SGLT2 inhibitors and cardiac remodelling: a systematic review and meta-analysis of randomized cardiac magnetic resonance imaging trials

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Abstract

Aims Recent large randomized controlled trials (RCTs) have demonstrated efficacy of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in both preventing and treating heart failure (HF). SGLT2i-induced reversal of left ventricular remodelling has been proposed as a mechanism contributing to this effect.

Methods and results We performed a systematic review and meta-analysis of RCTs to compare SGLT2i versus placebo (treatment duration > 3 months) on cardiac remodelling parameters as measured by cardiac magnetic resonance imaging (cMRI) in patients with HF and/or diabetes. The PubMed and ClinicalTrials.gov databases were searched until 15 June 2021. Our primary outcome was change in absolute left ventricular mass (LVM) from baseline to study endpoint. Secondary outcomes included changes in LVM indexed to body surface area, left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and left ventricular ejection fraction (LVEF) from baseline to study endpoint. The Cochrane Collaboration’s tool was used to assess risk of bias. Five studies representing 408 patients were included. SGLT2i was associated with greater LVM regression compared to placebo (MD, −5.76 g; 95% CI, −10.87 g to −0.64 g, I² = 73%; overall effect, P < 0.03; four RCTs). Statistical subgroup differences were not observed in our sensitivity analysis focusing on HF with reduced ejection fraction (P = 0.37) and were observed in our sensitivity analysis focusing on diabetes (P < 0.001). SGLT2i was not associated with statistical changes in LV mass indexed to body surface area (I² = 75%; P = 0.16; five RCTs), LVESV (I² = 87%; P = 0.07; five RCTs), LVEDV (I² = 81%; P = 0.20; five RCTs), nor LVEF (I² = 85%; P = 0.19; five RCTs) versus placebo. Sixty per cent of RCTs had low risk of bias.

Conclusions Sodium-glucose cotransporter-2 inhibitors treatment was associated with a reduction in left ventricular mass as assessed by cMRI.

Keywords SGLT2i; Cardiac magnetic resonance imaging; Cardiac remodelling; Diabetes; HFrEF

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Background

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been shown to prevent incident heart failure in patients with type 2 diabetes and treat heart failure with a reduced ejection fraction (HFrEF) in patients with and without diabetes.1–6 While several mechanisms have been suggested to mediate these benefits,7–9 there has been increasing interest in the effects of these therapies on ventricular reverse remodelling.
Aims

We performed a meta-analysis of randomized controlled trials (RCTs) comparing SGLT2i versus placebo that evaluated changes in left ventricular mass, volumes, and ejection fraction as assessed by cardiac magnetic resonance imaging (cMRI).

Methods

Search strategy and selection criteria

We searched the PubMed and ClinicalTrials.gov databases from inception to 15 June 2021 using groups of keywords for SGLT2i, diabetes mellitus, heart failure, and cardiac
| Baseline characteristics | Brown 2020 | Lee 2021 | Santos-Gallego 2021 | Singh 2020 | Verma 2019 |
|--------------------------|------------|----------|---------------------|------------|------------|
| Age (years)              | 64.25 ± 7.01 | 66.74 ± 6.62 | 68.2 ± 11.7 | 64.2 ± 10.9 | 66.9 ± 7.0 |
| SGLT2i                   | 67.4 ± 6.8  | 66.2 ± 10.6 | 59.9 ± 13.1 | 67.4 ± 6.8 | 64 (57, 69)b |
| Placebo                  | 66.9 ± 13.1 | 69.2 ± 10.6 | 59.9 ± 13.1 | 67.4 ± 6.8 | 64 (56, 72)b |
| Male sex                 | 20 (62.5) | 18 (52.9) | 34 (65.4) | 27 (64) | 18 (64.3) |
| SGLT2i                   | 27 (64) | 27 (64) | 43 (81.1) | 27 (64) | 19 (67.9) |
| Placebo                  | 18 (64) | 18 (64) | 63 (10.6) | 19 (67.9) | 44 (90) |
| BMI (kg/m²)              | 32.30 ± 4.66 | 32.59 ± 4.22 | 30.9 ± 5.9 | 30.4 ± 5.1 | 33.0 ± 5.5 |
| SGLT2i                   | 30.9 ± 5.9 | 30.4 ± 5.1 | 30.9 ± 5.9 | 30.4 ± 5.1 | 32 ± 5.2 |
| Placebo                  | 30 ± 6 | 30 ± 6 | 33.0 ± 5.5 | 32 ± 5.2 | 27.7 ± 4.7 |
| HbA1c (mmol/mol)         | 7.5 ± 1.6% | 7.0 ± 1.4% | 5.8 ± 0.3% | 5.8 ± 0.5% | 7.9 ± 0.8% |
| SGLT2i                   | 7.5 ± 1.6% | 7.0 ± 1.4% | 5.8 ± 0.3% | 5.8 ± 0.5% | 8.0 ± 0.9% |
| Placebo                  | 7.5 ± 1.6% | 7.0 ± 1.4% | 5.8 ± 0.3% | 5.8 ± 0.5% | 8.0 ± 0.9% |
| SBP (mmHg)               | 130.41 ± 9.62 | 127.67 ± 10.65 | 125.8 ± 18.2 | 130.3 ± 21.6 | NR |
| SGLT2i                   | 127.67 ± 10.65 | 125.8 ± 18.2 | 130.3 ± 21.6 | NR | 135 ± 15.4 |
| Placebo                  | NR | NR | NR | 135 ± 15.4 | 132.8 ± 18.8 |
| NYHA class of HF         | NR | NR | NR | 139 ± 15 | 138 ± 15 |
| Class I                  | NR | NR | 0 (0.0) | 0 (0.0) | NR |
| SGLT2i                   | NR | NR | 12 (42.9) | 13 (46.4) | NR |
| Placebo                  | NR | NR | 13 (46.4) | 11 (39.3) | NR |
| Class II                 | NR | NR | 37 (71.2) | 44 (83.0) | NR |
| SGLT2i                   | NR | NR | 13 (46.4) | 11 (39.3) | NR |
| Placebo                  | NR | NR | 3 (10.7) | 4 (14.3) | NR |
| Class III                | NR | NR | 15 (28.8) | 9 (17.0) | NR |
| SGLT2i                   | NR | NR | 3 (10.7) | 4 (14.3) | NR |
| Placebo                  | NR | NR | 0 (0.0) | 0 (0.0) | NR |
| Class IV                 | NR | NR | 0 (0.0) | 0 (0.0) | NR |
| Baseline LVM (g)         | 126.47 ± 20.54 | 121.61 ± 24.20 | 121.2 ± 36.5 | 131.9 ± 44.9 | NR |
| SGLT2i                   | 121.61 ± 24.20 | 121.2 ± 36.5 | 131.9 ± 44.9 | NR | NR |
| Placebo                  | 135.2 ± 45.2 | 131.8 ± 54.4 | 135.2 ± 45.2 | 131.8 ± 54.4 | NR |
| Baseline LVMi (g/m²)     | 60.92 ± 7.76 | 59.04 ± 8.73 | 61.2 ± 16.1 | 65.4 ± 19.6 | NR |
| SGLT2i                   | 59.04 ± 8.73 | 61.2 ± 16.1 | 65.4 ± 19.6 | NR | NR |
| Placebo                  | 67.9 ± 17.8 | 65.9 ± 19.8 | 67.9 ± 17.8 | 65.9 ± 19.8 | NR |
| Baseline LVEDV (mL)      | 37.17 ± 9.92 | 33.63 ± 11.13 | 157.5 ± 68.1 | 152.9 ± 58.4 | NR |
| SGLT2i                   | 33.63 ± 11.13 | 157.5 ± 68.1 | 152.9 ± 58.4 | NR | NR |
| Placebo                  | 143.6 ± 66.3 | 135.1 ± 54.8 | 143.6 ± 66.3 | 135.1 ± 54.8 | NR |
| Baseline LVEF (%)        | 127.63 ± 22.54 | 120.66 ± 25.29 | 224.8 ± 72.2 | 222.7 ± 60.1 | NR |
| SGLT2i                   | 120.66 ± 25.29 | 224.8 ± 72.2 | 222.7 ± 60.1 | NR | NR |
| Placebo                  | 219.8 ± 75.8 | 210.4 ± 68.9 | 219.8 ± 75.8 | 210.4 ± 68.9 | NR |
| Baseline LVEF (%)        | 71.31 ± 5.42 | 72.54 ± 6.27 | 31.7 ± 9.5 | 33.0 ± 9.5 | NR |
| SGLT2i                   | 72.54 ± 6.27 | 31.7 ± 9.5 | 33.0 ± 9.5 | NR | NR |
| Placebo                  | 36.2 ± 8.2 | 36.5 ± 8.2 | 44.5 ± 12.4 | 46.5 ± 11.7 | NR |

Data are mean ± SD, n (%) except where otherwise specified.

BM, body mass index; cMRI, cardiac magnetic resonance imaging; HbA1c, haemoglobin A1c; HF, heart failure; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMi, indexed left ventricular mass; LVESV, left ventricular end systolic volume; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

Indexed to body surface area.

Age provided as median (IQR) for this study.

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morphology and function. The search strategies are provided in Supporting Information, Appendix S1. A manual search of the reference lists of all included studies and relevant reviews was also conducted. Our search was limited to publications in the English language. The inclusion criteria were: 1) study design, randomized controlled trial; 2) population, patients with diabetes or heart failure; 3) intervention, SGLT2i therapy vs. placebo; 4) outcomes, reporting any of our primary or secondary outcomes; 5) length of treatment, intervention duration of at least 3 months. A flowchart outlining the study selection process is provided in Supporting Information, Figure S1.

Outcomes

The primary outcome was change in left ventricular mass (LVM) from baseline to study endpoint as measured by cMRI. Secondary outcomes included changes in LVM indexed to body surface area (LVMi), left ventricular end systolic volume

Figure 1  Cardiac magnetic resonance imaging-assessed changes in left ventricular mass (A) and left ventricular mass indexed to body surface area (B) from baseline to study endpoint in randomized controlled trials of patients treated with sodium glucose transporter-2 inhibitor therapy versus placebo.

A Left Ventricular Mass

| Study or Subgroup | SGLT2I | Placebo | Mean Difference |
|-------------------|--------|---------|----------------|
| Patients with HF/EF |       |         |                |
| Lee 2021          | -5.1   | 12.7    | 14.8           |
| Santos-Galego 2021| -17.8  | 31.9    | 41.8           |
| Subtotal (95% CI) | 80     | 88      | -11.65 [-30.52, 7.23] |

Heterogeneity: Tau² = 165.38; Chi² = 9.38; df = 1 (P = 0.002); I² = 89%
Test for overall effect: Z = 1.21 (P = 0.23)

| Study or Subgroup | SGLT2I | Placebo | Mean Difference |
|-------------------|--------|---------|----------------|
| Patients without HF/EF |       |         |                |
| Brown 2020        | -3.95  | 4.95    | 8.9           |
| Verma 2019        | -4.7   | 15.4    | 20.1           |
| Subtotal (95% CI) | 76     | 80      | -3.04 [-5.14, -0.94] |

Heterogeneity: Tau² = 0.00; Chi² = 0.24; df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.83 (P = 0.005)

Total (95% CI) 196 196 100.0% -5.76 [-10.87, -0.64]

B Left Ventricular Mass Indexed to Body Surface Area

| Study or Subgroup | SGLT2I | Placebo | Mean Difference |
|-------------------|--------|---------|----------------|
| Patients with HF/EF |       |         |                |
| Lee 2021          | -2.7   | 5.1     | 7.8            |
| Santos-Galego 2021| -8.5   | 15.9    | 24.3           |
| Singh 2020        | 4      | 11.1    | 15.1           |
| Subtotal (95% CI) | 198    | 116     | 8.23 [9.20, 3.86] |

Heterogeneity: Tau² = 26.97; Chi² = 11.71; df = 2 (P = 0.003); I² = 85%
Test for overall effect: Z = 2.21 (P = 0.03)

| Study or Subgroup | SGLT2I | Placebo | Mean Difference |
|-------------------|--------|---------|----------------|
| Patients without HF/EF |       |         |                |
| Brown 2020        | -0.58  | 2.29    | 2.87           |
| Verma 2019        | -2.6   | 7.8     | 10.4           |
| Subtotal (95% CI) | 76     | 80      | 2.02 [-0.23, 2.12] |

Heterogeneity: Tau² = 1.68; Chi² = 3.43; df = 1 (P = 0.11); I² = 59%
Test for overall effect: Z = 0.99 (P = 0.32)

Total (95% CI) 198 196 100.0% -1.89 [-4.52, 0.74]
Figure 2  Cardiac magnetic resonance imaging-assessed changes in left ventricular end systolic volume (A), left ventricular end diastolic volume (B), and left ventricular ejection fraction (C) from baseline to study endpoint in randomized controlled trials of patients treated with sodium glucose transporter-2 inhibitor therapy versus placebo.

### A  Left Ventricular End Systolic Volume

| Subgroup | SGLT2 | Placebo | Mean Difference | Mean Difference |
|----------|-------|---------|----------------|----------------|
| Study or Subgroup | Mean [mL] | SD [mL] | Total | Mean [mL] | SD [mL] | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Patients with HFpEF | | | | | | | | | |
| Lew 2021 | -15.1 | 24.2 | 42 | -2.8 | 23.7 | 50 | 19.6% | -12.30 [-22.09, -2.51] | |
| Santos-Gallego 2021 | -26.6 | 20.5 | 38 | -0.5 | 21.9 | 38 | 19.8% | -26.10 [-35.56, -16.56] | |
| Singh 2020 | -8.9 | 32.7 | 28 | -18.8 | 51 | 28 | 8.8% | 9.90 [-12.54, 32.34] | |
| Subtotal (95% CI) | 106 | 116 | 48.2% | -12.30 [-28.41, 3.82] | |
| Heterogeneity: Tau² = 153.13; Chi² = 9.90; df = 2 (p = 0.007); I² = 80% |
| Test for overall effect: Z = 3.50 (p < 0.001) |

| Subgroup | SGLT2 | Placebo | Mean Difference | Mean Difference |
|----------|-------|---------|----------------|----------------|
| Study or Subgroup | Mean [mL] | SD [mL] | Total | Mean [mL] | SD [mL] | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Patients without HFpEF | | | | | | | | | |
| Brown 2020 | -1.86 | 4.3 | 32 | -0.74 | 4.61 | 34 | 26.8% | -1.12 [-3.45, 1.21] | |
| Verma 2019 | -1.9 | 10 | 44 | 0.3 | 13 | 45 | 20.0% | -2.20 [-6.98, 2.58] | |
| Subtotal (95% CI) | 76 | 80 | 51.8% | -1.33 [-4.42, 1.77] | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.16; df = 1 (p = 0.69); I² = 0% |
| Test for overall effect: Z = 1.24 (p = 0.21) |

| Study or Subgroup | SGLT2 | Placebo | Mean Difference | Mean Difference |
|----------|-------|---------|----------------|----------------|
| | Mean [mL] | SD [mL] | Total | Mean [mL] | SD [mL] | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Total (95% CI) | 184 | 196 | 100.0% | -7.56 [-15.66, 0.54] | |
| Heterogeneity: Tau² = 0.30; Chi² = 0.49; df = 2 (p = 0.81); I² = 87% |
| Test for overall effect: Z = 1.83 (p = 0.07) |

| Study or Subgroup | SGLT2 | Placebo | Mean Difference | Mean Difference |
|----------|-------|---------|----------------|----------------|
| Subgroup | Mean [%] | SD [%] | Total | Mean [%] | SD [%] | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Patients with HFpEF | | | | | | | | | |
| Lew 2021 | 1.8 | 5.7 | 42 | 1.2 | 3.8 | 50 | 21.4% | 0.60 [-1.42, 2.62] | |
| Santos-Gallego 2021 | 6.4 | 4.3 | 38 | -0.1 | 3.9 | 36 | 21.0% | 6.16 [-2.20, 7.51] | |
| Singh 2020 | 2.6 | 6.7 | 28 | 1.4 | 6.6 | 28 | 14.7% | 1.20 [-1.14, 5.54] | |
| Subtotal (95% CI) | 108 | 116 | 58.0% | 2.78 [-1.35, 6.90] | |
| Heterogeneity: Tau² = 11.23; Chi² = 16.80; df = 2 (p = 0.002); I² = 68% |
| Test for overall effect: Z = 1.32 (p = 0.19) |

| Subgroup | SGLT2 | Placebo | Mean Difference | Mean Difference |
|----------|-------|---------|----------------|----------------|
| Study or Subgroup | Mean [%] | SD [%] | Total | Mean [%] | SD [%] | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Patients without HFpEF | | | | | | | | | |
| Brown 2020 | 1.45 | 4.08 | 32 | 0.66 | 3.76 | 34 | 21.7% | 0.79 [-1.11, 2.60] | |
| Verma 2019 | 0.72 | 5.1 | 44 | 1 | 6.5 | 46 | 20.3% | -0.28 [-2.69, 2.13] | |
| Subtotal (95% CI) | 76 | 80 | 42.0% | 0.38 [-1.91, 1.87] | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.47; df = 1 (p = 0.49); I² = 0% |
| Test for overall effect: Z = 0.50 (p = 0.62) |

| Study or Subgroup | SGLT2 | Placebo | Mean Difference | Mean Difference |
|----------|-------|---------|----------------|----------------|
| | Mean [%] | SD [%] | Total | Mean [%] | SD [%] | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Total (95% CI) | 194 | 196 | 100.0% | 1.76 [-0.88, 4.37] | |
| Heterogeneity: Tau² = 7.27; Chi² = 26.38; df = 4 (p < 0.001); I² = 85% |
| Test for overall effect: Z = 1.32 (p = 0.19) |

| Study or Subgroup | SGLT2 | Placebo | Mean Difference | Mean Difference |
|----------|-------|---------|----------------|----------------|
| Subgroup | Mean [%] | SD [%] | Total | Mean [%] | SD [%] | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Total (95% CI) | 194 | 196 | 100.0% | 1.76 [-0.88, 4.37] | |
| Heterogeneity: Tau² = 7.27; Chi² = 26.38; df = 4 (p < 0.001); I² = 85% |
| Test for overall effect: Z = 1.32 (p = 0.19) |

### B  Left Ventricular End Diastolic Volume

### C  Left Ventricular Ejection Fraction

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(LVESV), left ventricular end diastolic volume (LVEDV), and left ventricular ejection fraction (LVEF) from baseline to study endpoint as measured by cMRI.

Data extraction and quality assessment

Citations were independently screened by two reviewers (N. K. D. and N. M.) to select studies that met eligibility criteria and abstract data using a structured form which included study design, population characteristics, duration and dose of treatment, and outcomes. Discrepancies were resolved by a third author (C. D. M.). Two reviewers (N. M. and R. V.) assessed quality and risk of bias across the domains of sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting as per the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Risk of bias was graded as either being low, high, or unclear for each respective domain within each study.

Data synthesis

Data from all studies were combined to estimate the mean difference (MD) and 95% confidence interval (CI) for each outcome using an inverse variance approach and DerSimonian and Laird’s random effects-model. Missing data were not imputed. Statistical heterogeneity was tested using an inverse weighted $\chi^2$ test and was quantified by $I^2$, with values $>50\%$ being considered substantial heterogeneity. $P < 0.05$ was considered statistically significant. Publication bias was intended to be assessed by inspection of the funnel plot of the primary outcome; however, this was unable to be done due to too few studies meeting eligibility criteria. We planned a priori sensitivity analyses to evaluate potential differences in treatment effect amongst trials exclusively recruiting patients with HFrEF and trials exclusively recruiting patients with diabetes or prediabetes. All analyses were performed with Review Manager software (version 5.3). The protocol for this systematic review was not registered. This systematic review and meta-analysis adheres to PRISMA guidelines.

Results

Study characteristics and study population

A total of five studies, representing 408 patients, met the eligibility criteria and were included in the meta-analysis (Supporting Information, Figure S1). Table 1 summarizes the characteristics of included studies. The included studies assessed a dose of 10 mg of dapagliflozin or empagliflozin daily, and treatment durations ranged from 36 weeks to 1 year. Three RCTs exclusively enrolled patients with HFrEF, and four RCTs exclusively enrolled patients with diabetes or prediabetes. Sixty per cent of the studies had a low risk of bias in at least five out of the six domains (Supporting Information, Figure S2; justifications are summarized in Supporting Information, Table S2). An overview of relevant baseline patient characteristics and cMRI parameters according to treatment group is provided for each included study in Table 2.

Primary outcome

SGLT2i was associated with a greater regression in LVM relative to placebo (MD, $-5.76$ g; 95% CI, $-10.87$ g to $-0.64$ g, $I^2 = 73\%$; overall effect, $P < 0.03$; four trials; Figure 1A). The test for subgroup differences in our sensitivity analysis focusing on HFrEF did not reveal any differences ($P = 0.37$). We observed subgroup differences in our sensitivity analysis focusing on diabetes, where LVM regression by SGLT2i was larger in magnitude amongst patients without diabetes ($P < 0.001$; Supporting Information, Figure S3A).

Secondary outcomes

There were no significant differences between groups for all secondary outcomes of LVMi (MD, $-1.89$ g/m$^2$; 95% CI, $-4.52$ to $0.74$ g/m$^2$, $I^2 = 75\%$; overall effect, $P = 0.16$; five trials; Figure 1B), LVESV (MD, $-7.56$ mL; 95% CI, $-15.66$ to $0.54$ mL, $I^2 = 87\%$; overall effect, $P = 0.07$; five trials; Figure 1B), LVEDV (MD, $-6.66$ mL; 95% CI, $-16.82$ to $3.49$ mL, $I^2 = 81\%$; overall effect, $P = 0.20$; five trials; Figure 1B), or LVEF (MD, 1.76%; 95% CI, $-0.86$% to $4.37$%; $I^2 = 85\%$; overall effect, $P = 0.19$; five trials; Figure 1C). We observed no subgroup differences for each respective secondary outcome in our sensitivity analyses focusing on HFrEF. The results of our sensitivity analysis focusing on diabetes are presented in Supporting Information, Figures S3 and S4.

Conclusions

In this meta-analysis of double-blind placebo controlled RCTs evaluating left ventricular remodelling by cMRI, we observed that SGLT2i were associated with a significant reduction in left ventricular mass with a consistent benefit observed in people with and without diabetes or HFrEF. Other indices of left ventricular remodelling were not statistically significant, but there was a trend towards reduction in LVESV. The analyses are to be interpreted in the context of limitations including (i) substantial heterogeneity between studies, (ii) relatively small sample sizes amongst included studies, (iii) differing treatment durations across studies, and (iv) inconsistencies in the exact calculations for LVM indexed to body weight.

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Conflict of interest

Nitish K. Dhingra: none declared. Nikhil Mistry: none declared. Pankaj Puar: none declared. Raj Verma: none declared. Stefan Anker: Dr Anker reports grants and personal fees from Vifor International and Abbott Vascular and personal fees from AstraZeneca, Bayer, Brahms, Boehringer Ingelheim, Cardiac Dimensions, Novartis, Occlutech, Servier, and Vifor International. C. David Mazer: Advisory board honoraria from Amgen, AstraZeneca, and Boehringer Ingelheim. Subodh Verma: S.V. holds a Tier 1 Canada Research Chair in Cardiovascular Surgery. S.V. has also received grants and personal fees for speaker honoraria and advisory board participation from AstraZeneca, Bayer, Boehringer Ingelheim, Janssen, Amgen, HLS, Merck, Novartis, Sun Pharmaceuticals, Toronto Knowledge Translation Working Group, Phase Bio. He also serves as President of the Canadian Medical and Surgical Knowledge Translation Research Group.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Justification for Risk of Bias Assessment.
Figure S1. Study Selection.
Figure S2. Risk of Bias Assessment.
Figure S3. Changes in Left Ventricular Mass (Panel A) and Left Ventricular Mass indexed to Body Surface Area (Panel B) from Baseline to Study Endpoint in Randomized Controlled Trials of Patients Treated with Sodium Glucose Transporter-2 Inhibitor Therapy versus Placebo – Sensitivity Analysis Focusing on Diabetes.
Figure S4. Changes in Left Ventricular End Systolic Volume (Panel A), Left Ventricular End Diastolic Volume (Panel B), and Left Ventricular Ejection Fraction (Panel C) from Baseline to Study Endpoint in Randomized Controlled Trials of Patients Treated with Sodium Glucose Transporter-2 Inhibitor Therapy versus Placebo – Sensitivity Analysis Focusing on Diabetes.

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