# SUPPLEMENTAL MATERIAL

## Table S1. Outcome Characteristics.

| Outcomes | Pooled outcomes (95% CI) | No. of patients (no. of included studies) | Statistical heterogeneity | Quality of evidence (GRADE) |
|---|---|---|---|---|
| Composite of cardiovascular death and heart failure hospitalization | RR 0.78 (0.69 to 0.89) | 4,479 (2 studies) | $I^2$ = 0% (*P* = 0.51) | ⊕⊕⊕⊕ |
| Mean change in NT-proBNP (pg/ml) | WMD -104.76 (-282.93 to 73.42) | 2,707 (2 studies) | $I^2$ = 62% (*P* = 0.11) | ⊕⊕⊕⊖[a] |
| Mean change in body weight (kg) | WMD -1.21 (-1.82 to -0.61) | 969 (6 studies) | $I^2$ = 0% (*P* = 0.92) | ⊕⊕⊕⊕ |
| Mean change in BMI (kg/m$^2$) | WMD -0.47 (-0.73 to -0.21) | 600 (4 studies) | $I^2$ = 0% (*P* = 0.98) | ⊕⊕⊕⊕ |
| Mean change in waist circumference (cm) | WMD -1.26 (-3.43 to 0.90) | 408 (2 studies) | $I^2$ = 0% (*P* = 0.66) | ⊕⊕⊕⊕ |
| Mean change in systolic blood pressure (mmHg) | WMD -1.90 (-3.69 to -0.11) | 706 (5 studies) | $I^2$ = 0% (*P* = 0.43) | ⊕⊕⊕⊕ |
| Mean change in diastolic blood pressure (mmHg) | WMD 0.27 (-1.21 to 1.76) | 568 (4 studies) | $I^2$ = 0% (*P* = 0.58) | ⊕⊕⊕⊕ |
| Mean percentage change in HbA1c (%) | WMD -0.09 (-0.25 to 0.07) | 2737 (3 studies) | $I^2$ = 86% (*P* = 0.0009) | ⊕⊕⊖⊖[b] |
| Mean change in fasting plasma glucose (mmol/L) | WMD -0.38 (-0.77 to 0.01) | 130 (2 studies) | $I^2$ = 54% (*P* = 0.14) | ⊕⊕⊖⊖[c,d] |
| Mean change in LDL (mmol/L) | WMD 0.01 (-0.18 to 0.20) | 271 (2 studies) | $I^2$ = 0% (*P* = 0.86) | ⊕⊕⊕⊕ |
| Mean change in eGFR (mL/min/1.73 m²) | WMD -0.85 (-2.25 to 0.56) | 646 (3 studies) | $I^2$ = 0% (*P* = 0.93) | ⊕⊕⊕⊕ |

NT-proBNP, N-Terminal pro B-type Natriuretic Peptide; GRADE, Grades of Recommendation, Assessment, Development and Evaluation; RR, relative risk; WMD, weighted mean difference; ROM, ratio of means.

[a]Downgraded by one level for substantial statistical heterogeneity, but forest plots indicate a consistent direction favouring study-level treatment effect.

[b]Downgraded by two levels for severe statistical heterogeneity.

[c]Downgraded by one level for statistical imprecision.

[d]Downgraded by one level for moderate statistical heterogeneity.

## Table S2. Intervention Characteristics.

| Study | Article | Drug name | Drug dose | Drug frequency | Control group | Length of intervention | Mean length of follow-up |
|---|---|---|---|---|---|---|---|
| Bays 2014[24] | Canagliflozin: effects in overweight and obese subjects without diabetes mellitus | Canagliflozin | 50mg, 100mg, 300mg | Once daily | Placebo | 12 weeks | 12 weeks |
| Gonzalez-Ortiz 2016[25] | Effect of dapagliflozin on visceral adiposity and blood pressure in patients with overweight or obesity without diabetes mellitus | Dapagliflozin | 10 mg | Once daily | Placebo | 3 months | 3 months |
| Hollander 2017[13] | Coadministration of canagliflozin and phentermine for weight management in overweight and obese individuals without diabetes: A randomized clinical trial | Canagliflozin | 300 mg | Once daily | Placebo | 26 weeks | 26 weeks |
| Nassif 2019[26] | Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial | Dapagliflozin | 10 mg | Once daily | Placebo | 12 weeks | 13 weeks |
| Petrie 2020[27] | Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients with Heart Failure with and Without Diabetes | Dapagliflozin | 10 mg | Once daily | Placebo | 18 months (median) | 18 months (median) |
| Cherney 2020[12] | Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, | Dapagliflozin | 10 mg | Once daily | Placebo | 6 weeks | 12 weeks |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | double-blind, crossover trial | | | | | | |
| Diaz-Cruz 2020[28] | Effects of dapagliflozin on blood pressure variability in patients with prediabetes and prehypertension without pharmacological treatment: a randomized trial | Dapagliflozin | 10 mg | Once daily | Placebo | 12 weeks | 12 weeks |
| Packer 2020[10] | Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure (EMPEROR REDUCED) | Empagliflozin | 10 mg | Once daily | Placebo | NIL | 16 months (median) |

**Figure S1. Risk of Bias Graph.**

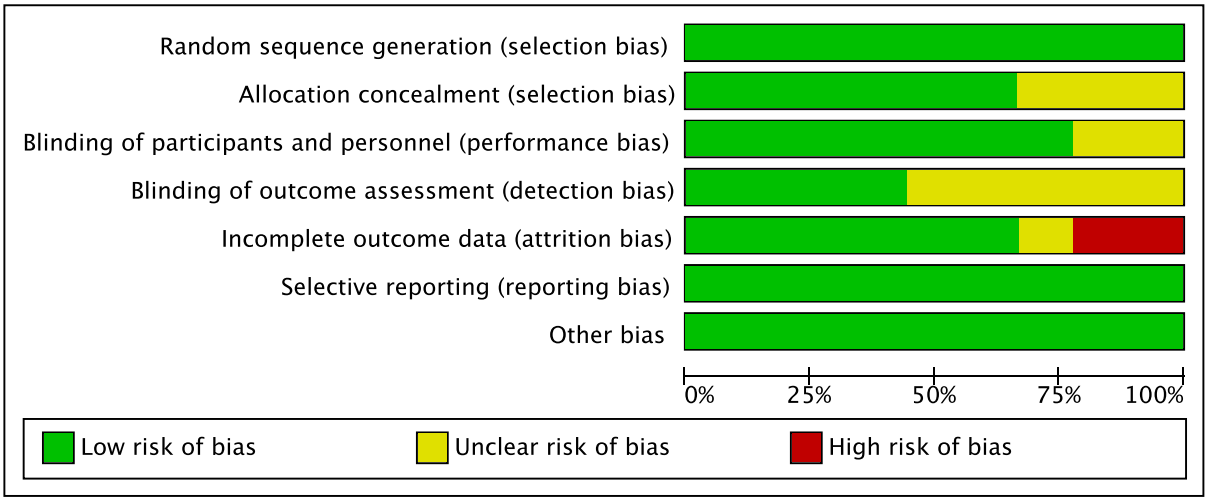

**Figure S2. PRISMA 2009 Checklist**

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3-4 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 5-6 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 6 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | NIL |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 8-9 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 7 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7-8 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 10 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 9-10 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 10 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 10-11 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 10-11 |

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 10 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | NIL |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 12 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 12-13 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 14-15 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 13-14 |
| Synthesis of results | 21 | Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency. | 13-14 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 14-15 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | NIL |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 15-17 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 18-19 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 19 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 19 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097