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Effect of SGLT2 inhibitors on cardiac structure and function assessed by cardiac magnetic resonance: a systematic review and meta-analysis

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Abstract

Background and aim Sodium-glucose cotransporter-2 inhibitors (SGLT2i) improve outcomes in patients with heart failure (HF) but underlying mechanisms remain incompletely understood. Cardiac magnetic resonance (CMR) is key in evaluating cardiac structure and function, enabling accurate assessment of reverse remodeling. Aim of this systematic review and meta-analysis was to assess the effects of SGLT2i on cardiac remodeling evaluated by CMR changes.

Methods We conducted a systematic review and meta-analysis of studies assessing changes in CMR parameters in patients treated with SGLT2i (PROSPERO registration: CRD42024574302). Databases were searched through April 30, 2025. Random-effects models were used to pool mean changes in left and right ventricular volumes, mass, function, stroke volume, global longitudinal strain, left atrial volume, and tissue characterization indices. Meta-regression and sensitivity analyses were performed to evaluate potential sources of heterogeneity.

Results Twenty-three studies and 1008 patients were included. Treatment with SGLT2i was associated with significant reductions in left ventricular (LV) end-diastolic volume (−7.10 mL; 95% CI: −13.01 to −1.19, $p=0.023$), left ventricular mass (−4.24 g; 95% CI: −7.88 to −0.60, $p=0.027$) and epicardial adipose tissue (-4.94 ml; 95% CI: -9.06, -0.82, $p=0.019$). A subgroup analysis in patients with reduced LV ejection fraction showed improvement in LV stroke volume. Meta-regression revealed no significant effect of age, male sex or diabetes prevalence on pooled estimates.

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Conclusions SGLT2i are associated with reductions in LV volumes and mass in line with an overall favorable reverse remodeling effects as assessed by CMR.

Keywords Heart failure, Sodium-glucose transport protein 2, Cardiovascular magnetic resonance, Reverse cardiac remodeling

Introduction

Initially proposed as glucose-lowering drugs, sodium-glucose cotransporter-2 inhibitors (SGLT2i) have shown robust beneficial effects on cardiovascular outcomes in patients with heart failure (HF) across different HF phenotypes and irrespective of glycemic control and diabetic status [1, 2]. For these reasons European guidelines recommend their use in both patients with HF with reduced ejection fraction and preserved ejection fraction to reduce the risk of cardiovascular death and HF hospitalization [1, 2]. Treatment with SGLT2i has been also associated with lower rates of further cardiovascular events in patients with diabetes and myocardial infarction, regardless of HF status [3]. Moreover, in patients with chronic kidney disease SGLT2i proved to slow disease progression and reduce the risk of death from renal or cardiovascular causes [4]. Despite the compelling evidence supporting their use, the precise mechanisms behind SGLT2i cardioprotective effects remain incompletely understood [5]. The occurrence and progression of HF is paralleled by changes in ventricular geometry, function and structure (i.e., cardiac remodeling) [6]. In this setting, cardiac magnetic resonance (CMR) is essential in being the gold standard modality for volumes, mass and function assessment but provides also unique insights on tissue characterization of cardiac chambers [7–9]. Aim of this systematic review and meta-analysis was to assess the effects of SGLT2i on cardiac remodeling evaluated by CMR changes.

Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic.

Reviews and Meta-Analyses (PRISMA) guidelines [10] (Supplementary Table 1). The protocol has been published in the PROSPERO International prospective register of systematic reviews (CRD42024574302).

Search strategy

Two independent investigators (A.C. and J.I.) performed a comprehensive literature search in PubMed, ClinicalTrials.gov, Embase, and the Cochrane Library using the following search terms: "SGLT2i" OR "Sodium-Glucose Transport Protein 2 Inhibitors" OR "SGLT2 Inhibitors" AND "Cardiac MRI" OR "Cardiac Magnetic Resonance" OR "Cardiovascular Magnetic Resonance" OR "CMR" in various combination. Full-text manuscripts published between January 1, 2000, through April 30, 2025 were screened for eligibility.

Study eligibility

Full-text manuscripts published in peer-reviewed journals assessing changes in CMR parameters in patients treated with SGLT2i were included. Non–English-language studies, editorials, letters, expert opinions, case reports or series, duplicated data and meta-analyses were excluded. No sample size restrictions were applied. Two authors (A.C. and J.I.) independently evaluated studies for eligibility, and discrepancies were resolved by a third reviewer (I.L.). Only studies that met all inclusion criteria were included in the final analysis (Table 1).

Data extraction

The following variables were collected: (i) first author, (ii) year of publication, (iii) study design, (iv) sample size, (v) main demographic, clinical and CMR baseline patient characteristics. In detail, CMR parameters included left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), left ventricular end-diastolic volume indexed (LVEDVi), left ventricular end-systolic volume (LVESV), left ventricular end-systolic volume indexed (LVESVi), left ventricular mass (LVM) and indexed mass (LVMi), left atrial volume indexed (LAVi), left ventricular stroke volume (LVSV), right ventricular end-diastolic volume indexed (RVEDVi), right ventricular end-systolic volume indexed (RVESVi), epicardial adipose tissue (EAT), native T1 mapping and extracellular volume (ECV). All indexed values are meant indexed for body surface area. At least three studies reporting CMR outcome variables were required to be eligible for the analysis. The individual quality of each study was assessed using the Newcastle-Ottawa Scale (NOS), with studies categorized as poor, fair, or good quality based on criteria related to selection, comparability, and outcome [11] (Supplementary Table 2).

Statistical analysis

The primary endpoint was the mean difference (baseline vs. follow-up evaluation) of CMR parameters. A random-effects model (DerSimonian and Laird method) [12] was used to estimate pooled mean differences and corresponding 95% confidence intervals (CIs) of reported average measures of CMR parameters before and after treatment with SGLT2i, accounting for anticipated heterogeneity across studies.

Table 1 Patients' baseline characteristics

Study	Study Design	Total cohort	No SGLT2i group	Age (y)	Male *n* (%)	Hypertension *n* (%)	Diabetes *n* (%)	CAD *n* (%)	HF *n* (%)	HbA1c (%)	eGFR at baseline (mL/min/1.73m2)	SGLT2i	Follow-up (days)
Bouchi et al. *2017*	Single-arm pilot study	19	No	55 ± 12	14 (74)	N/A	19 (100)	N/A	N/A	7.5 ± 0.7	69.7 ± 13.8	Luseogliflozin	84
Brown et al. *2020*	Single-centre, double-blind, placebo-controlled trial	66	Yes	67 ± 7	38 (56.6)	51 (77.3)	66 (100)	8 (12.1)	N/A	7.7 ± 3.1	101.9 ± 27.1	Dapagliflozin	365
Carberry et al. *2025*	Randomized, double-blind, placebo-controlled, multicentre trial	105	Yes	63 ± 11	86 (82.7)	35 (33.7)	9 (8.7)	105 (100)	105 (100)	N/A	78.8 ± 20.2	Empagliflozin	168
Cohen et al. *2019*	Matched cohort study	25	Yes	63.3 ± 7.6	16 (64)	N/A	25 (100)	6 (24)	N/A	8.1 ± 0.8	N/A	Empagliflozin	180
Connelly et al. *2023*	Multicentre, double-blind, placebo-controlled, randomized investigator-initiated clinical trial	169	Yes	59.3 ± 10.5	141 (83)	140 (82.8)	0 (0)	N/A ***	41 (24.3)	5.7 ± 0.5	80.5 ± 16	Empagliflozin	180
Dihoum et al. *2024*	Sub-study of a prospective, double-blind, randomized, placebo-controlled study	60	Yes	65.2 ± 6.9	36 (60)	47 (78.3)	60 (100)	8 (13.3)	N/A	7.8 ± 3.1	N/A	Dapagliflozin	365
Fukuda et al. *2017*	Single-arm pilot study	9	No	66 ± 8	6 (67)	N/A	9 (100)	N/A	N/A	7.2 ± 0.6	79.5 ± 17.1	Ipragliflozin	84
Gaborit et al. *2021*	Randomized, parallel-group, double-blind, phase 3 trial	51	Yes	56.9 ± 9.6	20 (39.2)	32 (62.7)	51 (100)	16 (31.4)	N/A	8.1 ± 1.1	N/A	Empagliflozin	84
Hassan et al. *2024*	Single-centre, prospective analytic study	23	No	42.1 ± 3.8	19 (82.6)	6 (26.1)	5 (21.7)	0 (0)	23 (100)	N/A	118.01 ± 39.3	Dapagliflozin	365 (270–600)*
Hsu et al. *2019*	Prospective study	35	No	63.5 ± 9.7	17 (48.6)	29 (82.9)	35 (100)	17 (48.6)	N/A	7 ± 1.1	82.3 ± 19.4	Empagliflozin	180
Hundertmark et al. *(HFrEF) 2023*	Prospective, randomized, double-blind, placebo-controlled trial	36	Yes	66 ± 13.5	23 (63.9)	8 (22.2)	5 (13.9)	0 (0)	36 (100)	N/A	71.2 ± 24.6	Empagliflozin	84
Hundertmark et al. *(HFpEF) 2023*	Prospective, randomized, double-blind, placebo-controlled trial	36	Yes	68.3 ± 11.5	19 (52.8)	12 (33.3)	4 (11.1)	0 (0)	36 (100)	N/A	68.1 ± 18.9	Empagliflozin	84
Lee et al. *2021*	Multicentre, randomized, double-blind, placebo- controlled trial	105	Yes	68.7 ± 11.1	77 (73.3)	74 (70.5)	82 (78.1)	74 (70.5)	105 (100)	7.2 ± 1.5	67.3 ± 22	Empagliflozin	252
Mason et al. *2021*	Sub-study of a double-blind randomized controlled trial	74	Yes		68 (91.9)	65 (87.8)	74 (100)	74 (100)	6 (8.1)	8 ± 1	88.4 ± 20	Empagliflozin	180
Oldgren et al. *2021*	Double-blind, randomized, parallel-group, exploratory, phase IV trial	49	Yes	64.4	26 (53)	37.2 (76)	49 (100)	2 (4.1)	0 (0)	6.7 ± 0.6	N/A	Dapagliflozin	42
Pourafkari et al. *2024*	Sub-study of a double-blind, randomized, controlled trial	90	Yes	64.5	83 (92.2)	91 (90)	90 (100)	90 (100)	N/A	7.9	N/A	Empagliflozin	180
Santos-Gallego et al. *2021*	Double-blind, placebo-controlled, randomized trial	84	Yes	62 ± 12.1	54 (64)	62 (74)	0 (0)	42 (50)	84 (100)	5.8 ± 0.4	81.5 ± 22	Empagliflozin	180

Table 1 (continued)

Study	Study Design	Total cohort	No SGLT2i group	Age (y)	Male *n* (%)	Hypertension *n* (%)	Diabetes *n* (%)	CAD *n* (%)	HF *n* (%)	HbA1c (%)	eGFR at baseline (mL/min/1.73m2)	SGLT2i	Follow-up (days)
Requena-Ibáñez et al. *2021*	Sub-study of a double-blind, placebo-controlled, randomized trial	84	Yes	62 ± 12.1	54 (64)	62 (74)	0(0)	42 (50)	84 (100)	5.8 ± 0.4	81.5 ± 22	Empagliflozin	180
Sarak et al. *2021*	Post-hoc analysis of single centre, double-blind, randomized, placebo-controlled, investigator-initiated phase IV trial	90	Yes	64	81 (90)	82 (91.1)	90 (100)	90 (100)	12 (13.3)	7.9	N/A	Empagliflozin	180
Satoh et al. *2024*	Single-centre prospective cohort study	10	No	67.8 ± 10	4 (40)	N/A	N/A	N/A	N/A	N/A	52.0 (44.2,55.7)	Empagliflozin	180
Singh et al. *2020*	Single-centre, placebo-controlled clinical trial	56	Yes	67.1	37 (66.1)	N/A	56 (100)	N/A	56 (100)	7.7	72	Dapagliflozin	365
Thirunavukarasu et al. *2021*	Single centre, open-label, cross-over trial	28	Yes	67 ± 9	21 (75)	21 (75)	28 (100)	18 (64.3)	N/A	7 ± 1	75.5 ± 30.4	Empagliflozin	84
Verma et al. *2019*	Double-blind, placebo-controlled, randomized investigator-initiated clinical trial	97	Yes	62.9 ± 9	90 (93)	88 (90.1)	97 (100)	97 (100)	6 (6.2)	N/A	87.5	Empagliflozin	180
Wang et al. *2024*	Double-blind, randomized trial	62	Yes	62 ± 10	51 (83)	38 (61.3)	62 (100)	N/A****	0 (0)	7.9 ± 0.9	N/A	Dapagliflozin	365

Categorial variables are given as absolute numbers and percentage, n (%). Continuous variables are given as mean ± standard deviation or * median (IQR, interquartile range). **The value is expressed as pmol/l. *** Myocardial Infarction 31 (18.3%), coronary artery bypass surgery 11 (6.5%), percutaneous coronary intervention 35 (20.7%). **** Myocardial Infarction 3 (4.8%), coronary artery bypass surgery 2 (3.2%), percutaneous coronary intervention 4 (6.5%)

CAD: coronary artery disease; *eGFR*: estimated glomerular filtration rate; *Hb1Ac*: glycated hemoglobin; *HF*: Heart Failure; *SGLT2i*: Sodium-Glucose Transport Protein 2 Inhibitors

Table 2 Main CMR parameters in patients treated with SGLT2i at baseline

Study	LVEDV (ml)	LVEDVi (ml/m^2)	LVESV (ml)	LVESVi (ml/m^2)	LVEF (%)	LVM (g)	LVMi (g/m^2)	LAVi (ml/m^2)	LVSV (ml)	LVGLS (%)	ECV (%)	T1 (ms)
Brown et al. *2020*	127.6 ± 22.5	N/A	37.2 ± 9.9	N/A	71.3 ± 5.4	126.5 ± 20.5	60.9 ± 7.8	N/A	90.5 ± 16.4	N/A	N/A	N/A
Carberry et al. *2025*	N/A	97.8 ± 19.8	N/A	65.6 ± 17	33.4 ± 6	N/A	62.2 ± 13.7	34.3 ± 12.7	N/A	N/A	N/A	N/A
Cohen et al. *2019*	155.2 ± 8.7	N/A	N/A	N/A	63.4 ± 1.7	93.1 ± 4.9	N/A	N/A	N/A	N/A	N/A	989.8 ± 25.3
Connelly et al. *2023*	145.8 ± 39	74.2 ± 20.2	60.2 ± 28	30.7 ± 15	59.9 ± 10.7	124.4 ± 35.6	63.2 ± 17.9	N/A	N/A	N/A	N/A	N/A
Dihoum et al. *2024*	124.1 ± 20.2	N/A	35.6 ± 9.4	N/A	71.7 ± 5.4	124.7 ± 21.5	73.9 ± 9.9	N/A	N/A	−17.8 ± 2.1	N/A	N/A
Gaborit et al. *2021*	N/A	N/A	N/A	N/A	63.1 ± 8.2	117 (93,150)	58 (51,66)	N/A	N/A	N/A	N/A	N/A
Hassan et al. *2024*	N/A	178.3 ± 11	N/A	140 ± 44.3	23.8± 9.2	N/A	N/A	N/A	41.2 ± 3.9*	N/A	33.7 ± 1.3	N/A
Hsu et al. *2019*	94.4 ± 28.2	53.5 ± 16.2	24.5 ± 19.6	13.8 ± 11.9	77.2 ± 12.1	N/A	95.1 ± 28.3	N/A	N/A	N/A	27.4 ± 4.1	N/A
Hundertmark et al. *(HFrEF) 2023*	242 ± 78.5	N/A	N/A	N/A	36.8 ± 9.2	146.6 ± 8.3	75.4 ± 4.7	N/A	85.3 ± 6.3	−6.8 ± 1.4	30.3 ± 2.1	1190.1 ± 11.2
Hundertmark et al. (*HFpEF) 2023*	174.2 ± 18.6	N/A	N/A	N/A	52.6 ± 2.2	127.7 ± 14.5	62.2 ± 5.9	N/A	88.8 ± 7.4	−14.2 ± 1	29.7 ± 1	1177.9 ± 11.3
Lee et al. 2021	224.8 ± 72.2	114.7 ± 37	157.5 ± 68.1	80.8 ± 37.2	31.7 ± 9.9	121.2 ± 36.5	61.2 ± 16.1	40.5 ± 13.3	N/A	−7± 2.1	31.8± 4.5	N/A
Mason et al. *2021*	N/A	62.2 ± 15.7	N/A	26.6 ± 9.9	58.0 ± 6.8	N/A	59.1 ± 10.1	N/A	N/A	N/A	29.6 ± 4.6	1246 ± 42
Oldgren et al. *2021*	N/A	83.1 ± 16.7	N/A	32.8 ± 8.2	60.7 ± 3.8	N/A	44.8 ± 8.6	33.1 ± 13.6	50.3 ± 9.7*	N/A	N/A	N/A
Requena-Ibáñez et al. *2021*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	30.3 ± 4.2	N/A
Pourafkari et al. *2024*	N/A	62.9 ± 15.4	N/A	26.7 ± 9.9	58.4 ± 7	N/A	59.2 ± 10.7	26.4 ± 8.4	N/A	N/A	N/A	N/A
Santos-Gallego et al. *2021*	219.8 ± 75.8	N/A	143.6 ± 66.3	N/A	36.2± 8.2	135.2± 45.2	N/A	N/A	N/A	N/A	N/A	N/A
Satoh et al. *2024*	N/A	70.1 ± 15.3	N/A	29.5 ± 7.5	N/A	N/A	N/A	N/A	N/A	−13.8 ± 2.0	N/A	N/A
Singh et al. *2020*	172.4± 47.7	85.9± 24.1	99.2± 40.7	49.4± 21.3	44.5± 12.4	N/A	69.5± 16.3	49± 18.8	36.6 ± 10.4	N/A	N/A	N/A
Thirunavukarasu et al. *2021*	163 ± 50	86 ± 27	83 ± 45	44 ± 25	52 ± 13	119 ± 33	61 ± 15	30 ± 16	81 ±20	−10 ± 3	25 ± 3	1.285 ± 104

Table 2 (continued)

Study	LVEDV (ml)	LVEDVi (ml/m²)	LVESV (ml)	LVESVi (ml/m²)	LVEF (%)	LVM (g)	LVMi (g/m²)	LAVi (ml/m²)	LVSV (ml)	LVGLS (%)	ECV (%)	T1 (ms)
Verma et al. *2019*	124.1 ± 33	63.3 ± 15.5	53 ± 20.8	27.1 ± 10.5	58 ± 7.5	116.5 ± 26.3	59.3 ± 10.9	N/A	N/A	N/A	N/A	N/A
Wang et al. *2024*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	−12.9 ± 3.4	27.7 ± 2.9	N/A

Categorial variables are given as absolute numbers and percentage, n (%). Continuous variables are given as mean ± standard deviation or * median (IQR, interquartile range)

LVEDV: left ventricular end-diastolic volume; *LVEDVi*: left ventricular end-diastolic volume indexed; *LVESV*: left ventricular end-systolic volume; *LVESVi*: left ventricular end-systolic volume indexed; *LVEF*: left ventricular ejection fraction; *LVM*: left ventricular mass; *LVMi*: left ventricular mass indexed; *ECV*: extracellular volume; *LAVi*: index left atrial volume; *LVSV*: left ventricular stroke volume; *LVGLS*: left ventricular longitudinal strain

For each study, the effect size was defined as the mean difference in the outcome of interest. The standard error (SE) of the mean difference was calculated from the reported change in standard deviation (SD) and sample size. When SDs were not directly reported, they were imputed based on available information according to Cochrane Handbook recommendations [13], using available confidence intervals, p-values from parametric tests of change, or from correlation coefficients. When correlation coefficients were not provided in the study, they were either extracted or imputed based on data from similar studies.

For studies that included a control group (patients not treated with SGLT2i), we extracted the mean difference in CMR parameters from baseline to follow-up separately for treated (a) and untreated (b) patients. The difference between these two changes (a minus b) was calculated to assess the treatment effect attributable to SGLT2i treatment. Measures of variability for these differences were derived accordingly.

Studies without available control group data were included in the pre-versus-post treatment meta-analysis but excluded from between-group comparisons.

Heterogeneity was assessed using the Cochran Q test and quantified with the I^2 statistic, with I^2 values above 50% indicating substantial heterogeneity [14]. Publication bias was evaluated using visual inspection of funnel plots and Egger's regression test, with a p value < 0.10 considered indicative of significant asymmetry.

Sensitivity analyses were performed by excluding one study at a time (leave-one-out analysis) to identify potential sources of heterogeneity and assess the robustness of the pooled effect estimates. A subgroup analysis was conducted stratifying studies by reduced LVEF (< 50%) at baseline. Effect of potential confounders on the pooled estimates for main CMR outcomes were assessed by meta-regression analysis. All statistical analyses were performed using JASP (University of Amsterdam, v. 0.19.3), and a two-tailed p-value < 0.05 was considered statistically significant.

Results

Literature search

The study flow-chart is reported in Fig. 1. Initially, 1,640 articles were identified, with 114 duplicates removed. After screening the titles and abstracts of 464 articles, 45 were selected for full-text evaluation. Ultimately, 23 articles were deemed eligible for quantitative analysis of SGLT2i effects on CMR parameters [15–37]. Four studies [16, 17, 20, 26], were conducted to analyze different parameters (i.e. left ventricular, right ventricular and left atrial) on the same cohort of patients. Similarly, Dihoum et al. [21] performed a sub-analysis of the DAPA-LVH study including a previously unpublished assessment of

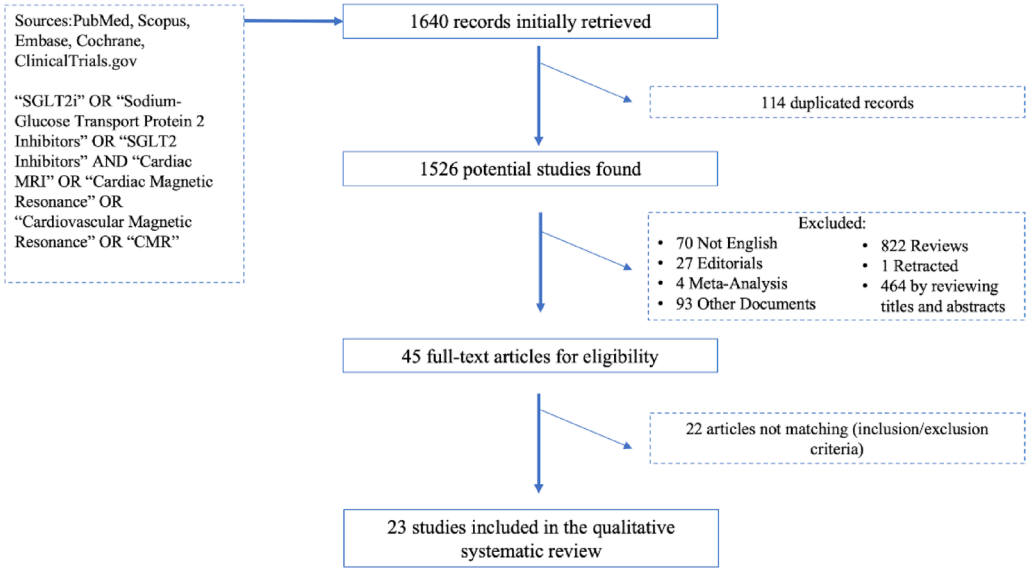

Fig. 1 Study screening flow diagram

Table 3 Other CMR parameters in patients treated with SGLT2i at baseline

Study	RVEDVi (ml/m^2)	RVESVi (ml/m^2)	RVEF (%)	Epicardial fat (cm^3)
Bouchi et al. *2017*	N/A	N/A	N/A	117 (96 – 136)
Fukuda et al. *2017*	N/A	N/A	N/A	102 (79–126)
Hassan et al. *2024*	100 (78,111)	60 (31,79)	38.1 ± 4.1	N/A
Hsu et al. *2019*	N/A	N/A	N/A	32.3 (5.7–82.8)
Requena-Ibáñez et al. *2021*	N/A	N/A	N/A	
Sarak et al. *2021*	62 ± 13.2	28.9 ± 6.5	53.2 ± 4.9	N/A
Satoh et al. *2024*	79 ± 16.9	36.4 ± 16.1	N/A	N/A
Thirunavukarasu et al. *2021*	79 ± 19	38 ± 15	53 ± 9	N/A

Categorial variables are given as absolute numbers and percentage, n (%). Continuous variables are given as mean ± standard deviation or * median (IQR, interquartile range)

RVEDVi: right ventricular end-diastolic volume indexed; *RVESVi:* right ventricular end-systolic volume indexed; *RVEF:* right ventricular ejection fraction

Left Ventricular Global Longitudinal Strain (GLS), while Requena-Ibáñez et al. [18] performed a sub-analysis of the EMPA-TROPISM study on EAT and ECV values; these studies have been included in the analysis and the population overlap was taken into account when summarizing main results (Table 1).

Study characteristics

A total of 1008 patients (74% males; mean age ± SD equal to 62 ± 11 years) undergoing baseline and follow-up CMR [median follow-up of 180 days [IQR: 96 days]) were included for quantitative analysis. Among them, 553 (55%) patients were treated with SGLT2i and 455 (45%) patients were not. Main CMR characteristics are summarized in Tables 2 and 3.

The smallest study had a population of 9 patients [27] and the largest 169 [30]. Fifteen studies [15–20, 22, 25, 26, 29–31, 33, 35, 37], included patients treated with empaglifozin, six studies with dapaglifozin [21, 23, 24, 32, 34, 36], one with ipraglifozin [27] and one with luseoglifozin [28]. Six studies [15, 19, 22, 24, 25, 32] included patients with reduced LVEF at baseline. Six studies [27, 28, 32, 33, 35, 36] did not report data for a control group and were therefore analyzed as single-arm cohorts.

Meta-analyses

Effects on left heart volumes, mass, and function

Treatment with SGLT2i was associated with a significant reduction in LVEDV (−7.10 mL [95% CI: −13.01, −1.19]; 10 studies, I^2 = 69%, p = 0.023), whereas no significant changes were observed in LVESV (−5.97 mL [95% CI: −13.80, 1.87]; 8 studies, I^2 = 80%, p = 0.115), LVEDVi (−0.53 mL/m^2 [95% CI: −3.24, 2.18]; 10 studies, I^2 = 46%, p = 0.668), LVESVi (−1.09 mL/m^2 [95% CI: −2.94, 0.75], 9 studies, I^2 = 40%, p = 0.213), LVEF (1.14% [95% CI: −0.39, 2.68]; 14 studies, I^2 = 80%, p = 0.133) (Figs. 2 and 3), and GLS (−0.16% [95% CI: −2.67, 2.35]; 5 studies, I^2 = 83%, p = 0.878). A non-significant trend towards increase in LVSV was observed (1.41 ml [95% CI: −0.12, 2.94]; 4 studies, I^2 = 0, p = 0.063, Supplementary Fig. 1). A significant decrease in LVM was observed (−4.24 g [95%

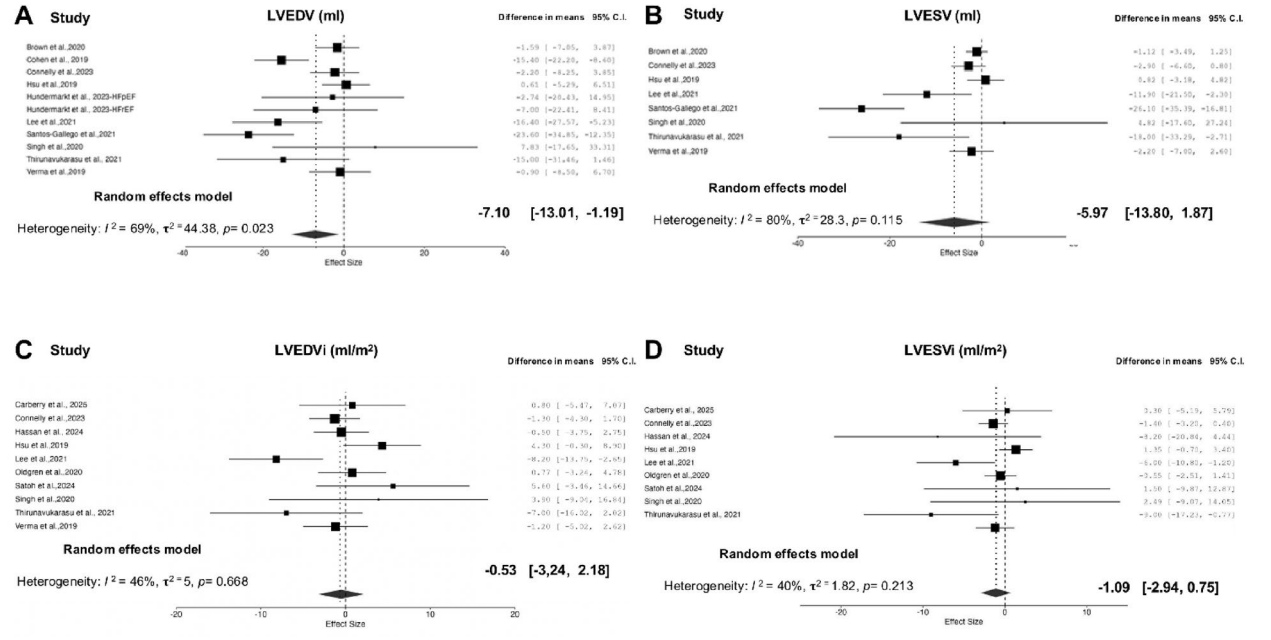

Fig. 2 Effect of SGLT2i on cardiac imaging parameters measured by CMR. Forest plots: meta-analyses on LVEDV (**A**), LVESV (**B**), LVEDVi (**C**) and LVESVi (**D**). Effect sizes: differences in means between baseline and follow-up measurements. LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEDVi: left ventricular end-diastolic volume indexed; LVESVi: left ventricular end-systolic volume indexed

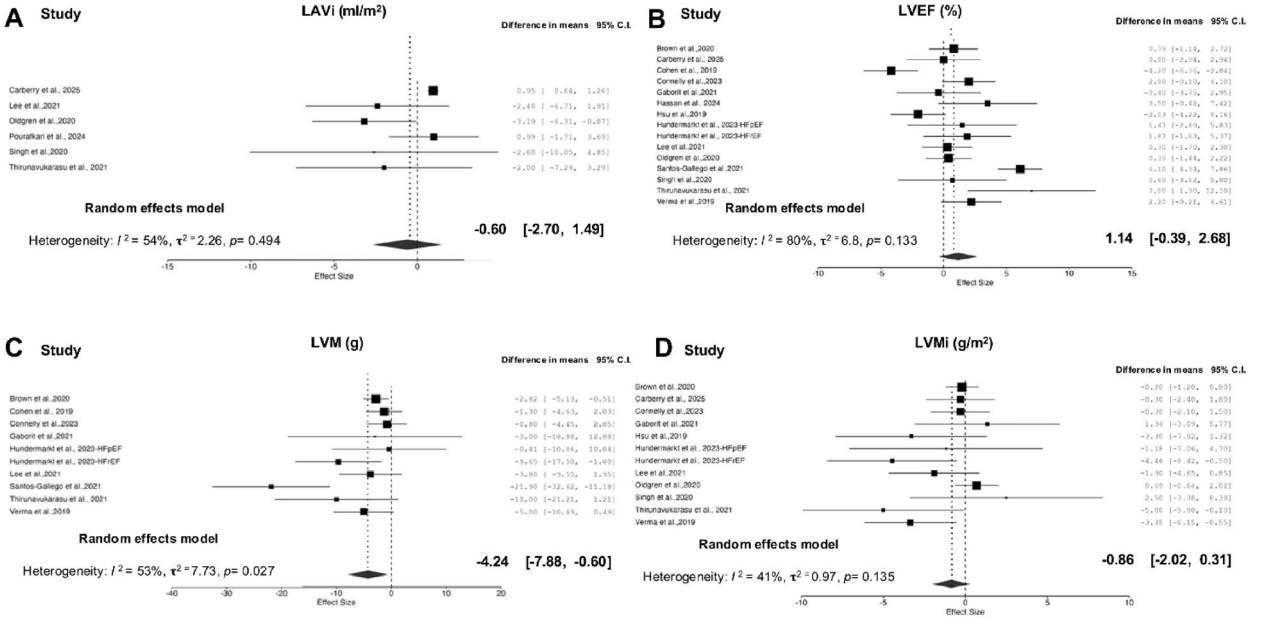

Fig. 3 Effect of SGLT2i on cardiac imaging parameters measured by CMR. Forest plots: meta-analyses on LAVi (**A**), LVEF (**B**), LVM (**C**) and LVMi (**D**). Effect sizes: differences in means between baseline and follow-up measurements. LAVi: left atrial volume indexed; LVEF: left ventricular ejection fraction; LVM: left ventricular mass; LVMi: left ventricular mass indexed

CI: −7.88, −0.60]; 9 studies, I^2 = 53%, p = 0.027), while LVMi showed no significant change (−0.86 g/m² [95% CI: −2.02, 0.31]; 11 studies, I^2 = 41%, p = 0.135). There was no significant change in LAVi values (−0.60 mL/m² [95% CI: −2.70, 1.49]; 6 studies, I^2 = 54%, p = 0.494) (Fig. 3).

Effects on right heart volumes and function

Both RVEDVi and RVESVi remained unchanged (−0.03 mL/m² [95% CI: −2.54, 2.49]; 4 studies, I^2 = 0%, p = 0.975; −0.31 mL/m² [95% CI: −1.61, 0.99]; 4 studies, I^2 = 0%, p = 0.502, respectively). No effect was also noted on RVEF (1.29% [95% CI: −1.33,3.92]; 3 studies, I^2 = 40%, p = 0.502) (Supplementary Fig. 2).

Effects on tissue characterization

There were no differences in ECV (−0.27% [95% CI: −1.16, 0.61]; 8 studies, I^2 = 78%, p = 0.547), or T1 mapping (4.6 ms [95% CI: −14.97, 24.17]; 4 studies, I^2 = 74%, p = 0.645). (Supplementary Fig. 1).

Effect on epicardial adipose tissue

There was a significant reduction in EAT after SGLT2i (− 4.94 mL [95% CI: −9.06, −0.82]; 4 studies, I^2 = 0%, p = 0.019). (Supplementary Fig. 2).

Effects in patients with heart failure

In patients with LVEF at baseline < 50%, LVSV increased significantly (1.83 mL [95% CI: 0.86, 2.80]; 2 studies, I^2 = 0%, p = 0.027). A non-significant trend towards increase in LVEF was also noted (2.61% [95% CI: −0.50, 5.70]; 5 studies, I^2 =80%, p = 0.08). No significant differences were observed for the other parameters.

Effects in patients with diabetes

In patients with diabetes, there was a significant reduction in LVM (−4.61 g [95% CI: − 8.59, − 0.63]; 3 studies, I^2 = 0%, p = 0.024). EAT also decreased significantly (−5.14 mL [95% CI: − 9.94, 0.95]; 3 studies, I^2 = 0%, p = 0.036). No significant differences were found for LVEDV, LVESV, LVMi, LVEF, or ECV.

Sensitivity analysis

A sensitivity analysis including only studies with a control group (n = 15) was conducted, confirming both the decrease in LVEDV (− 7.73 mL [95% CI: −14.68, − 0.78]; I^2 = 70.4%, p = 0.033) and LVM (− 3.96 g [95% CI: −7.84, − 0.08]; I^2 = 55.4%, p = 0.047). Leave one-out analyses were performed to assess the robustness of the meta-analytic estimates across all imaging-derived parameters; for LVEDV, pooled effect estimates ranged from − 5.38 to − 8.23 mL, with all but one iteration (Cohen et al. [29], p = 0.064) maintaining statistical significance; heterogeneity varied between 59.5% and 75.5%, indicating moderate-to-high between-study variability. No single study exerted a disproportionate influence on the overall estimate. In contrast, LVESV analysis revealed greater sensitivity to individual studies, with a significant drop in heterogeneity when removing Santos-Gallego et al. [15] (I^2 = 46.5%). For indexed LV volumes (LVEDVi and LVESVi), all iterations produced non-significant results. While effect sizes remained consistently small, heterogeneity decreased substantially when Lee et al. [25] (LVEDVi I^2 = 10.0%) or Hsu et al. [33] (LVESVi I^2 = 17.7%) were excluded. The analysis of LVM demonstrated consistent effect estimates across all exclusions (range: − 2.73 to − 5.02 g), with all the iterations but Hundermarkt et al. [19] (p = 0.065) retaining statistical significance. Heterogeneity varied modestly, with Santos-Gallego et al. [15] being a key contributor (I^2 = 0% upon exclusion). For LVEF, removal of Cohen et al. [29] yielded a statistically significant result (p = 0.029), with heterogeneity remaining steadily high across all iterations. For LVSV, statistical significance was observed upon exclusion of Brown et al. [23] (p = 0.014, mean difference 1.88) and heterogeneity remained null across all exclusions. Both LVMi and LAVi analyses revealed non-significant effects with moderate, stable, heterogeneity for LVMi (I^2 range: 30.3–46.3%) and notable reduction in heterogeneity after the exclusion of Oldgren et al. [34] (I^2 = 7.9%) or Carberry et al. [22] (I^2 = 12.9%) for LAVi (Supplementary Table 3).

Meta-regression analyses

At meta-regression analyses, none of the predictors included in the model (i.e., age, male sex and diabetes) revealed a significant effect modification on LVEDV, LVESV, LVEDVi, LVESVi, LVEF, LAVi, LVM, LVMi (all p-values > 0.05). Meta-regression analyses were not performed on other CMR parameters due to the limited number of studies available.

Publication bias and grading of evidence

Funnel plots were visually inspected for asymmetry and assessed using Egger's regression test across all cardiac structural, functional, and tissue parameters. No substantial visual asymmetry was observed for most outcomes, except for ECV and LAVi. Egger's test results statistically confirmed possible publication bias for both parameters (p = 0.04 and 0.031, respectively) (Fig. 4 and Supplementary Fig. 3).

According to the GRADE Working Group system [38], the level of certainty for the association between SGLT2i treatment and CMR outcomes was moderate for most outcomes but in 7, in which were adjudicated to be low (Supplementary Table 4).

Discussion

The present updated systematic review and meta-analysis demonstrated an association between SGLT2i treatment and decrease of LVEDV and LVM, providing evidence for favorable effects on cardiac remodeling. These results were confirmed in a sensitivity analysis including only studies with control group and were not affected by baseline patient characteristics including age, sex and diabetes. Patients with reduced LVEF also showed a significant, although modest, increase in LVSV after SGLT2i treatment.

Our data on favorable LV remodeling are in line with a previous meta-analysis including 9 randomized controlled trials (3 of which were CMR-based) demonstrating a significant reduction in LV volumes and indexed LV mass with significant increase in LVEF in the whole population [39]. However, the use of different imaging

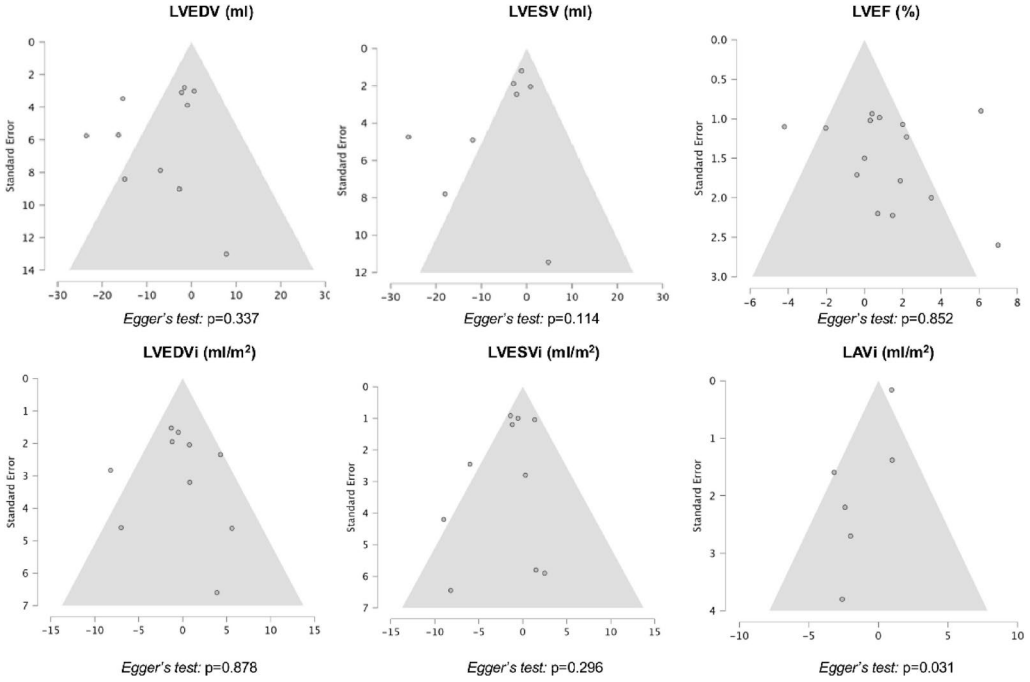

Fig. 4 Evaluation for publication bias. Funnel plots with 95% confidence intervals for LVEDV, LVESV, LVEF on the top, LVEDVi, LVESVi, LAVi on the bottom. LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEDVi: left ventricular end-diastolic volume indexed; LVESVi: left ventricular end-systolic volume indexed; LVEF: left ventricular ejection fraction; LAVi: left atrial volume indexed

modalities to assess cardiac remodeling in that study may have introduced variability and potentially obscured subtle treatment effects. CMR is in fact considered the gold standard for quantifying ventricular volumes, mass, and tissue characterization, offering superior spatial resolution and interobserver consistency [40, 41]. In contrast, echocardiography is more widely available and used in clinical practice but is subject to greater operator dependence and geometric assumptions, that may be unneglectable particularly in patients with abnormal ventricular shapes [42].

A recent meta-analysis [43] focusing only on CMR studies ($n = 5,408$ patients) was able to confirm only LVM regression after SGLT2i administration, likely due to the limited number of studies available at the time of publication. Cardiac remodeling reflects complex molecular and structural changes, involving inflammation, fibrosis, and metabolic dysregulation [5]. Maladaptive remodeling is associated with worse clinical outcomes, and represents one of the main targets of HF therapy [44]. In this regard, SGLT2i have proven in several trials to reduce key cardiovascular endpoints as hospitalizations and HF-related mortality, irrespective of the glycemic status [45–49]. The exact mechanisms subtended to these beneficial effects are not yet fully understood, with different hypothesis generated so far [5].

By blocking glucose reabsorption in the proximal renal tubule, these agents promote glycosuria, reduce insulin levels, and increase glucagon secretion—facilitating lipolysis and fat oxidation, with consequent reduction in visceral adiposity [50]. Moreover, their natriuretic effect determines unloading and suppresses the renin-angiotensin-aldosterone system, with favorable effect on blood pressure [51]. However, these metabolic and hemodynamic changes alone do not fully account for the observed CV benefits. Improvements in endothelial function and arterial stiffness, reduced oxidative stress [52], inflammation [53], vascular resistance [46], and a shift toward more efficient metabolic pathways [5] have been demonstrated in clinical and pre-clinical models and may all contribute to the positive observed effect [54, 55]. In this regard, preclinical studies have demonstrated that SGLT2i administrations prevent cardiac remodeling in mice fed with a high-fat, high sucrose diet, inducing the expression of oxidative phosphorylation and fatty acid metabolism genes [56, 57]. However, Hundertmark et al. [19] found no differences in cardiac energetics—measured by the MRS-derived phosphocreatine-to-ATP ratio—either at rest in patients with HFrEF and HFpEF, or in HFrEF patients during dobutamine stress. Moreover, Hsu et al. [33] failed to demonstrate significant changes in intracardiac triglycerid content. Our meta-analysis demonstrated a significant reduction in EAT; despite different techniques have been used to assess EAT in the studies included in the analysis (whole heart coronary angiography for the study conducted by Fukuda [27] and Bouchi [28] and cine images for the others), the

result is interesting given the established adverse prognostic role of EAT accumulation [58].

We also found no impact of SGLT2i treatment on tissue characterization indices such as T1 mapping and ECV in the whole population; this result should be interpret carefully given the limited number of studies included in the analysis for these parameters, with possible publication bias for ECV [17–19, 25, 32, 33, 35, 36]. Therefore, the reduction in LVM observed following SGLT2i treatment appears to result primarily from LV unloading rather than from a decrease in extracellular volume. However, pre-clinical studies in animal models demonstrated reduced intramyocardial fibrosis after empaglifozin with lower collagen deposition and decreased extracellular volume [5, 55]. Moreover, in some studies a significant reduction in LVM was observed even in the absence of LV unloading [26].

Remarkably, the demonstrated effect on LV volumes may have a significant impact on clinical outcomes; in a pooled analysis, a 10 mL decrease in end-diastolic volume was associated with a 5% relative reduction in the odds of mortality [41]. However, the relationship between changes in LVEDV and symptomatic or functional improvement remains uncertain and heterogeneous across studies. Santos-Gallego et al., [15] demonstrated a reduction in LVEDV after empagliflozin associated with significant improvements in peak oxygen consumption, 6-minute walking test performance, and Kansas City Cardiomyopathy Questionnaire scores. Similarly, Lee et al. [25] demonstrated a significant reduction in LVEDV; however, they found no corresponding improvement in either Kansas City Cardiomyopathy Questionnaire scores or 6-minute walking test performance.

Our study also found no evidence of significant changes in RV volumes and function. This is in line with the results of the post-hoc analysis of the EMPA-HEART CardioLink-6 that failed to demonstrate any impact of empaglifozin treatment on RV parameters (including RV mass) on 90 patients with diabetes and coronary artery disease [16].

Limitations

This study has several limitations. First, the number of included studies for some parameters—particularly right ventricular volumes, strain, and tissue characterization markers—was limited, reducing the statistical power of the analysis. Heterogeneity was also moderate to high for several outcomes, potentially reflecting differences in patient populations, imaging protocols, follow-up durations, and background therapies; the significant heterogeneity in the study populations, which included patients with varying baseline characteristics, may also affect the comparability of results across studies and limits the generalizability of our findings to specific clinical subgroups. Although sensitivity analyses were performed for selected sub-populations, residual confounding cannot be excluded. Therefore, while the observed reductions in LVEDV and LVM are of interest, they should be interpreted with caution and considered hypothesis-generating rather than conclusive evidence of a class effect. Finally, some of the included studies had relatively small sample sizes and were not blinded or randomized, increasing the risk of bias. Prospective studies with standardized CMR endpoints and longer follow-up will certainly provide more information, particularly regarding effects on tissue-level changes.

Conclusions

This meta-analysis demonstrated an association between SGLT2i treatment and reductionsin both LVEDV and LVM. However, these effectswere not confirmed in the sub-group analysis limited to patients with heart failure, while a significant reduction in LVM was observed among patients with diabetes. The heterogeneity of the study populations included in the meta-analysis limits the generalizability of the results; the results should be thus considered hypothesis-generating. Nonetheless, they support the mechanistic hypothesis that reverse left ventricular remodeling may contribute to the cardiovascular benefits observed with SGLT2i therapy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02904-4.

Supplementary Material 1
Supplementary Material 2
Supplementary Material 3
Supplementary Material 4
Supplementary Material 5
Supplementary Material 6
Supplementary Material 7
Supplementary Material 8
Supplementary Material 9

Author contributions

I.L.: conceptualization, statistical analysis, drafting of the main manuscript. N.S.: conceptualization, drafting main manuscript. A.C. and J.I.: systematic review, data extraction, figure preparation. S.F., K.S., S.D.R., S.D, G.C., critical revision of the manuscript.C.B.D. and D.T.: Senior review, and critical revision of the manuscript. All authors contributed to manuscript review and approved the final version.

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Data availability
The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Competing interests
The authors declare no competing interests.

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