Can SGLT-2 Inhibitors Treat Heart Failure with Preserved Ejection Fraction? A Systematic Review

Rania Maggay | Supervisor: Dr. Derek Steele School of Biomedical Sciences, Faculty of Biological Sciences, University of Leeds

UNIVERSITY OF LEEDS

Introduction

- The NHS spends £5 billion a year on cardiovascular disease.
 Heart failure is the leading cause of hospitalisations worldwide and there is currently no cure for the disease
- However, emerging studies have shown that sodium-glucose co-transporter 2 inhibitors (SGLT-2is) may treat heart failure with preserved ejection fraction (HFpEF)
- This systematic review investigated the effectiveness of SGLT-2is as a potential treatment for HFpEF, regardless of a patient's diabetic status

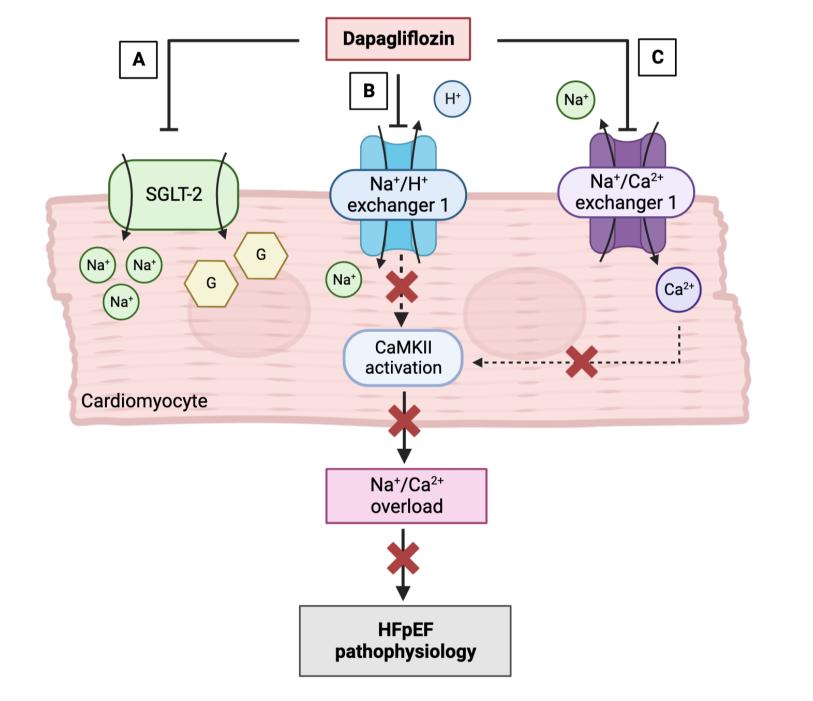


Figure 1. Mechanism of action of Dapagliflozin.

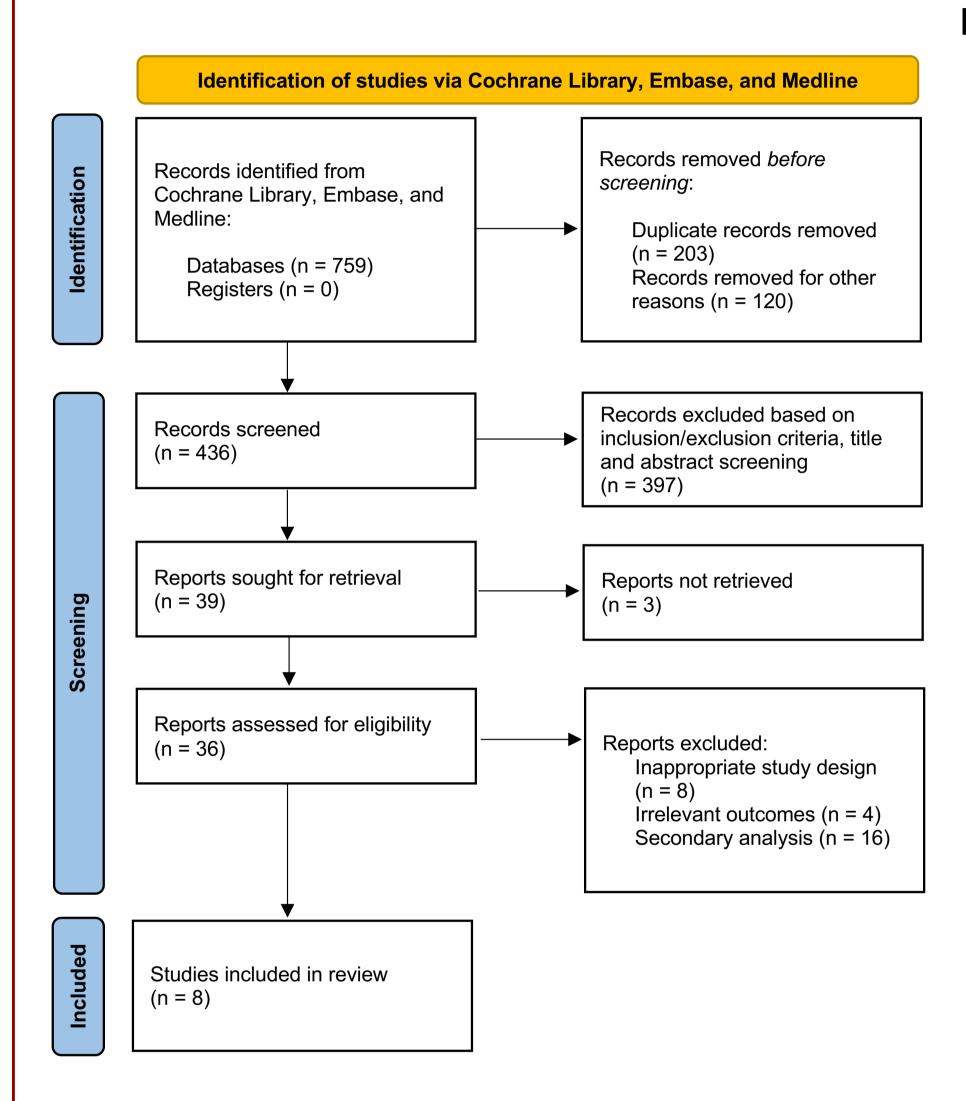


Figure 2. PRISMA flow diagram of the screening process.

Results

	SGLT-2 In	hibitors	Cont	trol		Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Anker et al., EMPEROR-Preserved	478	2997	613	2991	51.0%	0.78 [0.70 , 0.87]	
Solomon et al., DELIVER	462	3131	505	3132	48.7%	0.92 [0.81 , 1.03]	_
Ueda et al., CANONICAL	1	42	1	40	0.3%	0.95 [0.06 , 14.72]	
Total (95% CI)		6170		6163	100.0%	0.84 [0.73 , 0.97]	•
Total events:	941		1119				Y
Heterogeneity: Tau ² = 0.01; Chi ² = 4.	01, df = 2 (P	$= 0.13); I^2$	² = 50%			0.	.05 0.2 1 5 20
Test for overall effect: $Z = 2.44$ (P = 0	0.01)						GLT-2 Inhibitors Favours control
Test for subgroup differences: Not ap	plicable						
	SGLT-2 Inhi	bitors		Control		Mean difference	Mean difference
Study or Subgroup M	ean SD	Total	Mean	SD	Total V	Veight IV, Random, 95% C	IV, Random, 95% CI

SGLT	-2 Inhibit	ors	(Control			Mean difference	Mean difference
Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
5.47	3.73	157	4.685	5.1	158	16.4%	0.79 [-0.20 , 1.77]	-
4.51	0.31	2997	3.18	0.31	2991	17.5%	1.33 [1.31 , 1.35]	
9.81	1.27	18	4.24	1.39	18	16.6%	5.57 [4.70 , 6.44]	-
4.95	2.78	253	2.86	3.71	251	17.1%	2.09 [1.52 , 2.66]	
8.3	20.3	1316	5.2	21.1	1311	15.0%	3.10 [1.52 , 4.68]	-
9.2	1.27	222	4.9	1.27	226	17.4%	4.30 [4.06 , 4.54]	
		4963			4955	100.0%	2.86 [1.24 , 4.47]	
2.90, df = 5	5 (P < 0.0	0001); I² =	= 99%					
.0005)							-10	-5 0 5
	5.47 4.51 9.81 4.95 8.3 9.2	Mean SD 5.47 3.73 4.51 0.31 9.81 1.27 4.95 2.78 8.3 20.3 9.2 1.27 2.90, df = 5 (P < 0.0	5.47 3.73 157 4.51 0.31 2997 9.81 1.27 18 4.95 2.78 253 8.3 20.3 1316 9.2 1.27 222 4963 2.90, df = 5 (P < 0.00001); l ² =	Mean SD Total Mean 5.47 3.73 157 4.685 4.51 0.31 2997 3.18 9.81 1.27 18 4.24 4.95 2.78 253 2.86 8.3 20.3 1316 5.2 9.2 1.27 222 4.9 4963 2.90, df = 5 (P < 0.00001); l² = 99%	Mean SD Total Mean SD 5.47 3.73 157 4.685 5.1 4.51 0.31 2997 3.18 0.31 9.81 1.27 18 4.24 1.39 4.95 2.78 253 2.86 3.71 8.3 20.3 1316 5.2 21.1 9.2 1.27 222 4.9 1.27 4963 2.90, df = 5 (P < 0.00001); l² = 99%	Mean SD Total Mean SD Total 5.47 3.73 157 4.685 5.1 158 4.51 0.31 2997 3.18 0.31 2991 9.81 1.27 18 4.24 1.39 18 4.95 2.78 253 2.86 3.71 251 8.3 20.3 1316 5.2 21.1 1311 9.2 1.27 222 4.9 1.27 226 4963 4955 2.90, df = 5 (P < 0.00001); l² = 99%	Mean SD Total Mean SD Total Weight 5.47 3.73 157 4.685 5.1 158 16.4% 4.51 0.31 2997 3.18 0.31 2991 17.5% 9.81 1.27 18 4.24 1.39 18 16.6% 4.95 2.78 253 2.86 3.71 251 17.1% 8.3 20.3 1316 5.2 21.1 1311 15.0% 9.2 1.27 222 4.9 1.27 226 17.4% 4963 2.90, df = 5 (P < 0.00001); l² = 99%	Mean SD Total Weight IV, Random, 95% CI 5.47 3.73 157 4.685 5.1 158 16.4% 0.79 [-0.20 , 1.77] 4.51 0.31 2997 3.18 0.31 2991 17.5% 1.33 [1.31 , 1.35] 9.81 1.27 18 4.24 1.39 18 16.6% 5.57 [4.70 , 6.44] 4.95 2.78 253 2.86 3.71 251 17.1% 2.09 [1.52 , 2.66] 8.3 20.3 1316 5.2 21.1 1311 15.0% 3.10 [1.52 , 4.68] 9.2 1.27 222 4.9 1.27 226 17.4% 4.30 [4.06 , 4.54]

Figure 3. Forest plots of trials that investigated CV death or HF hospitalisations (A) and KCCQ-TSS (B) in HFpEF patients treated with SGLT-2is or placebo.

Author and Trial	Intervention	Intervention Mean Distance (m)	Placebo Mean Distance (m)	Mean Difference (m) (95% CI)
Abraham et al. (2021), EMPERIAL-Preserved	Empagliflozin	10.50±7.95 (n = 157)	5.75±10.0 (n = 158)	4.75(2.76-6.74)
McMurray et al. (2023), DETERMINE	Dapagliflozin	10.0±9.25 (n = 253)	9.50±8.90 (n = 251)	0.50(-1.08-2.08)
Nassif et al. (2021), PRESERVED-HF	Dapagliflozin	16.50±2.44 (n = 162)	2.25±2.24 (n = 162)	14.25(13.72-14.78)

Table 2. Summary of 6MWTD. Mean distances reported as the mean change from baseline to the endpoints of each study ± SD, m: metres.

- Figure 3A shows a significant reduction that was observed in CV death or HHF for patients administered with SGLT-2is
- HHF reduced significantly for patients treated with SGLT-2is (P=0.003)
- SGLT-2is improved KCCQ-TSS (Figure 3B) but did not improve 6MWT distances (P=0.19)

Methods

Database	Search Strategy	Search Results
Cochrane Library	(HFpEF OR Heart Failure with Preserved Ejection Fraction OR Diastolic Heart Failure) AND (SGLT-2	160
Embase	Inhibitors OR Empagliflozin OR Canagliflozin OR Dapagliflozin OR Ertugliflozin) AND (RCT OR RCTs OR	467
PubMed/Medline	Randomised OR Randomized OR Placebo OR Controlled Clinical Trial OR Randomised Control Trial OR Double Blinding OR Double Blind Trial)	132

Table 1. Summary of the databases, search strategies, and outcomes for data collection. Searches were conducted on Ovid Online.

- PICOS formulated:
 - o **Population**: HFpEF Patients
 - o Intervention: SGLT-2is
 - Comparator: placebo / standard diabetic treatment
 - Outcomes: CV death, HF hospitalisations, all-cause mortality, KCCQ-TSS, 6MWTD
 - Study Design: any study excluding SRs
- Meta-analysis of 13,950 participants using random effects model was performed to calculate mean difference with inverse variance at 95% CI

Conclusions

Dapagliflozin, empagliflozin and canagliflozin reduced the rate of HF hospitalisations and improved the quality of life of patients with HFpEF, supporting the use of SGLT-2 inhibitors as the primary treatment for HFpEF. This discovery will aid the development of novel therapeutics that target the pathophysiology of HFpEF.