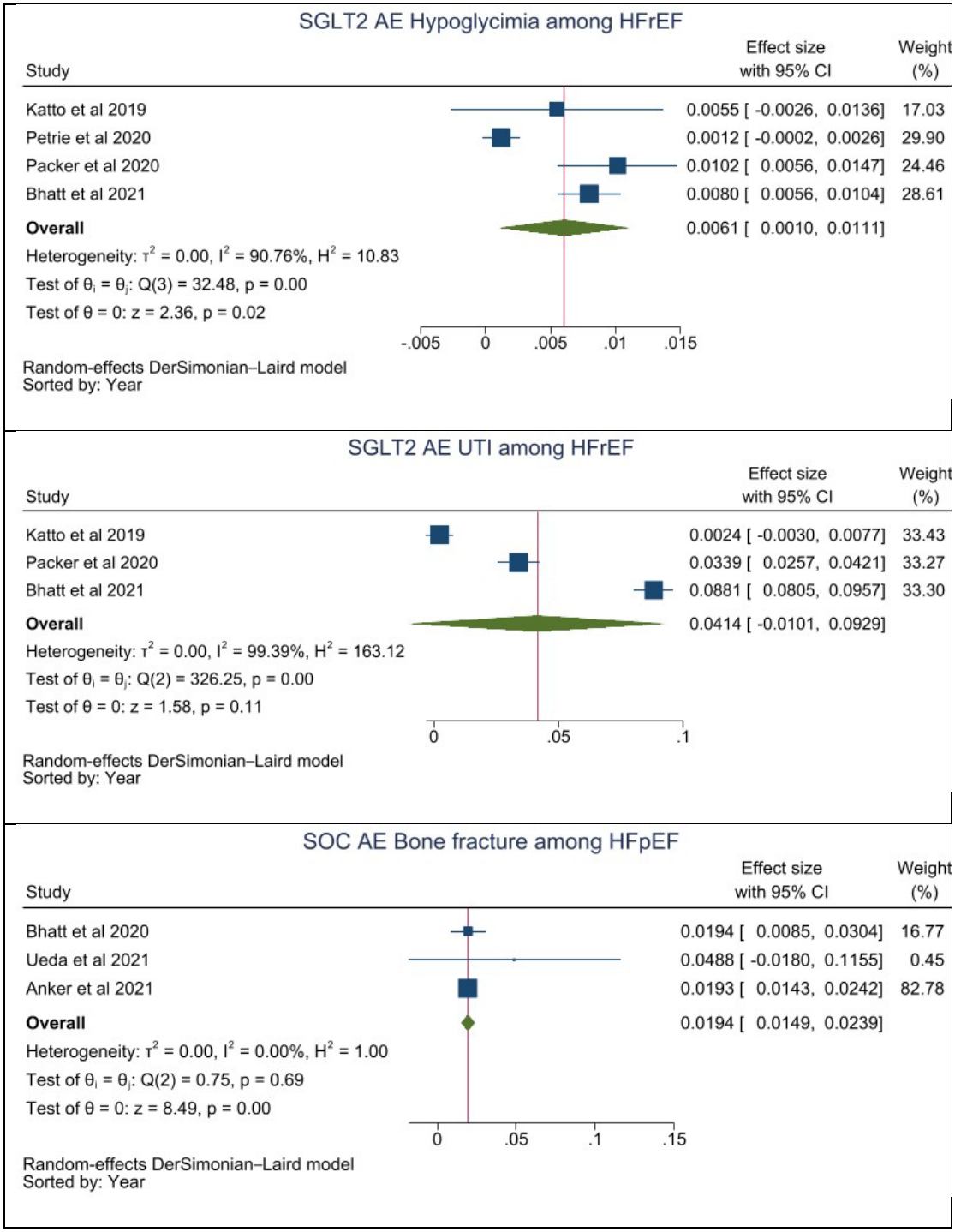
APPENDICES

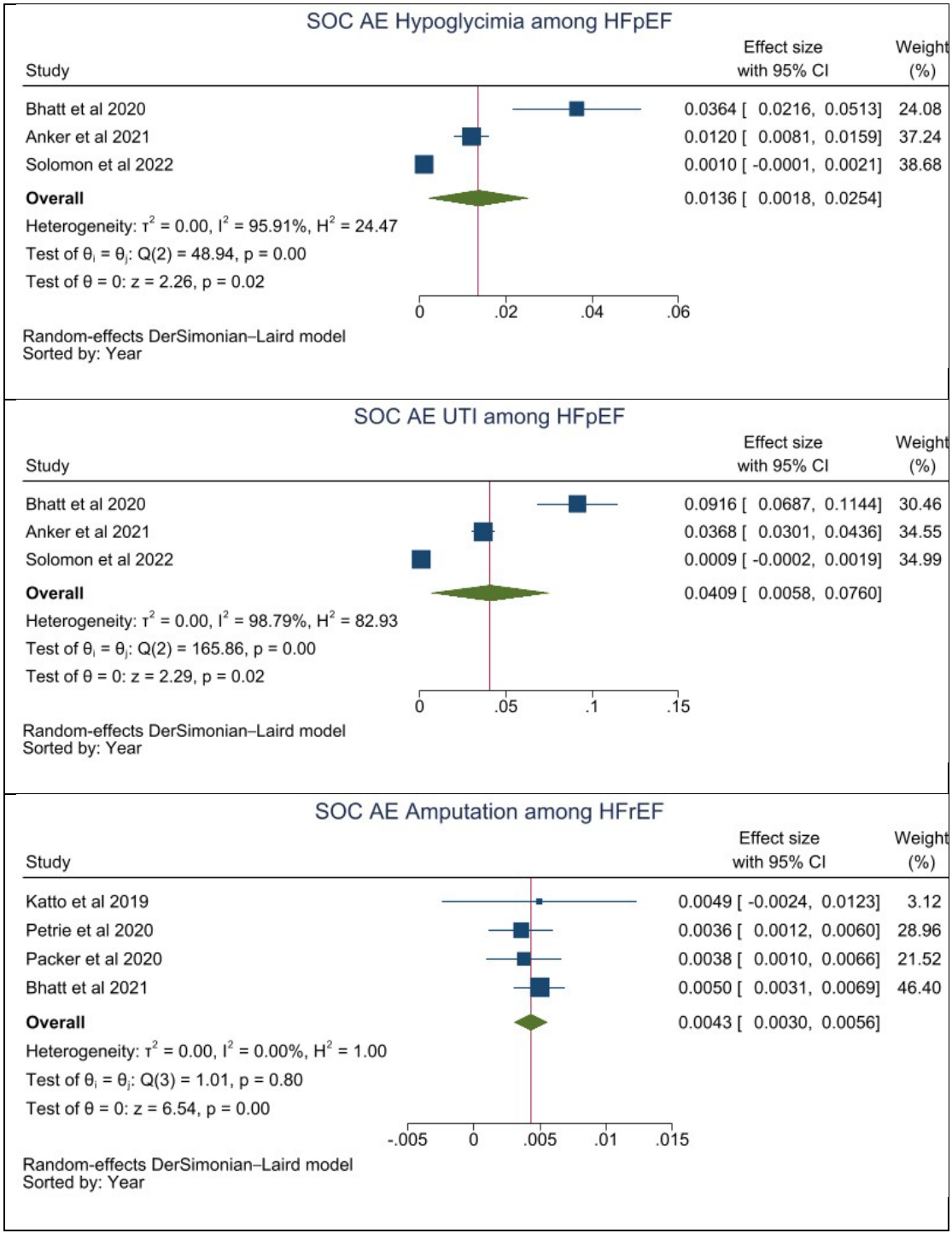
Appendix 1 Meta-analysis Forest plot for probabilities/AEs

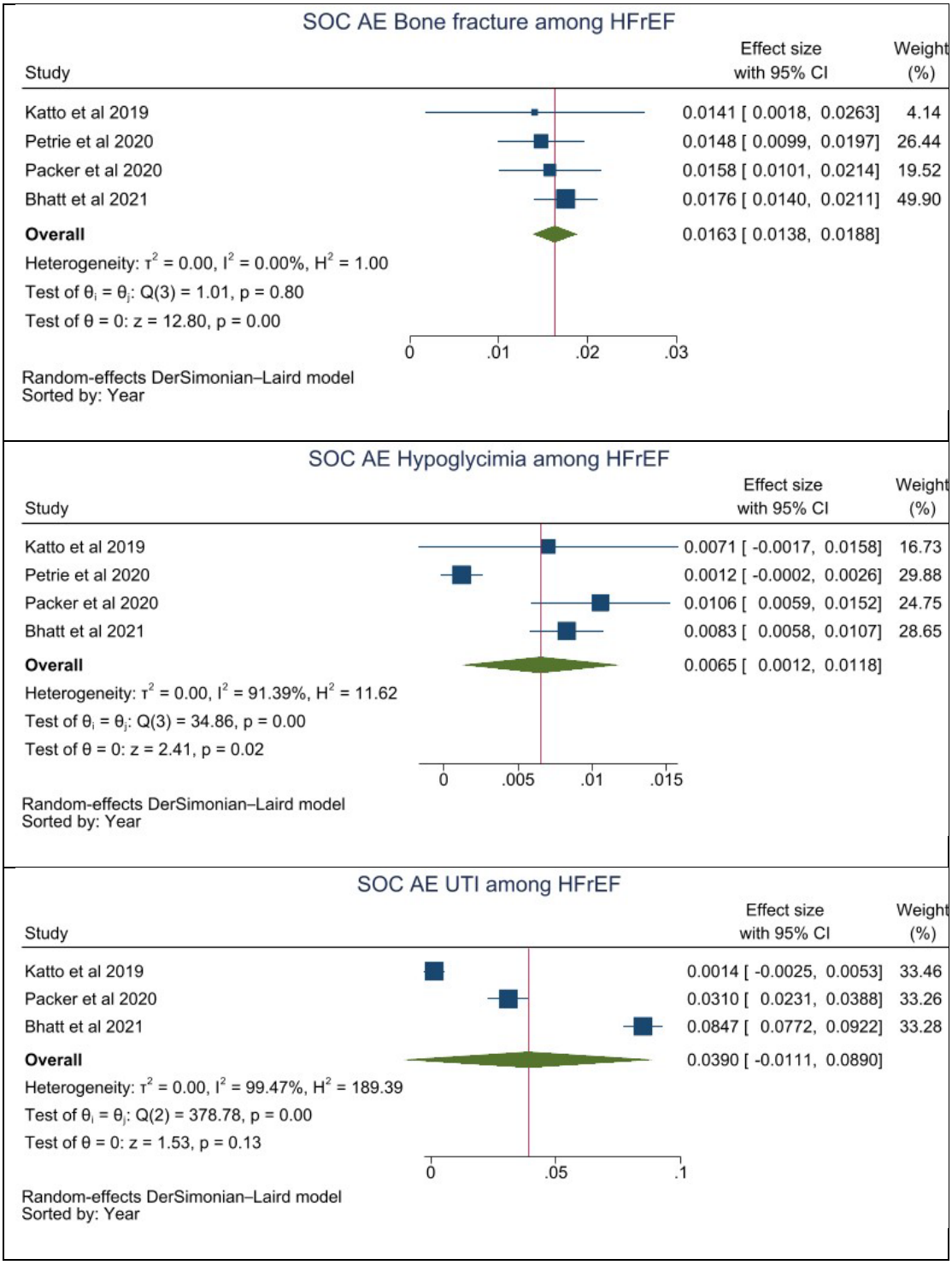



SGLT2 HHF among HFrEF
Study
Effect size with 95% CI
Weight (%)
Katto et al 2019 0.0317 [0.0125, 0.0510] 18.62
Petrie et al 2020 0.0692 [0.0590, 0.0794] 20.51
Packer et al 2020 0.0890 [0.0761, 0.1019] 20.03
Cosentno et al 2020 0.0182 [0.0035, 0.0328] 19.68
Bhatt et al 2021 0.0364 [0.0313, 0.0414] 21.15
Overall 0.0492 [0.0260, 0.0724]
Heterogeneity: τ² = 0.00, I² = 95.65%, H² = 22.99
Test of θi = θj: Q(4) = 91.98, p = 0.00
Test of θ = 0: z = 4.15, p = 0.00
0 .05 .1
Random-effects DerSimonian–Laird model
Sorted by: Year
SOC All cause death among HFrEF
Study
Effect size with 95% CI
Weight (%)
Katto et al 2019 0.0470 [0.0249, 0.0691] 19.44
Petrie et al 2020 0.0880 [0.0769, 0.0990] 21.06
Packer et al 2020 0.0957 [0.0823, 0.1090] 20.79
Cosentno et al 2020 0.0485 [0.0151, 0.0819] 17.18
Bhatt et al 2021 0.0365 [0.0315, 0.0416] 21.53
Overall 0.0637 [0.0333, 0.0942]
Heterogeneity: τ² = 0.00, I² = 96.60%, H² = 29.44
Test of θi = θj: Q(4) = 117.75, p = 0.00
Test of θ = 0: z = 4.11, p = 0.00
.02 .04 .06 .08 .1
Random-effects DerSimonian–Laird model
Sorted by: Year
SOC CVD among HFrEF
Study
Effect size with 95% CI
Weight (%)
Katto et al 2019 0.0327 [0.0142, 0.0513] 19.66
Petrie et al 2020 0.0781 [0.0673, 0.0889] 20.87
Packer et al 2020 0.0735 [0.0617, 0.0854] 20.73
Cosentno et al 2020 0.0379 [0.0082, 0.0676] 17.30
Bhatt et al 2021 0.0254 [0.0211, 0.0296] 21.44
Overall 0.0500 [0.0221, 0.0778]
Heterogeneity: τ² = 0.00, I² = 96.70%, H² = 30.29
Test of θi = θj: Q(4) = 121.15, p = 0.00
Test of θ = 0: z = 3.52, p = 0.00
0 .05 .1
Random-effects DerSimonian–Laird model
Sorted by: Year


SOC HHF among HFrEF
Study
Effect size with 95% CI
Weight (%)
Katto et al 2019 0.0436 [0.0223, 0.0649] 19.38
Petrie et al 2020 0.0965 [0.0847, 0.1084] 20.70
Packer et al 2020 0.1213 [0.1065, 0.1361] 20.35
Cosentno et al 2020 0.0308 [0.0039, 0.0577] 18.38
Bhatt et al 2021 0.0530 [0.0469, 0.0590] 21.18
Overall 0.0700 [0.0391, 0.1009]
Heterogeneity: τ² = 0.00, I² = 96.28%, H² = 26.91
Test of θi = θj: Q(4) = 107.64, p = 0.00
Test of θ = 0: z = 4.44, p = 0.00
0 .05 .1 .15
Random-effects DerSimonian–Laird model
Sorted by: Year
SGLT2 AE Amputation among HFrEF
Study
Effect size with 95% CI
Weight (%)
Katto et al 2019 0.0086 [-0.0015, 0.0188] 1.75
Petrie et al 2020 0.0039 [0.0014, 0.0064] 28.80
Packer et al 2020 0.0049 [0.0017, 0.0081] 17.85
Bhatt et al 2021 0.0048 [0.0030, 0.0067] 51.61
Overall 0.0046 [0.0033, 0.0060]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(3) = 1.02, p = 0.80
Test of θ = 0: z = 6.77, p = 0.00
0 .005 .01 .015 .02
Random-effects DerSimonian–Laird model
Sorted by: Year
SGLT2 AE Bone fracture among HFrEF
Study
Effect size with 95% CI
Weight (%)
Katto et al 2019 0.0179 [0.0033, 0.0325] 2.92
Petrie et al 2020 0.0145 [0.0097, 0.0193] 26.76
Packer et al 2020 0.0169 [0.0111, 0.0228] 18.10
Bhatt et al 2021 0.0166 [0.0132, 0.0201] 52.21
Overall 0.0162 [0.0137, 0.0186]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(3) = 0.65, p = 0.88
Test of θ = 0: z = 12.71, p = 0.00
0 .01 .02 .03
Random-effects DerSimonian–Laird model
Sorted by: Year


SGLT2 AE Hypoglycimia among HFrEF
Study
Effect size with 95% CI
Weight (%)
Katto et al 2019 0.0055 [-0.0026, 0.0136] 17.03
Petrie et al 2020 0.0012 [-0.0002, 0.0026] 29.90
Packer et al 2020 0.0102 [0.0056, 0.0147] 24.46
Bhatt et al 2021 0.0080 [0.0056, 0.0104] 28.61
Overall 0.0061 [0.0010, 0.0111]
Heterogeneity: τ² = 0.00, I² = 90.76%, H² = 10.83
Test of θi = θj: Q(3) = 32.48, p = 0.00
Test of θ = 0: z = 2.36, p = 0.02
-.005 0 .005 .01 .015
Random-effects DerSimonian–Laird model
Sorted by: Year
SGLT2 AE UTI among HFrEF
Study
Effect size with 95% CI
Weight (%)
Katto et al 2019 0.0024 [-0.0030, 0.0077] 33.43
Packer et al 2020 0.0339 [0.0257, 0.0421] 33.27
Bhatt et al 2021 0.0881 [0.0805, 0.0957] 33.30
Overall 0.0414 [-0.0101, 0.0929]
Heterogeneity: τ² = 0.00, I² = 99.39%, H² = 163.12
Test of θi = θj: Q(2) = 326.25, p = 0.00
Test of θ = 0: z = 1.58, p = 0.11
0 .05 .1
Random-effects DerSimonian–Laird model
Sorted by: Year
SOC AE Bone fracture among HFpEF
Study
Effect size with 95% CI
Weight (%)
Bhatt et al 2020 0.0194 [0.0085, 0.0304] 16.77
Ueda et al 2021 0.0488 [-0.0180, 0.1155] 0.45
Anker et al 2021 0.0193 [0.0143, 0.0242] 82.78
Overall 0.0194 [0.0149, 0.0239]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(2) = 0.75, p = 0.69
Test of θ = 0: z = 8.49, p = 0.00
0 .05 .1 .15
Random-effects DerSimonian–Laird model
Sorted by: Year


SOC AE Hypoglycimia among HFpEF
Study
Effect size with 95% CI
Weight (%)
Bhatt et al 2020
0.0364 [0.0216, 0.0513]
24.08
Anker et al 2021
0.0120 [0.0081, 0.0159]
37.24
Solomon et al 2022
0.0010 [-0.0001, 0.0021]
38.68
Overall
0.0136 [0.0018, 0.0254]
Heterogeneity: τ² = 0.00, I² = 95.91%, H² = 24.47
Test of θi = θj: Q(2) = 48.94, p = 0.00
Test of θ = 0: z = 2.26, p = 0.02
0
.02
.04
.06
Random-effects DerSimonian–Laird model
Sorted by: Year
SOC AE UTI among HFpEF
Study
Effect size with 95% CI
Weight (%)
Bhatt et al 2020
0.0916 [0.0687, 0.1144]
30.46
Anker et al 2021
0.0368 [0.0301, 0.0436]
34.55
Solomon et al 2022
0.0009 [-0.0002, 0.0019]
34.99
Overall
0.0409 [0.0058, 0.0760]
Heterogeneity: τ² = 0.00, I² = 98.79%, H² = 82.93
Test of θi = θj: Q(2) = 165.86, p = 0.00
Test of θ = 0: z = 2.29, p = 0.02
0
.05
.1
.15
Random-effects DerSimonian–Laird model
Sorted by: Year
SOC AE Amputation among HFrEF
Study
Effect size with 95% CI
Weight (%)
Katto et al 2019
0.0049 [-0.0024, 0.0123]
3.12
Petrie et al 2020
0.0036 [0.0012, 0.0060]
28.96
Packer et al 2020
0.0038 [0.0010, 0.0066]
21.52
Bhatt et al 2021
0.0050 [0.0031, 0.0069]
46.40
Overall
0.0043 [0.0030, 0.0056]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(3) = 1.01, p = 0.80
Test of θ = 0: z = 6.54, p = 0.00
-.005
0
.005
.01
.015
Random-effects DerSimonian–Laird model
Sorted by: Year


SOC AE Bone fracture among HFrEF
Study
Effect size with 95% CI
Weight (%)
Katto et al 2019
0.0141 [0.0018, 0.0263]
4.14
Petrie et al 2020
0.0148 [0.0099, 0.0197]
26.44
Packer et al 2020
0.0158 [0.0101, 0.0214]
19.52
Bhatt et al 2021
0.0176 [0.0140, 0.0211]
49.90
Overall
0.0163 [0.0138, 0.0188]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(3) = 1.01, p = 0.80
Test of θ = 0: z = 12.80, p = 0.00
0
.01
.02
.03
Random-effects DerSimonian–Laird model
Sorted by: Year
SOC AE Hypoglycimia among HFrEF
Study
Effect size with 95% CI
Weight (%)
Katto et al 2019
0.0071 [-0.0017, 0.0158]
16.73
Petrie et al 2020
0.0012 [-0.0002, 0.0026]
29.88
Packer et al 2020
0.0106 [0.0059, 0.0152]
24.75
Bhatt et al 2021
0.0083 [0.0058, 0.0107]
28.65
Overall
0.0065 [0.0012, 0.0118]
Heterogeneity: τ² = 0.00, I² = 91.39%, H² = 11.62
Test of θi = θj: Q(3) = 34.86, p = 0.00
Test of θ = 0: z = 2.41, p = 0.02
0
.005
.01
.015
Random-effects DerSimonian–Laird model
Sorted by: Year
SOC AE UTI among HFrEF
Study
Effect size with 95% CI
Weight (%)
Katto et al 2019
0.0014 [-0.0025, 0.0053]
33.46
Packer et al 2020
0.0310 [0.0231, 0.0388]
33.26
Bhatt et al 2021
0.0847 [0.0772, 0.0922]
33.28
Overall
0.0390 [-0.0111, 0.0890]
Heterogeneity: τ² = 0.00, I² = 99.47%, H² = 189.39
Test of θi = θj: Q(2) = 378.78, p = 0.00
Test of θ = 0: z = 1.53, p = 0.13
0
.05
.1
Random-effects DerSimonian–Laird model
Sorted by: Year

Appendix 2

Presentation of heart failure

Presentation of heart failure	International studies	NHFR	MHFR	Our Model
HFrEF	~50 to 70%	65.2%	82.9%	80%
HFmrEF	~ 7 to 20%	22%		
HFpEF	~20 to 30%	12.7%	17.1%	20%

HF incidence levels at 0.0017 from Amezcua et al 2020

Standard of care drugs used in the model for heart failure

Prescription of disease modifying agents in heart failure (SoC)	HFrEF	HFpEF
Angiotensin-converting enzyme inhibitors (Enalapril) /Angiotensin receptor blockers (Losartan)	60%	55%
Beta Blockers (Bisoprolol, Carvedilol, Metoprolol, Nebivolol)	78%	72%
Mineralocorticoid receptor antagonists (Spironolactone)	73%	51%

Appendix 3

Scenario Analysis- Results: Empagliflozin Market Price

	SGLT2	SOC
Total Cost	₹ 364,123	₹ 301,346
Total LY	5.2098	4.1161
Total QALY	3.2584	3.1386
NMB	₹ 374,776	₹ 410,370
Ic Cost	₹ 62,776	
Ic_LY	1.0936	
Ic_QALY	0.1199	
ICER per LY	₹ 57,401	
ICER per QALY	₹ 5,23,709	
INB	₹ -35,594	

Scenario Analysis- Results: Dapagliflozin Market Price

	SGLT2	SOC
Total Cost	₹ 355,267	₹ 301,346
Total LY	5.2098	4.1161
Total QALY	3.2584	3.1386
NMB	₹ 383,632	₹ 410,370
Ic Cost	₹ 53,920	
Ic_LY	1.0936	
Ic_QALY	0.1199	
ICER per LY	₹ 49,303	
ICER per QALY	₹ 4,49,829	
INB	₹ -26,738	

Scenario Analysis- Results: Canagliflozin Market Price

	SGLT2	SOC
Total Cost	₹ 421,645	₹ 301,346
Total LY	5.2098	4.1161
Total QALY	3.2584	3.1386
NMB	₹ 317,254	₹ 410,370
Ic Cost	₹ 120,299	
Ic_LY	1.0936	
Ic_QALY	0.1199	
ICER per LY	₹ 109,998	
ICER per QALY	₹ 10,03,590	
INB	₹ -93,117	

Appendix 4 CHEERS 2022 Checklist (Model-based economic evaluation of SGLT2i vs SC)

Topic	No.	Item	Location where item is reported
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Yes
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	NA
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision-making in policy or practice.	Yes
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Yes
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Yes
Setting and location	6	Provide relevant contextual information that may influence findings.	Yes
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Yes
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Yes
Time horizon	9	State the time horizon for the study and why appropriate.	Yes
Discount rate	10	Report the discount rate(s) and reason chosen.	Yes
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Yes
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Yes
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Yes
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Yes
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Yes
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Yes
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Yes
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Yes
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Yes
Characterising uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	Yes
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Yes
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Yes
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Yes
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Yes
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Yes
Discussion			

Topic	No.	Item	Location where item is reported
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Yes
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	NA
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	NA

From: Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25. doi:10.1016/j.jval.2021.10.008

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