Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Effect of Hemoglobin A1c Reduction or Weight Reduction on Blood Pressure in Glucagon-Like Peptide-1 Receptor Agonist and Sodium-Glucose Cotransporter-2 Inhibitor Treatment in Type 2 Diabetes Mellitus: A Meta-Analysis

Mengdie Hu, MD; Xiaoling Cai, MD; Wenjia Yang, MD; Simin Zhang, MD; Lin Nie, MD; Linong Ji, MD

BACKGROUND: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) have shown their beneficial effects on cardiovascular outcomes and multiple cardiovascular risk factors, including hypertension. However, the mechanism of blood pressure (BP)–lowering effects of these agents has not been elucidated. This study aims to evaluate the effect of hemoglobin A1c reduction or body weight reduction with GLP-1RA treatment and SGLT2i treatment on BP changes in patients with type 2 diabetes mellitus.

METHODS AND RESULTS: Studies were identified by a search of MEDLINE, EMBASE, and the Cochrane Central Register until June 2019. Meta-regression analysis was performed to evaluate the association between hemoglobin A1c reduction or body weight reduction and changes of BP. A total of 184 trials were included. Both GLP-1RA and SGLT2i led to significant reductions in systolic BP (weighted mean difference, −2.856 and −4.331 mm Hg, respectively; $P<0.001$ for both) and diastolic BP (weighted mean difference, −0.898 and −2.279 mm Hg, respectively; $P<0.001$ for both). For both drug classes, hemoglobin A1c reduction was not independently associated with systolic BP reduction or diastolic BP reduction. In GLP-1RA treatment, weight reduction was positively associated with systolic BP reduction and diastolic BP reduction ($\beta=0.821$ and $\beta=0.287$, respectively; $P<0.001$ for both). In SGLT2i treatment, weight loss was significantly associated with systolic BP reduction ($\beta=0.820$; $P=0.001$) but was not associated with diastolic BP reduction.

CONCLUSIONS: Treatment with GLP-1RA and SGLT2i led to significant reductions in BP in patients with type 2 diabetes mellitus. Weight reduction was significantly and independently associated with BP reductions in GLP-1RA treatment and SGLT2i treatment.

Key Words: blood pressure ■ glucagon-like peptide-1 receptor agonists ■ meta-analysis ■ sodium-glucose cotransporter-2 inhibitors ■ type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is associated with a high risk of macrovascular events and microvascular disease.[1–3] Hypertension is a common comorbidity that affects more than half of patients with T2DM and contributes to the risk of cardiovascular disease and microvascular complications.[4,5] It was demonstrated that optimal blood pressure (BP) control could reduce the risks of all-cause mortality,

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Supplementary material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015323

For Sources of Funding and Disclosures see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- To date, 2 classes of antidiabetic agents, glucagon-like peptide-1 receptor agonist (GLP-1RA) and sodium-glucose cotransporter-2 inhibitor (SGLT2i), have been shown to improve cardiovascular outcomes and multiple cardiovascular risk factors, including hypertension; however, the mechanism of blood pressure (BP)–lowering effects of these drugs has not been fully elucidated.
- Evidence for the association between glycemic control or weight reduction and the BP changes provided a mix of results.
- The effect of hemoglobin A1c reduction or weight reduction on BP changes in GLP-1RA treatment and SGLT2i treatment is evaluated in this study.

What Are the Clinical Implications?

- Weight reduction, not hemoglobin A1c reduction, is positively associated with BP reductions in GLP-1RA treatment and SGLT2i treatment.
- The findings of the present study might offer some insight into the potential mechanism by which GLP-1RA and SGLT2i reduce BP in patients with diabetes mellitus.
- Treatment with GLP-1RA and SGLT2i results in weight loss and BP reduction in patients with diabetes mellitus, and these effects are attractive therapeutic properties in the management of type 2 diabetes mellitus.

Nonstandard Abbreviations and Acronyms

DBP	diastolic blood pressure
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
SBP	systolic blood pressure
SGLT2i	sodium-glucose cotransporter-2 inhibitor
T2DM	type 2 diabetes mellitus
WMD	weighted mean difference

cardiovascular disease, stroke, as well as diabetic retinopathy and albuminuria in patients with T2DM.[6] BP control is therefore an important strategy for improving the prognosis of patients with T2DM.

Two classes of antidiabetic agents, glucagon-like peptide-1 receptor agonists (GLP-1RAs)[7–10] and sodium-glucose cotransporter-2 inhibitors (SGLT2is),[11–13] showed their beneficial effects on cardiovascular outcomes and multiple cardiovascular risk factors, including hypertension. The BP-lowering effects of these 2 agents were established recently,[14–16] but the exact mechanisms accounting for their antihypertensive effects were not elucidated yet. It was suggested that the BP reduction of GLP-1RA treatment and SGLT2i treatment might be in part via weight loss.[17–19] In addition, it was supposed that endothelial dysfunction and arterial stiffness induced by hyperglycemia might be involved in the pathogenesis of hypertension.[20,21] Thus, improvement in glycemic control may indirectly contribute to the BP-lowering effect of these agents.

Previously, a pooled data analysis demonstrated that improved glycemic control and weight reduction was associated with BP reduction in patients with T2DM treated with exenatide.[22] Furthermore, pooled analyses indicated that the weight loss associated with dapagliflozin and canagliflozin contributed to the reduction in systolic BP (SBP).[23,24] However, results from another study found a weak correlation between weight lost and reduction in SBP in exenatide-treated patients.[25] In addition, in a meta-analysis evaluating the effects of SGLT2i on 24-hour ambulatory BP, no significant association was observed between 24-hour ambulatory BP and change in body weight.[26] Some researchers indicated that the BP-lowering effect occurred earlier than any significant weight loss in GLP-1RA treatment[27–29] and SGLT2i treatment,[30] suggesting that the BP reduction may be mediated through mechanisms other than weight loss. To date, evidence for the association between blood glucose changes or weight reduction and the BP changes provided a mix of results.

Therefore, the aim of this meta-analysis is to evaluate the effect of hemoglobin A1c (HbA1c) reduction or body weight reduction on BP changes in GLP-1RA treatment and SGLT2i treatment in patients with T2DM.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Search Strategy

This meta-analysis was conducted according to the approach recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[31] The study protocol is available in the International Prospective Register of Systematic Reviews, PROSPERO (registration Nos. CRD42018108738 and CRD42018105041).

Studies were identified by a literature search of MEDLINE, EMBASE, and the Cochrane Central Register

of Controlled Trials until June 2019. The overall searching strategy was performed using T2DM separately with the following terms: GLP-1RA, albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, taspoglutide, SGLT2i, dapagliflozin, canagliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, ertugliflozin, remogliflozin, and sotagliflozin. Complete details of the search strategy are shown in Data S1.

Study Selection and Data Extraction

Studies were included if they met the following criteria: (1) randomized controlled trials comparing the efficacy and safety of GLP-1RA or SGLT2i with placebo or other antidiabetic agents in participants with T2DM; (2) studies with duration ≥4 weeks; (3) the primary outcome was change in HbA1c, weight, or BP; cardiovascular outcome trials that reported BP changes from baseline were also included; and (4) studies that reported BP changes from baseline with mean difference.

The exclusion criteria were as follows: (1) non–randomized controlled trials; (2) studies in patients with type 1 diabetes mellitus; (3) studies with duration <4 weeks; (3) studies that did not report BP changes from baseline; and (4) studies that did not report SD, SE, or 95% CI of BP changes. Extension studies were excluded from this meta-analysis to minimize the variations.

Two review authors (M.H. and S.Z.) independently performed the data extraction from each publication using a standardized form: publication data (study title, first author, publication year, and source of publication), study design, baseline characteristics of the study population (sample size, sex, age, body mass index [BMI], duration of T2DM, and baseline BP), description of the study drugs and dosages, duration of follow-up, and changes of HbA1c, body weight, SBP, and diastolic BP (DBP) from baseline to study end point. Disagreements or discrepancies were resolved by discussion among the 2 review authors and a third investigator (W.Y.).

Assessment of Methodological Quality

The quality of each study was evaluated according to criteria provided in the Cochrane Handbook.[32] Each trial was judged into low, high, or unclear risk of bias for the following aspects: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.

Statistical Analysis

In this meta-analysis, weighted mean difference (WMD) and 95% CI were calculated using inverse variance weighted random effect model to evaluate the changes of HbA1c, body weight, SBP, and DBP from baseline in GLP-1RA and SGLT2i treatments. For placebo-controlled trials and active-controlled trials, variables compared with placebo or different classes of comparators were also calculated. Meta-regression analysis was performed to evaluate the association between HbA1c reduction or body weight reduction and changes of BP. Confounding factors, including age, sex, BMI, and duration of diabetes mellitus, were adjusted by using multivariable meta-regression analysis. Subgroup analyses were performed by pooling data for each individual GLP-1RA and SGLT2i separately. If trials with >1 intervention group were identified, we determined which treatment groups in the study are relevant to our meta-analysis/subgroup analysis, according to the Cochrane Handbook,[32] and only these treatment groups were used in analyses. The number of observations refers to the number of treatment group (group of participants who receive GLP-1RA or SGLT2i treatment) of studies. The heterogeneity among studies was assessed using the Higgins I^2 statistics. Publication bias was assessed via a visual inspection of the funnel plot and Egger's test. All statistical analyses were conducted using STATA statistical software package, version 14.0.

RESULTS

Search Selection and Characteristics

Details of the study selection process are presented by a flowchart (Figure 1). Finally, a total of 184 studies were included in the meta-analysis, including 89 studies with GLP-1RA treatment and 94 studies with SGLT2i treatment. One study compared the efficacy and safety of coinitiation of the GLP-1RA and SGLT2i with either drug alone.[33] A total of 44 trials compared a GLP-1RA with a placebo, and 85 trials compared a SGLT2i with a placebo.

This meta-analysis was based on data from 61 299 individuals in the GLP-1RA treatment and 40 874 individuals in the SGLT2i treatment. Characteristics of the individuals receiving GLP-1RA treatment and SGLT2i treatment in this meta-analysis were shown in Table S1. The range of age of the patients who received treatment with GLP-1RA and SGLT2i was from 46.7 to 68.0 years and from 50.6 to 70.9 years, with the male percentage ranging from 24.8% to 83.0% and from 28.3% to 83.2%, respectively. The mean SBP level at randomization was 132.30 mm Hg (range, 122–138 mm Hg) in GLP-1RA trials and 131.90 mm Hg (range, 122–151 mm Hg) in SGLT2i trials. Mean DBP level at baseline was 78.66 mm Hg (range, 72.9–84.8 mm Hg) in GLP-1RA trials and 78.89 mm Hg

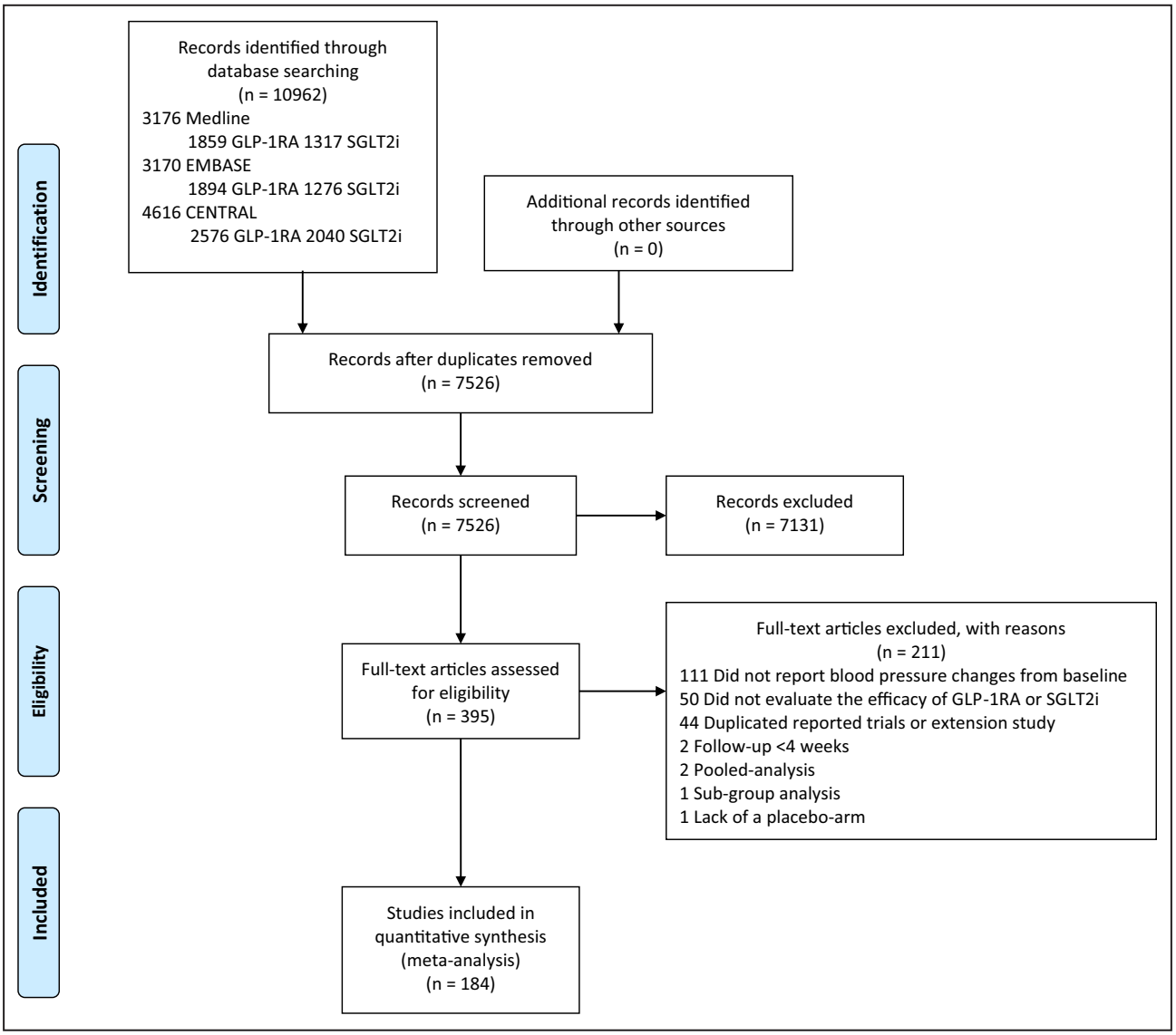

Figure 1. Flowchart of trial identification for meta-analysis.
CENTRAL indicates Cochrane Central Register of Controlled Trials; GLP-1RA, glucagon-like peptide-1 receptor agonist; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

(range, 73.5–91.2 mm Hg) in SGLT2i trials. Clinical characteristics of included studies with GLP-1RA treatment and SGLT2i treatment are presented as Tables S2 and S3. The risk of bias was assessed with the Cochrane Handbook. Details of the quality of bias assessment were shown in Tables S4 and S5.

BP Changes in GLP-1RA Treatment

Analysis of the pooled data across all studies showed that GLP-1RA led to significant decreases in SBP (WMD, –2.856 mm Hg; 95% CI, –3.017 to –2.695 mm Hg; $P<0.001$) and DBP (WMD, –0.898 mm Hg; 95% CI, –1.007 to –0.789 mm Hg; $P<0.001$) from baseline (Figure 2 and Table S6). Compared with placebo, GLP-1RA resulted in a significantly greater decrease in SBP (WMD, –1.724 mm Hg; 95% CI, –2.043 to –1.404 mm Hg; $P<0.001$). GLP-1RA treatment was also associated with a significantly greater reduction in SBP in comparison with insulin treatment (WMD, –2.763 mm Hg; 95% CI, –3.306 to –2.220 mm Hg; $P<0.001$), sulfonylurea treatment (WMD, –2.721 mm Hg; 95% CI, –3.459 to –1.983 mm Hg; $P<0.001$), and dipeptidyl-peptidase-4 inhibitor treatment (WMD, –1.150 mm Hg; 95% CI, –1.657 to –0.644 mm Hg; $P<0.001$). No significant difference in DBP was found when GLP-1RA treatment compared with placebo or active comparator treatment, except for sulfonylureas treatment (WMD, –1.318 mm Hg; 95% CI, –1.944 to –0.693 mm Hg; $P<0.001$). The changes in SBP and DBP with each individual GLP-1RA treatment were

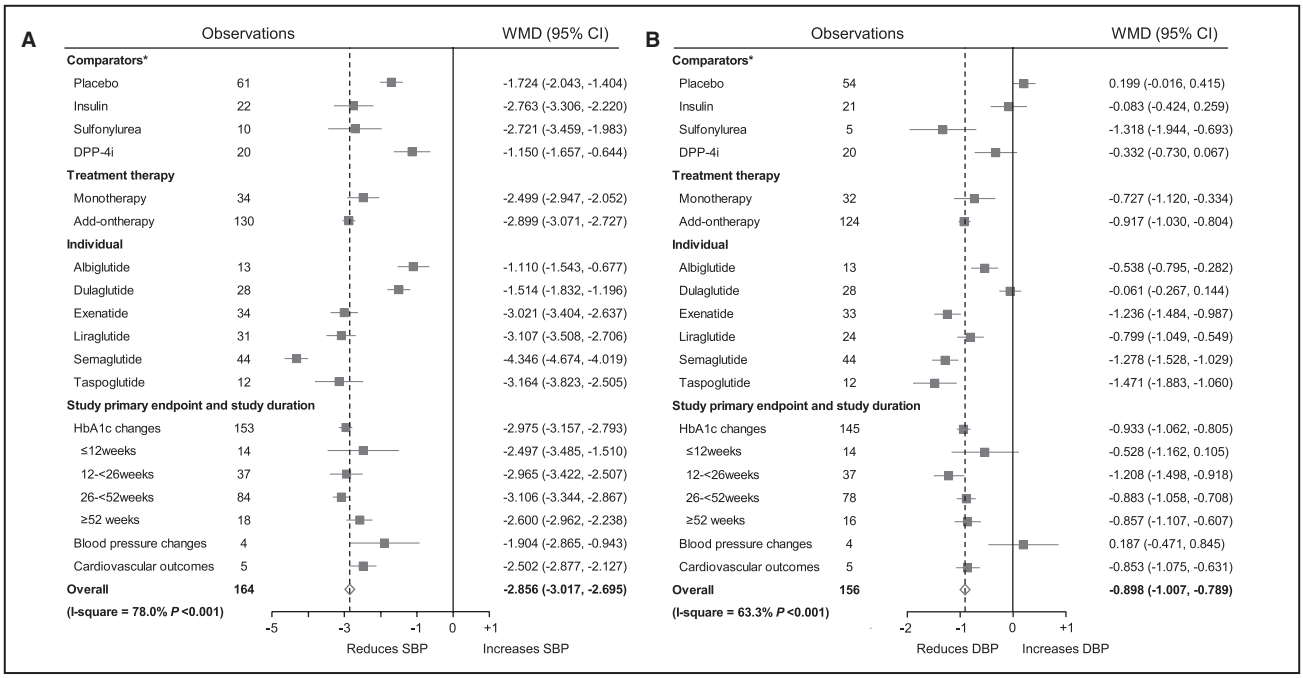

Figure 2. Forest plots of systolic blood pressure (SBP) changes (A) and diastolic blood pressure (DBP) changes (B) in glucagon-like peptide-1 receptor agonist (GLP-1RA) treatment.
*Weighted mean difference (WMD) and 95% CI were calculated for a change from baseline to the study end point for GLP-1RA vs placebo or different classes of comparators. DPP-4i indicates dipeptidyl-peptidase-4 inhibitor; and HbA1c, hemoglobin A1c.

also shown in Table S6. Subgroup analysis stratified by treatment strategy (monotherapy or combination therapy), study duration, and study primary end point showed that the results were similar as the total group, except for DBP changes in studies with BP change as the primary end point (WMD, 0.187 mm Hg; 95% CI, −0.471–0.845 mm Hg; *P*=0.577; Table S7), which may be attributed to the limited number of studies included in this subgroup. Statistical tests for the comparisons of the effect sizes among subgroups were shown in Table S8. HbA1c and weight changes in GLP-1RA treatment were shown in Table S9.

BP Changes in SGLT2i Treatment

Treatment with SGLT2i resulted in significant decreases in SBP (WMD, −4.331 mm Hg; 95% CI, −4.476 to −4.185 mm Hg; *P*<0.001) and DBP (WMD, −2.279 mm Hg; 95% CI, −2.376 to −2.182 mm Hg; *P*<0.001) from baseline (Figure 3 and Table S6). Compared with placebo, SGLT2i treatment led to a significantly greater reduction in SBP (WMD, −3.612 mm Hg; 95% CI, −3.844 to −3.379 mm Hg; *P*<0.001) and led to a significantly greater reduction in DBP (WMD, −1.559 mm Hg; 95% CI, −1.713 to −1.406 mm Hg; *P*<0.001). SGLT2i treatment was also associated with significantly greater decreases in SBP and DBP in comparison with metformin, sulfonylurea, and dipeptidyl-peptidase-4 inhibitor treatment. The changes in SBP and DBP with each individual SGLT2i treatment were also shown in Table S6. No significant differences in BP changes were found by subgroup analysis stratified by treatment strategy (monotherapy or combination therapy) and study duration. The effect of SGLT2i on SBP changes was greater in studies in which the primary end point was changes in BP (WMD, −6.331 mm Hg; 95% CI, −6.853 to −5.809 mm Hg; *P*<0.001; Table S7). The possible reason is that the baseline SBP levels of participants were higher in those studies. Statistical test for the comparisons of the effect sizes among subgroups were shown in Table S8. HbA1c and weight changes in SGLT2i treatment were shown in Table S10.

Effect of HbA1c Change or Weight Reduction on BP Changes in GLP-1RA Treatment

In terms of absolute BP changes, HbA1c change from baseline was significantly associated with SBP reduction (β=2.538; 95% CI, 1.652–3.425; *P*<0.001, adjusted for age, sex, BMI, and duration of diabetes mellitus; Figure 4A) and was also significantly associated with DBP reduction (adjusted β=0.727; 95% CI, 0.226–1.227; *P*=0.005; Figure 4B). In terms of placebo-corrected BP changes, HbA1c reduction was positively associated with placebo-corrected reduction in SBP (adjusted β=3.614; 95% CI, 2.107–5.122; *P*<0.001; Figure S1A) and HbA1c reduction was also positively

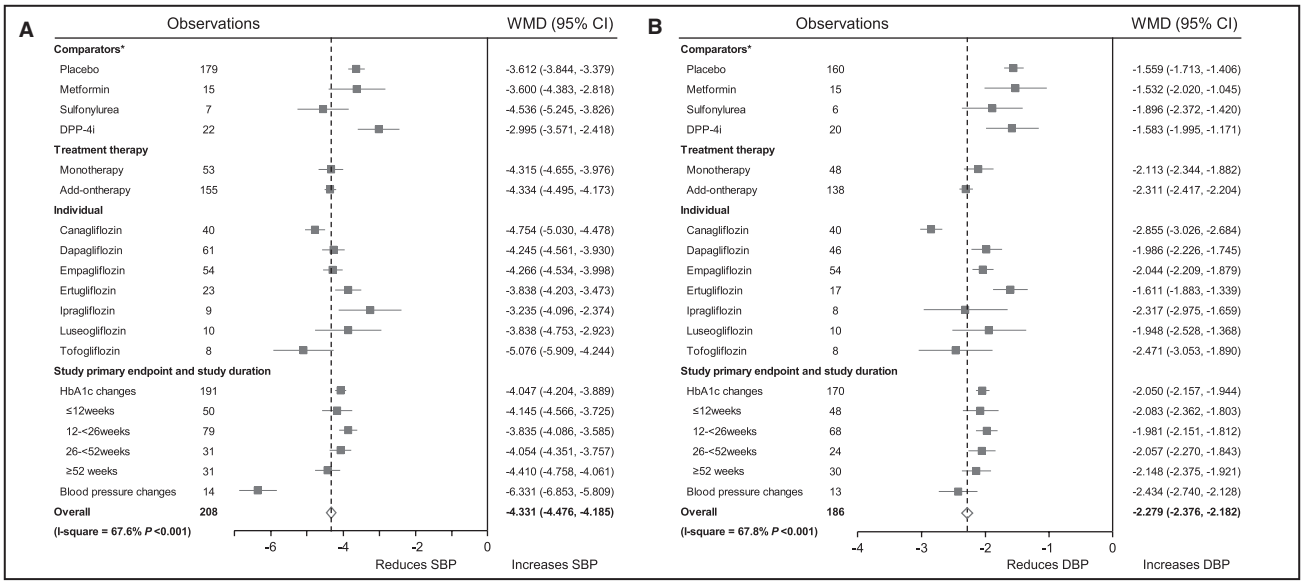

Figure 3. Forest plots of systolic blood pressure (SBP) changes (A) and diastolic blood pressure (DBP) changes (B) in sodium-glucose cotransporter-2 inhibitor (SGLT2i) treatment.
*Weighted mean difference (WMD) and 95% CI were calculated for a change from baseline to the study end point for SGLT2i vs placebo or different classes of comparators. DPP-4i indicates dipeptidyl-peptidase-4 inhibitor; and HbA1c, hemoglobin A1c.

associated with placebo-corrected reduction in DBP (adjusted β=1.397; 95% CI, 0.280–2.515; *P*=0.015; Figure S1B).

Weight change from baseline was significantly associated with net changes in SBP and DPB (adjusted β=0.904 [95% CI, 0.739–1.070] and adjusted β=0.296 [95% CI, 0.196–0.396], respectively; *P*<0.001 for both) in GLP-1RA treatment (Figure 4C and 4D). In terms of placebo-corrected BP changes, weight reduction was positively associated with placebo-corrected SBP reduction with significance (adjusted β=0.523; 95% CI, 0.270–0.776; *P*<0.001), but was not associated with placebo-corrected DBP reduction (Figure S1C and S1D). Details were shown in Table 1 and Figures S1 through S3.

Effect of HbA1c Change or Weight Reduction on BP Changes in SGLT2i Treatment

HbA1c reduction was not associated with SBP reduction or DBP reduction in SGLT2i treatment (Figure 5A and 5B). In terms of absolute BP changes, weight reduction in SGLT2i was positively associated with SBP reduction with significance (adjusted β=0.771; 95% CI, 0.314–1.228; *P*=0.001), but was not associated with DBP reduction (Figure 5C and 5D). In addition, weight change from baseline was significantly associated with SBP reduction in SGLT2i monotherapy (adjusted β=1.211; 95% CI, 0.140–2.283; *P*=0.028), and weight reduction was also significantly associated with SBP reduction in SGLT2i add-on therapy (adjusted β=0.711; 95% CI, 0.204–1.219; *P*=0.007). No significant association was observed between weight reduction and DBP reduction, as either monotherapy or add-on therapy. In terms of placebo-corrected BP changes, weight reduction was associated with placebo-corrected reduction in SBP (adjusted β=0.965; 95% CI, 0.456–1.473; *P*<0.001; Figure S4C) and weight reduction was also associated with placebo-corrected reduction in DBP (adjusted β=0.385; 95% CI, 0.042–0.728; *P*=0.028; Figure S4D). Details were shown in Table 2 and Figures S4 through S6.

Effects of HbA1c and Weight Reduction on BP Changes in GLP-1RA and SGLT2i Treatment

Analyses were conducted to explore the joint effects of HbA1c and weight reduction on BP changes (Table 3). In GLP-1RA treatment, the associations between HbA1c reduction and SBP or DBP reduction became insignificant after further adjustment for weight change (Figure 4A and 4B). Weight reduction was positively associated with SBP reduction (β=0.821; 95% CI, 0.631–1.011; *P*<0.001), and weight reduction was also positively associated with DBP reduction (β=0.287; 95% CI, 0.172–0.403; *P*<0.001), independent of age, sex, BMI, duration of diabetes mellitus, and change in HbA1c (Figure 4C and 4D). In SGLT2i treatment, the effect of weight reduction on SBP change was also significant after adjustment for age, sex, BMI, duration of diabetes mellitus, and HbA1c change from baseline (β=0.820;

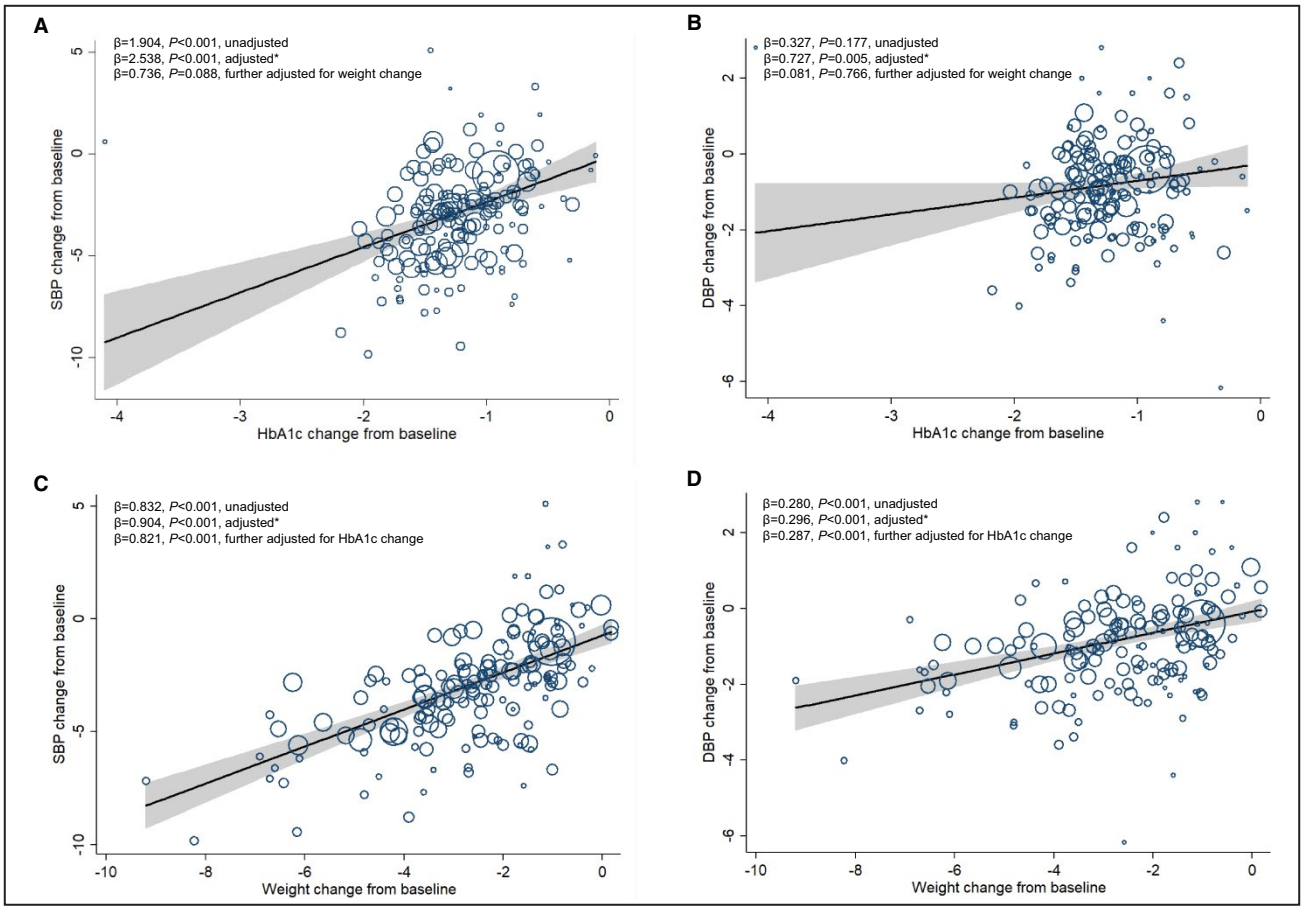

Figure 4. Meta-regression analysis of the associations between hemoglobin A1c (HbA1c) reduction or body weight reduction and blood pressure changes in glucagon-like peptide-1 receptor agonist (GLP-1RA) treatment.
A, Association between HbA1c change from baseline and systolic blood pressure (SBP) change from baseline. **B**, Association between HbA1c change from baseline and diastolic blood pressure (DBP) change from baseline. **C**, Association between weight change from baseline and SBP change from baseline. **D**, Association between weight change from baseline and DBP change from baseline. The size of circles is proportional to the weight of each study in the meta-regression. *Analyses were adjusted for age, sex, body mass index (BMI), and duration of diabetes mellitus.

95% CI, 0.332–1.307; *P*=0.001; Figure 5C). Sex and antihypertensive therapy did not affect the association between weight loss and BP reductions in GLP-1RA treatment and SGLT2i treatment (Tables S11 and S12). When data from GLP-1RA studies and SGLT2i studies were merged into one data set, weight reduction was also positively and independently associated with SBP reduction and DBP reduction (β=0.903 [95% CI, 0.736–1.070] and β=0.375 [95% CI, 0.269–0.482], respectively; *P*<0.001 for both; Figure S7). Taken together, weight reduction was significantly and independently associated with BP reductions in GLP-1RA treatment and SGLT2i treatment.

Publication Bias

The funnel plots for SBP and DBP analysis in GLP-1RA studies were symmetry (Figure S8), but Egger's regression analysis suggested the presence of publication bias in the analysis of DBP (Egger's test *P*=0.044). The funnel plot of SBP changes in SGLT2i studies showed slight asymmetry (Figure S9A), and Egger's regression analysis also detected a potential publication bias (*P*=0.025). No evidence of publication bias was found for DBP analysis in SGLT2i studies by funnel plot or Egger's test (*P*=0.682; Figure S9B). Imputation of possibly unpublished negative studies by trim-and-fill method[34] did not significantly alter the general results, suggesting that the publication bias did not impact the interpretation of the results.

DISCUSSION

To date, among various classes of antihyperglycemic agents, both GLP-1RA and SGLT2i have been shown to improve cardiovascular outcomes in patients with T2DM.[35–37] The cardiovascular benefits of these drugs

Table 1. Effect of HbA1c Reduction or Weight Reduction on BP Changes in GLP-1RA Treatment

Variable	SBP Changes			DBP Changes		
	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value
HbA1c change from baseline, %						
Total	2.538	1.652, 3.425	<0.001	0.727	0.226, 1.227	0.005
Placebo controlled	3.614	2.107, 5.122	<0.001	1.397	0.280, 2.515	0.015
Active controlled	2.392	1.341, 3.443	<0.001	0.580	−0.005, 1.166	0.052
Insulin	1.255	−0.251, 2.761	0.096	0.327	−0.647, 1.302	0.484
Sulfonylurea	2.919	−9.527, 15.365	0.419	…	…	…
DPP-4i	3.491	0.689, 6.292	0.018	0.228	−1.775, 2.232	0.810
Monotherapy	2.144	−0.414, 4.702	0.097	−0.092	−1.653, 1.469	0.904
Add-on therapy	2.598	1.595, 3.600	<0.001	0.790	0.249, 1.331	0.005
Individual						
Albiglutide	4.102	−6.201, 14.405	0.378	1.257	−3.472, 5.987	0.550
Dulaglutide	3.281	0.526, 6.037	0.022	0.570	−0.476, 1.616	0.271
Exenatide	2.105	−0.100, 4.309	0.061	0.362	−1.073, 1.797	0.608
Liraglutide	0.457	−1.453, 2.3681	0.626	0.065	−1.565, 1.695	0.934
Semaglutide	4.290	2.432, 6.148	<0.001	1.186	0.176, 2.196	0.023
Taspoglutide	−2.503	−6.628, 1.621	0.188	−0.141	−2.708, 2.426	0.898
Weight change from baseline, kg						
Total	0.904	0.739, 1.070	<0.001	0.296	0.196, 0.396	<0.001
Placebo controlled	0.523	0.270, 0.776	<0.001	0.036	−0.130, 0.203	0.661
Active controlled	0.876	0.660, 1.093	<0.001	0.264	0.134, 0.395	<0.001
Insulin	0.403	−0.159, 0.965	0.147	0.109	−0.244, 0.463	0.518
Sulfonylurea	0.931	−3.359, 5.221	0.449	…	…	…
DPP-4i	0.733	0.206, 1.259	0.010	0.087	−0.292, 0.466	0.631
Monotherapy	1.114	0.530, 1.698	0.001	0.342	−0.060, 0.744	0.092
Add-on therapy	0.881	0.697, 1.064	<0.001	0.262	0.154, 0.371	<0.001
Individual						
Albiglutide	1.481	−7.048, 10.010	0.694	1.621	−2.208, 5.450	0.350
Dulaglutide	0.710	−0.081, 1.501	0.076	0.170	−0.135, 0.474	0.260
Exenatide	1.811	1.155, 2.468	<0.001	0.610	0.053, 1.167	0.033
Liraglutide	0.277	−0.427, 0.981	0.425	0.151	−0.392, 0.695	0.565
Semaglutide	0.904	0.595, 1.214	<0.001	0.281	0.104, 0.457	0.003
Taspoglutide	0.654	−0.324, 1.632	0.153	0.160	−0.449, 0.769	0.544

Analyses were adjusted for age, sex, body mass index, and duration of diabetes mellitus by meta-regression. BP indicates blood pressure; DBP, diastolic BP; DPP-4i, dipeptidyl-peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; and SBP, systolic BP.

may partly be attributable to their BP-lowering effects. The present meta-analysis showed that weight reduction, not HbA1c reduction, was significantly and independently associated with BP reductions in GLP-1RA and SGLT2i treatment. These results indicated that weight loss contributed to the BP-lowering effects of GLP-1RA and SGLT2i.

The BP-lowering effects of GLP-1RA and SGLT2i have been well documented in clinical trials and previous meta-analyses.[38–42] It has been reported that GLP-1RA treatment was associated with significant reductions in SBP and DBP in comparison with placebo or other antidiabetic drugs.[16,43] Similar results of favorable effects of SGLT2i on BP have also been reported in recent meta-analyses and systematic reviews.[26,44,45]

The exact mechanism responsible for the BP-lowering effects with these agents has not been fully understood. Weight loss may be one of the important factors because evidence in clinical trials and epidemiologic studies showed that weight loss was associated with reduced BP.[46–48] A pooled analysis of 6 randomized controlled trials reported a weak correlation between weight loss and reduction in SBP for exenatide-treated subjects.[25] Similarly, a weak but statistically significant association between weight reduction and SBP lowering was observed in another pooled analysis of randomized controlled trials.[49] Both studies showed that the SBP reduction in GLP-1RA treatment weakly associated with

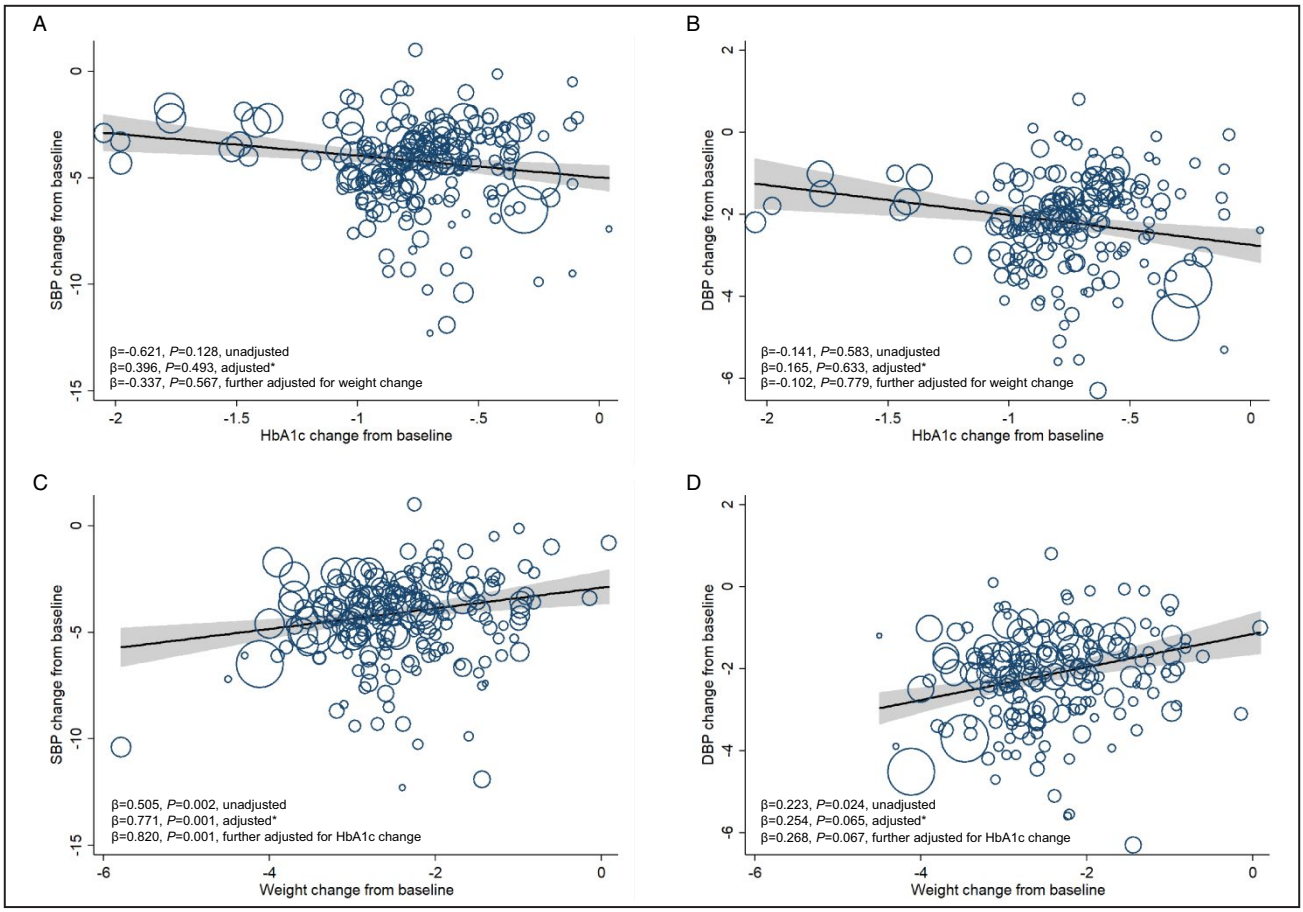

Figure 5. Meta-regression analysis of the associations between hemoglobin A1c (HbA1c) reduction or body weight reduction and blood pressure changes in sodium-glucose cotransporter-2 inhibitor (SGLT2i) treatment.
A, Association between HbA1c change from baseline and systolic blood pressure (SBP) change from baseline. **B**, Association between HbA1c change from baseline and diastolic blood pressure (DBP) change from baseline. **C**, Association between weight change from baseline and SBP change from baseline. **D**, Association between weight change from baseline and DBP change from baseline. The size of circles is proportional to the weight of each study in the meta-regression. *Analyses were adjusted for age, sex, body mass index (BMI), and duration of diabetes mellitus.

weight loss, but both studies included only 6 trials and the relationship was calculated by linear correlation without adjusting for possible confounding factors. In addition, in a meta-analysis of 33 GLP-1RA trials, the degree of SBP change was not related to weight loss or improvement in HbA1c, but trials of patients without T2DM were also included.[50] Paul et al have reported that short-term dynamics of BP in exenatide treatment were related to concomitant effects on glycemia and body weight, demonstrating that improved glycemic control and weight reduction were associated with BP reduction in treatment with exenatide.[22] Meta-regression analysis in our study found that weight reduction was significantly associated with BP lowering in GLP-1RA treatment, even after adjusting for possible confounding factors, including age, sex, BMI, duration of diabetes mellitus, and change in HbA1c, indicating that weight loss may contribute to the BP-lowering effect of GLP-1RA. However, results of the joint effects of HbA1c reduction and weight reduction on BP showed that HbA1c reduction was not correlated with BP changes after adjusting for weight loss. It is likely that glycemic control can be improved by weight loss; therefore, the effect of HbA1c reduction on BP changes may be dependent on reduction in weight.

Some researchers indicated that the BP reductions observed in the clinical trials occurred earlier than any significant weight loss, suggesting that GLP-1RA treatment may provide extra benefits independent of weight loss that lead to BP lowering.[51,52] Vasodilatation and natriuresis mediated by activation of glucagon-like peptide-1 (GLP-1) receptor on cardiovascular and renal tissue likely contribute to the antihypertensive effect.[19,53] A study found that infusion of recombinant GLP-1 improved endothelial function in patients with T2DM and established coronary artery disease.[54] Moreover, infusion of GLP-1

Table 2. Effect of HbA1c Reduction or Weight Reduction on BP Changes in SGLT2i Treatment

Variable	SBP Changes			DBP Changes		
	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value
HbA1c change from baseline, %						
Total	0.396	−0.745, 1.537	0.493	0.165	−0.517, 0.846	0.633
Placebo controlled	−0.237	−1.262, 0.788	0.647	−0.296	−1.005, 0.414	0.410
Active controlled	2.099	−0.256, 4.455	0.078	1.593	−0.036, 3.221	0.055
Metformin	…	…	…	…	…	…
Sulfonylurea	…	…	…	…	…	…
DPP-4i	4.235	−0.735, 9.206	0.086	1.364	−3.183, 5.911	0.501
Monotherapy	0.587	−2.337, 3.510	0.684	0.597	−1.273, 2.467	0.516
Add-on therapy	0.350	−0.850, 1.550	0.564	0.198	−0.546, 0.943	0.597
Individual						
Canagliflozin	−0.412	−2.373, 1.549	0.669	−0.277	−1.275, 0.721	0.572
Dapagliflozin	−0.386	−2.179, 1.407	0.665	−0.303	−1.614, 1.008	0.638
Empagliflozin*	1.059	−0.889, 3.007	0.280	0.574	−0.667, 1.814	0.357
Ertugliflozin	0.870	−1.250, 2.990	0.394	1.891	−1.489, 5.272	0.233
Ipragliflozin	−3.190	−2.651, 2.173	0.773	−3.958	−45.880, 37.964	0.724
Luseogliflozin	13.433	−2.002, 28.868	0.073	6.465	−0.086, 13.016	0.052
Tofogliflozin	−6.672	−36.852, 23.509	0.442	−8.437	−28.661, 11.788	0.215
Weight change from baseline, kg						
Total	0.771	0.314, 1.228	0.001	0.254	−0.016, 0.524	0.065
Placebo controlled	0.965	0.456, 1.473	<0.001	0.385	0.042, 0.728	0.028
Active controlled	0.924	0.052, 1.796	0.039	0.634	−0.035, 1.302	0.062
Metformin	…	…	…	…	…	…
Sulfonylurea	…	…	…	…	…	…
DPP-4i	0.296	−1.504, 2.096	0.714	−0.519	−2.234, 1.196	0.487
Monotherapy	1.211	0.140, 2.283	0.028	0.767	−0.038, 1.572	0.061
Add-on therapy	0.711	0.204, 1.219	0.007	0.238	−0.063, 0.540	0.119
Individual						
Canagliflozin	0.763	−0.226, 1.752	0.125	0.343	−0.175, 0.861	0.184
Dapagliflozin	0.818	−0.054, 1.691	0.065	−0.143	−0.812, 0.526	0.662
Empagliflozin	0.292	−0.263, 0.847	0.295	0.327	−0.035, 0.689	0.076
Ertugliflozin	0.397	−0.642, 1.435	0.426	0.470	−0.847, 1.788	0.434
Ipragliflozin	1.681	−7.405, 10.766	0.597	0.421	−10.693, 11.536	0.885
Luseogliflozin	3.246	0.113, 6.378	0.045	1.365	−0.065, 2.795	0.057
Tofogliflozin	−0.534	−8.765, 7.698	0.806	−2.684	−8.459, 3.092	0.184

Analyses were adjusted for age, sex, body mass index, and duration of diabetes mellitus by meta-regression. BP indicates blood pressure; DBP, diastolic BP; DPP-4i, dipeptidyl-peptidase-4 inhibitor; HbA1c, hemoglobin A1c; SBP, systolic BP; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

*For empagliflozin, analyses were adjusted for age, sex, and body mass index because most of the studies did not report duration of diabetes mellitus.

enhanced acetylcholine-mediated vasodilation.[55] In patients with T2DM, the administration of exenatide was associated with increased plasma concentrations of a series of vasodilator and suppression of renin-angiotensin system.[56] These results indicated a potentially direct benefit on vascular factors of GLP-1 in humans. On the other hand, sustained liraglutide administration increased urinary sodium excretion in hypertensive subjects with T2DM.[57] Similarly, another study observed intravenous infusions of GLP-1 promoted natriuresis in both healthy and insulin-resistant obese men.[58] Therefore, GLP-1–induced natriuresis may provide another mechanism for antihypertensive effect associated with GLP-1RA.

Several studies reported the association between weight reduction and BP changes in treatment with SGLT2i. A previous meta-analysis that involved 6 trials reported SGLT2i significantly reduced 24-hour ambulatory SBP and DBP. However, no significant association between change in body weight and 24-hour BP was observed in the study.[26] Pooled data from placebo-controlled studies in patients with T2DM

Table 3. Effects of HbA1c and Weight Reduction on BP Changes in GLP-1RA and SGLT2i Treatment

Change From Baseline	SBP Changes			DBP Changes		
	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value
GLP-1RA						
HbA1c change, %	0.736	−0.111, 1.584	0.088	0.081	−0.454, 0.616	0.766
Weight change, kg	0.821	0.631, 1.011	<0.001	0.287	0.172, 0.403	<0.001
SGLT2i						
HbA1c change, %	−0.337	−1.501, 0.826	0.567	−0.102	−0.820, 0.616	0.779
Weight change, kg	0.820	0.332, 1.307	0.001	0.268	−0.019, 0.556	0.067

Analysis was performed using meta-regression, with age, sex, body mass index, duration of diabetes mellitus, HbA1c change from baseline, and weight change from baseline as covariates. BP indicates blood pressure; DBP, diastolic BP; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; SBP, systolic BP; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

indicated that weight loss contributed to reductions in BP in treatment with dapagliflozin[24] or canagliflozin.[23] Data from our meta-analysis also support the evidence that weight reduction was positively associated with BP reduction, independent of age, sex, BMI, duration of diabetes mellitus, and HbA1c reduction. However, reductions in BP in SGLT2i treatment were also observed before body weight reductions,[30,59] suggesting that the BP-lowering effect of SGLT2i cannot solely be ascribed to weight loss. Osmotic diuresis and mild natriuresis are thought to be the most likely explanations for the antihypertensive effect of SGLT2i.[59–62] The glucose-based osmotic diuresis leads to an excess urinary output by 110 to 470 mL/d.[63] A 7% reduction in plasma volume was observed in patients with T2DM treated with dapagliflozin, indicating the diuretic-like capacity of dapagliflozin possibly resulted from enhanced sodium excretion or osmotic diuresis.[64] In addition, reduction in arterial stiffness induced by SGLT2i might also play a part in BP lowering.[65,66] Further studies are needed to elucidate the underlying mechanism by which GLP-1RA and SGLT2i reduce BP in patients with T2DM.

In the current analysis, there was a greater effect of GLP-1RA and SGLT2i on SBP compared with DBP. The differential effects may be attributed to the mechanism for the antihypertensive actions of both drugs. In the present study, we demonstrated that weight loss was associated with BP reductions in GLP-1RA treatment and SGLT2i treatment. A difference in response in SBP compared with DBP to weight reduction was observed in previous meta-analysis, in which the effects of weight loss appear to be larger on SBP than on DBP.[46,67] Moreover, the BP-lowering effects of GLP-1RA treatment and SGLT2i treatment are thought to be partly mediated through enhanced urinary sodium excretion. The magnitude of the association between serum sodium levels and SBP was greater than DBP.[68] Wannamethee et al[69] found a positive association between serum sodium and SBP in hypertensive individuals. Although there was also a slight tendency for DBP to increase with increasing serum sodium, the trend was not significant. Another possible explanation of these finding is that the plasma volume reduction resulting from the increase in urinary glucose excretion induced by SGLT2i[62,70] and the relative reduction in intravascular volume resulting from vasodilation induced by GLP-1RA[71,72] would be more likely to result in reductions in SBP compared with DBP.

Our meta-analysis involved a substantial number of placebo-controlled trials and active-controlled trials for GLP-1RA or SGLT2i treatment. With data from 61 299 individuals in the GLP-1RA treatment and 40 874 individuals in the SGLT2i treatment, our analysis provided sufficient power to evaluate the effect of HbA1c reduction or weight reduction on BP changes in patients with T2DM receiving GLP-1RA treatment and SGLT2i treatment. However, we acknowledge several limitations of our study. First, there was some moderate level of heterogeneity across studies, which may influence the interpretation of the results. Data from separate studies were combined for analysis. Baseline characteristic, agent dosage, and duration of follow-up varied across studies, which may cause a high level of heterogeneity. Confounding factors, such as the presence or absence of hypertension diagnosis in the study population, the background antihypertensive therapies, and changes in medication during the course of trial, were not available in many of the included studies, which might be another possible explanation for the heterogeneity. Second, most of the included studies were clinical assessment of efficacy of GLP-1RA and SGLT2i treatment. Therefore, glycemic control was the primary end point in most of the studies and changes of BP were typically reported as safety outcomes or secondary outcomes. Third, the association examined by meta-regression analysis may not be interpreted as a causal effect. Last, funnel plot analysis suggested the presence of publication

bias. Although we used trim-and-fill method to further assess the impact of publication bias, our results should be interpreted with caution.

CONCLUSIONS

Treatment with GLP-1RA and SGLT2i led to significant reductions in BP in patients with T2DM. Weight reduction was significantly and independently associated with BP reductions in GLP-1RA treatment and SGLT2i treatment. These results indicated that weight loss contributed to the BP-lowering effects of GLP-1RA and SGLT2i. Further studies are needed to elucidate the underlying mechanism of the BP-lowering effects of these 2 drugs and its potential impact on cardiovascular outcomes.

ARTICLE INFORMATION

Received November 20, 2019; accepted March 2, 2020.

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Acknowledgments

Design of this meta-analysis: Drs Cai and Ji study selection and data extraction: Drs Hu, Yang, Zhang, and Nie; statistical analyses: Drs Cai and Hu; manuscript writing: Drs Hu, Cai, Zhang, and Ji. All authors contributed to the manuscript drafts and gave final approval for this manuscript.

Sources of Funding

This meta-analysis was supported by grants from the National Key Research and Development Program of China (2016YFC1304901) and the National Natural Science Foundation of China (81970698, 81970708). The funding agencies had no role in the study design, data collection or analysis, decision to publish, or preparation of the manuscript.

Disclosures

Dr Ji has received fees for lecture presentations from AstraZeneca, Merck, Novartis, Lilly, Roche, Sanofi-Aventis, and Takeda. Dr Ji has received consulting fees from companies including AstraZeneca, Merck, Novartis, Lilly, Roche, Sanofi-Aventis, and Takeda. Dr Ji has received grants/research support from AstraZeneca, Bristol-Myers Squibb, Merck, Novartis, and Sanofi-Aventis. The remaining authors have no disclosures to report.

Supplementary Materials

Data S1
Tables S1–S12
Figures S1–S9
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REFERENCES

1. Woodward M, Zhang X, Barzi F, Pan W, Ueshima H, Rodgers A, MacMahon S; Asia Pacific Cohort Studies Consortium. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. *Diabetes Care*. 2003;26:360–366.
2. American Diabetes Association. 10: Cardiovascular disease and risk management: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42:S103–S123.
3. American Diabetes Association. 11: Microvascular complications and foot care: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42:S124–S138.
4. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ*. 2000;321:412–419.
5. de Boer IH, Bangalore S, Benetos A, Davis AM, Michos ED, Muntner P, Rossing P, Zoungas S, Bakris G. Diabetes and hypertension: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40:1273–1284.
6. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2015;313:603–615.
7. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB Sr, Granger CB, Jones NP, Leiter LA, Rosenberg AE, Sigmon KN, Somerville MC, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*. 2018;392:1519–1529.
8. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834–1844.
9. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322.
10. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Riesmeyer JS, Riddle MC, Ryden L, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394:121–130.
11. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657.
12. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–357.
13. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
14. Blonde L, Russell-Jones D. The safety and efficacy of liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the lead 1-5 studies. *Diabetes Obes Metab*. 2009;11(suppl 3):26–34.
15. Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2014;16:457–466.
16. Wang B, Zhong J, Lin H, Zhao Z, Yan Z, He H, Ni Y, Liu D, Zhu Z. Blood pressure-lowering effects of GLP-1 receptor agonists exenatide and liraglutide: a meta-analysis of clinical trials. *Diabetes Obes Metab*. 2013;15:737–749.
17. Horton ES, Silberman C, Davis KL, Berria R. Weight loss, glycemic control, and changes in cardiovascular biomarkers in patients with type 2 diabetes receiving incretin therapies or insulin in a large cohort database. *Diabetes Care*. 2010;33:1759–1765.
18. Oliva RV, Bakris GL. Blood pressure effects of sodium-glucose co-transport 2 (SGLT2) inhibitors. *J Am Soc Hypertens*. 2014;8:330–339.
19. Petrie JR. The cardiovascular safety of incretin-based therapies: a review of the evidence. *Cardiovasc Diabetol*. 2013;12:130.
20. Ferreira MT, Leite NC, Cardoso CR, Salles GF. Correlates of aortic stiffness progression in patients with type 2 diabetes: importance of glycemic control: the Rio de Janeiro type 2 diabetes cohort study. *Diabetes Care*. 2015;38:897–904.
21. Vallon V. The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. *Annu Rev Med*. 2015;66:255–270.
22. Paul S, Best J, Klein K, Han J, Maggs D. Effects of HBA1C and weight reduction on blood pressure in patients with type 2 diabetes mellitus treated with exenatide*. *Diabetes Obes Metab*. 2012;14:826–834.
23. Cefalu WT, Stenlof K, Leiter LA, Wilding JP, Blonde L, Polidori D, Xie J, Sullivan D, Usiskin K, Canovatchel W, et al. Effects of canagliflozin on body weight and relationship to HbA1c and blood pressure changes in patients with type 2 diabetes. *Diabetologia*. 2015;58:1183–1187.

24. Sjostrom CD, Hashemi M, Sugg J, Ptaszynska A, Johnsson E. Dapagliflozin-induced weight loss affects 24-week glycated haemoglobin and blood pressure levels. *Diabetes Obes Metab*. 2015;17:809–812.
25. Okerson T, Yan P, Stonehouse A, Brodows R. Effects of exenatide on systolic blood pressure in subjects with type 2 diabetes. *Am J Hypertens*. 2010;23:334–339.
26. Baker WL, Buckley LF, Kelly MS, Bucheit JD, Parod ED, Brown R, Carbone S, Abbate A, Dixon DL. Effects of sodium-glucose cotransporter 2 inhibitors on 24-hour ambulatory blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc*. 2017;6:e005686. DOI: 10.1161/JAHA.117.005686.
27. Kumarathurai P, Anholm C, Fabricius-Bjerre A, Nielsen OW, Kristiansen O, Madsbad S, Haugaard SB, Sajadieh A. Effects of the glucagon-like peptide-1 receptor agonist liraglutide on 24-h ambulatory blood pressure in patients with type 2 diabetes and stable coronary artery disease: a randomized, double-blind, placebo-controlled, crossover study. *J Hypertens*. 2017;35:1070–1078.
28. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, Zdravkovic M, During M, Matthews DR; Group L-S. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the lead (Liraglutide Effect and Action in Diabetes)-2 study. *Diabetes Care*. 2009;32:84–90.
29. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, Zdravkovic M, Ravn GM, Simo R, Liraglutide E, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia*. 2009;52:2046–2055.
30. Majewski C, Bakris GL. Blood pressure reduction: an added benefit of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes. *Diabetes Care*. 2015;38:429–430.
31. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. *Ann Intern Med*. 2009;151:264–269, W264.
32. Higgins JPT, Green S; *Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, England; Hoboken, NJ: Wiley-Blackwell; 2008.
33. Frias JP, Guja C, Hardy E, Ahmed A, Dong F, Ohman P, Jabbour SA. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2016;4:1004–1016.
34. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56:455–463.
35. Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ, Pagidipati NJ, Chan JC, Gustavson SM, Iqbal N, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol*. 2018;6:105–113.
36. Wu JH, Foote C, Blomster J, Toyama T, Perkovic V, Sundstrom J, Neal B. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2016;4:411–419.
37. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393:31–39.
38. Weber MA, Mansfield TA, Cain VA, Iqbal N, Parikh S, Ptaszynska A. Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combination antihypertensive therapy: a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Diabetes Endocrinol*. 2016;4:211–220.
39. Ferdinand KC, White WB, Calhoun DA, Lonn EM, Sager PT, Brunelle R, Jiang HH, Threlkeld RJ, Robertson KE, Geiger MJ. Effects of the once-weekly glucagon-like peptide-1 receptor agonist dulaglutide on ambulatory blood pressure and heart rate in patients with type 2 diabetes mellitus. *Hypertension*. 2014;64:731–737.
40. Kario K, Okada K, Kato M, Nishizawa M, Yoshida T, Asano T, Uchiyama K, Niijima Y, Katsuya T, Urata H, et al. 24-Hour blood pressure-lowering effect of an SGLT-2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: results from the randomized, placebo-controlled sacra study. *Circulation*. 2018;139:2089–2097.
41. Liakos A, Lambadiari V, Bargiota A, Kitsios K, Avramidis I, Kotsa K, Gerou S, Boura P, Tentolouris N, Dimitriadis G, et al. Effect of liraglutide on ambulatory blood pressure in patients with hypertension and type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2019;21:517–524.
42. Mancia G, Cannon CP, Tikkanen I, Zeller C, Ley L, Woerle HJ, Broedl UC, Johansen OE. Impact of empagliflozin on blood pressure in patients with type 2 diabetes mellitus and hypertension by background antihypertensive medication. *Hypertension*. 2016;68:1355–1364.
43. Sun F, Wu S, Guo S, Yu K, Yang Z, Li L, Zhang Y, Quan X, Ji L, Zhan S. Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Res Clin Pract*. 2015;110:26–37.
44. Mazidi M, Rezaie P, Gao HK, Kengne AP. Effect of sodium-glucose cotransport-2 inhibitors on blood pressure in people with type 2 diabetes mellitus: a systematic review and meta-analysis of 43 randomized control trials with 22 528 patients. *J Am Heart Assoc*. 2017;6:e004007. DOI: 10.1161/JAHA.116.004007.
45. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, Sarigianni M, Matthews DR, Tsapas A. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med*. 2013;159:262–274.
46. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*. 2003;42:878–884.
47. Semlitsch T, Jeitler K, Berghold A, Horvath K, Posch N, Poggenburg S, Siebenhofer A. Long-term effects of weight-reducing diets in people with hypertension. *Cochrane Database Syst Rev*. 2016;3:CD008274.
48. Siebenhofer A, Jeitler K, Horvath K, Berghold A, Posch N, Meschik J, Semlitsch T. Long-term effects of weight-reducing drugs in people with hypertension. *Cochrane Database Syst Rev*. 2016;3:CD007654.
49. Fonseca VA, Devries JH, Henry RR, Donsmark M, Thomsen HF, Plutzky J. Reductions in systolic blood pressure with liraglutide in patients with type 2 diabetes: insights from a patient-level pooled analysis of six randomized clinical trials. *J Diabetes Complications*. 2014;28:399–405.
50. Katout M, Zhu H, Rutsky J, Shah P, Brook RD, Zhong J, Rajagopalan S. Effect of GLP-1 mimetics on blood pressure and relationship to weight loss and glycemia lowering: results of a systematic meta-analysis and meta-regression. *Am J Hypertens*. 2014;27:130–139.
51. Wijkman MO, Dena M, Dahlqvist S, Sofizadeh S, Hirsch I, Tuomilehto J, Martensson J, Torffvit O, Imberg H, Saeed A, et al. Predictors and correlates of systolic blood pressure reduction with liraglutide treatment in patients with type 2 diabetes. *J Clin Hypertens*. 2019;21:105–115.
52. Vilsboll T, Zdravkovic M, Le-Thi T, Krarup T, Schmitz O, Courreges JP, Verhoeven R, Buganova I, Madsbad S. Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. *Diabetes Care*. 2007;30:1608–1610.
53. Vilsboll T, Garber AJ. Non-glycaemic effects mediated via GLP-1 receptor agonists and the potential for exploiting these for therapeutic benefit: focus on liraglutide. *Diabetes Obes Metab*. 2012;14(suppl 2):41–49.
54. Nystrom T, Gutniak MK, Zhang Q, Zhang F, Holst JJ, Ahren B, Sjoholm A. Effects of glucagon-like peptide-1 on endothelial function in type 2 diabetes patients with stable coronary artery disease. *Am J Physiol Endocrinol Metab*. 2004;287:E1209–E1215.
55. Basu A, Charkoudian N, Schrage W, Rizza RA, Basu R, Joyner MJ. Beneficial effects of GLP-1 on endothelial function in humans: dampening by glyburide but not by glimepiride. *Am J Physiol Endocrinol Metab*. 2007;293:E1289–E1295.
56. Chaudhuri A, Ghanim H, Makdissi A, Green K, Abuaysheh S, Batra M, N DK, Dandona P. Exenatide induces an increase in vasodilatory and a decrease in vasoconstrictive mediators. *Diabetes Obes Metab*. 2017;19:729–733.
57. Lovshin JA, Barnie A, DeAlmeida A, Logan A, Zinman B, Drucker DJ. Liraglutide promotes natriuresis but does not increase circulating levels of atrial natriuretic peptide in hypertensive subjects with type 2 diabetes. *Diabetes Care*. 2015;38:132–139.

58. Gutzwiller JP, Tschopp S, Bock A, Zehnder CE, Huber AR, Kreyenbuehl M, Gutmann H, Drewe J, Henzen C, Goeke B, et al. Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men. *J Clin Endocrinol Metab*. 2004;89:3055–3061.
59. Muskiet MHA, van Bommel EJ, van Raalte DH. Antihypertensive effects of SGLT2 inhibitors in type 2 diabetes. *Lancet Diabetes Endocrinol*. 2016;4:188–189.
60. Brown E, Rajeev SP, Cuthbertson DJ, Wilding JPH. A review of the mechanism of action, metabolic profile and haemodynamic effects of sodium-glucose co-transporter-2 inhibitors. *Diabetes Obes Metab*. 2019;21(suppl 2):9–18.
61. Reed JW. Impact of sodium-glucose cotransporter 2 inhibitors on blood pressure. *Vasc Health Risk Manag*. 2016;12:393–405.
62. Kawasoe S, Maruguchi Y, Kajiya S, Uenomachi H, Miyata M, Kawasoe M, Kubozono T, Ohishi M. Mechanism of the blood pressure-lowering effect of sodium-glucose cotransporter 2 inhibitors in obese patients with type 2 diabetes. *BMC Pharmacol Toxicol*. 2017;18:23.
63. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. *Diabetes Care*. 2009;32:650–657.
64. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab*. 2013;15: 853–862.
65. Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, Johansen OE. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. *Diabetes Obes Metab*. 2015;17:1180–1193.
66. Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, Woerle HJ, von Eynatten M, Broedl UC. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovasc Diabetol*. 2014;13:28.
67. Aucott L, Poobalan A, Smith WC, Avenell A, Jung R, Broom J. Effects of weight loss in overweight/obese individuals and long-term hypertension outcomes: a systematic review. *Hypertension*. 2005;45:1035–1041.
68. Gao S, Cui X, Wang X, Burg MB, Dmitrieva NI. Cross-sectional positive association of serum lipids and blood pressure with serum sodium within the normal reference range of 135-145 mmol/l. *Arterioscler Thromb Vasc Biol*. 2017;37:598–606.
69. Wannamethee G, Whincup PH, Shaper AG, Lever AF. Serum sodium concentration and risk of stroke in middle-aged males. *J Hypertens*. 1994;12:971–979.
70. Weir MR, Januszewicz A, Gilbert RE, Vijapurkar U, Kline I, Fung A, Meininger G. Effect of canagliflozin on blood pressure and adverse events related to osmotic diuresis and reduced intravascular volume in patients with type 2 diabetes mellitus. *J Clin Hypertens*. 2014;16:875–882.
71. Clarke SJ, Giblett JP, Yang LL, Hubsch A, Zhao T, Aetesam-Ur-Rahman M, West NEJ, O'Sullivan M, Figg N, Bennett M, et al. GLP-1 is a coronary artery vasodilator in humans. *J Am Heart Assoc*. 2018;7:e010321. DOI: 10.1161/JAHA.118.010321.
72. Kim M, Platt MJ, Shibasaki T, Quaggin SE, Backx PH, Seino S, Simpson JA, Drucker DJ. GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure. *Nat Med*. 2013;19:567–575.
73. Rosenstock J, Reusch J, Bush M, Yang F, Stewart M. Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing. *Diabetes Care*. 2009;32:1880–1886.
74. Nauck MA, Stewart MW, Perkins C, Jones-Leone A, Yang F, Perry C, Reinhardt RR, Rendell M. Efficacy and safety of once-weekly GLP-1 receptor agonist albiglutide (Harmony 2): 52 week primary endpoint results from a randomised, placebo-controlled trial in patients with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetologia*. 2016;59:266–274.
75. Grunberger G, Chang A, Garcia Soria G, Botros FT, Bsharat R, Milicevic Z. Monotherapy with the once-weekly GLP-1 analogue dulaglutide for 12 weeks in patients with type 2 diabetes: dose-dependent effects on glycaemic control in a randomized, double-blind, placebo-controlled study. *Diabetic Med*. 2012;29:1260–1267.
76. Miyagawa J, Odawara M, Takamura T, Iwamoto N, Takita Y, Imaoka T. Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: a 26-week randomized phase III study. *Diabetes Obes Metab*. 2015;17:974–983.
77. Moretto TJ, Milton DR, Ridge TD, Macconell LA, Okerson T, Wolka AM, Brodows RG. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther*. 2008;30:1448–1460.
78. Aroda VR, Rosenstock J, Terauchi Y, Altuntas Y, Lalic NM, Morales Villegas EC, Jeppesen OK, Christiansen E, Hertz CL, Haluzik M. Pioneer 1: randomized clinical trial comparing the efficacy and safety of oral semaglutide monotherapy with placebo in patients with type 2 diabetes. *Diabetes Care*. 2019;42:1724–1732.
79. Sorli C, Harashima SI, Tsoukas GM, Unger J, Karsbol JD, Hansen T, Bain SC. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5:251–260.
80. Raz I, Fonseca V, Kipnes M, Durrwell L, Hoekstra J, Boldrin M, Balena R. Efficacy and safety of taspoglutide monotherapy in drug-naive type 2 diabetic patients after 24 weeks of treatment: results of a randomized, double-blind, placebo-controlled phase 3 study (T-emerge 1). *Diabetes Care*. 2012;35:485–487.
81. Ahren B, Johnson SL, Stewart M, Cirkel DT, Yang F, Perry C, Feinglos MN. Harmony 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. *Diabetes Care*. 2014;37:2141–2148.
82. Dungan KM, Weitgasser R, Perez Manghi F, Pintilei E, Fahrbach JL, Jiang HH, Shell J, Robertson KE. A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). *Diabetes Obes Metab*. 2016;18: 475–482.
83. Ludvik B, Frias JP, Tinahones FJ, Wainstein J, Jiang H, Robertson KE, Garcia-Perez LE, Woodward DB, Milicevic Z. Dulaglutide as add-on therapy to sglt2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2018;6:370–381.
84. Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, Atisso C, Kuhstoss D, Lakshmanan M. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care*. 2014;37:2159–2167.
85. Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). *Diabetes Care*. 2014;37:2149–2158.
86. Gill A, Hoogwerf BJ, Burger J, Bruce S, Macconell L, Yan P, Braun D, Giaconia J, Malone J. Effect of exenatide on heart rate and blood pressure in subjects with type 2 diabetes mellitus: a double-blind, placebo-controlled, randomized pilot study. *Cardiovasc Diabetol*. 2010;9:6.
87. Apovian CM, Bergenstal RM, Cuddihy RM, Qu Y, Lenox S, Lewis MS, Glass LC. Effects of exenatide combined with lifestyle modification in patients with type 2 diabetes. *Am J Med*. 2010;123:468.e9–468.e7.
88. Liutkus J, Rosas Guzman J, Norwood P, Pop L, Northrup J, Cao D, Trautmann M. A placebo-controlled trial of exenatide twice-daily added to thiazolidinediones alone or in combination with metformin. *Diabetes Obes Metab*. 2010;12:1058–1065.
89. Gadde KM, Vetter ML, Iqbal N, Hardy E, Ohman P. Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: the duration-neo-2 randomized clinical study. *Diabetes Obes Metab*. 2017;19:979–988.
90. Guja C, Frias JP, Somogyi A, Jabbour S, Wang H, Hardy E, Rosenstock J. Effect of exenatide qw or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: the duration-7 randomized study. *Diabetes Obes Metab*. 2018;20:1602–1614.
91. Buse JB, Bergenstal RM, Glass LC, Heilmann CR, Lewis MS, Kwan AY, Hoogwerf BJ, Rosenstock J. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med*. 2011;154:103–112.
92. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, et al. Effects of

once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:1228–1239.
93. Lind M, Hirsch IB, Tuomilehto J, Dahlqvist S, Ahren B, Torffvit O, Attvall S, Ekelund M, Filipsson K, Tengmark BO, et al. Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI liraglutide trial). *BMJ*. 2015;351:h5364.
94. Vanderheiden A, Harrison L, Warshauer J, Li X, Adams-Huet B, Lingvay I. Effect of adding liraglutide vs placebo to a high-dose insulin regimen in patients with type 2 diabetes: a randomized clinical trial. *JAMA Intern Med*. 2016;176:939–947.
95. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, Hale PM, Zdravkovic M, Blonde L. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care*. 2009;32:1224–1230.
96. Ahmann A, Rodbard HW, Rosenstock J, Lahtela JT, de Loredo L, Tornoe K, Boopalan A, Nauck MA. Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: a randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2015;17:1056–1064.
97. Davies MJ, Bain SC, Atkin SL, Rossing P, Scott D, Shamkhalova MS, Bosch-Traberg H, Syren A, Umpierrez GE. Efficacy and safety of liraglutide versus placebo as add-on to glucose-lowering therapy in patients with type 2 diabetes and moderate renal impairment (LIRA-RENAL): a randomized clinical trial. *Diabetes Care*. 2016;39:222–230.
98. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjoth TV, Andreasen AH, Jensen CB, DeFronzo RA. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the scale diabetes randomized clinical trial. *JAMA*. 2015;314:687–699.
99. Nauck MA, Petrie JR, Sesti G, Mannucci E, Courreges JP, Lindegaard ML, Jensen CB, Atkin SL. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients with type 2 diabetes. *Diabetes Care*. 2016;39:231–241.
100. Davies M, Pieber TR, Hartoft-Nielsen ML, Hansen OKH, Jabbour S, Rosenstock J. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial. *JAMA*. 2017;318:1460–1470.
101. Lingvay I, Desouza CV, Lalic KS, Rose L, Hansen T, Zacho J, Pieber TR. A 26-week randomized controlled trial of semaglutide once daily versus liraglutide and placebo in patients with type 2 diabetes suboptimally controlled on diet and exercise with or without metformin. *Diabetes Care*. 2018;41:1926–1937.
102. Pratley R, Amod A, Hoff ST, Kadowaki T, Lingvay I, Nauck M, Pedersen KB, Saugstrup T, Meier JJ. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet*. 2019;394:39–50.
103. Rodbard HW, Lingvay I, Reed J, de la Rosa R, Rose L, Sugimoto D, Araki E, Chu PL, Wijayasinghe N, Norwood P. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. *J Clin Endocrinol Metab*. 2018;103:2291–2301.
104. Zinman B, Bhosekar V, Busch R, Holst I, Ludvik B, Thielke D, Thrasher J, Woo V, Philis-Tsimikas A. Semaglutide once weekly as add-on to sglt-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2019;7:356–367.
105. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenzon O, Pedersen SD, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381:841–851.
106. Bergenstal RM, Forti A, Chiasson JL, Woloschak M, Boldrin M, Balena R. Efficacy and safety of taspoglutide versus sitagliptin for type 2 diabetes mellitus (T-emerge 4 trial). *Diabetes Ther*. 2012;3:13.
107. Henry RR, Mudaliar S, Kanitra L, Woloschak M, Balena R. Efficacy and safety of taspoglutide in patients with type 2 diabetes inadequately controlled with metformin plus pioglitazone over 24 weeks: T-emerge 3 trial. *J Clin Endocrinol Metab*. 2012;97:2370–2379.
108. Umpierrez G, Tofe Povedano S, Perez Manghi F, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). *Diabetes Care*. 2014;37:2168–2176.
109. Chen YH, Huang CN, Cho YM, Li P, Gu L, Wang F, Yang J, Wang WQ. Efficacy and safety of dulaglutide monotherapy compared with glimepiride in East-Asian patients with type 2 diabetes in a multicentre, double-blind, randomized, parallel-arm, active comparator, phase III trial. *Diabetes Obes Metab*. 2018;20:2121–2130.
110. Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, Gonzalez JG, Chan M, Wolka AM, Boardman MK. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. *Diabetes Care*. 2012;35:252–258.
111. Xu W, Bi Y, Sun Z, Li J, Guo L, Yang T, Wu G, Shi L, Feng Z, Qiu L, et al. Comparison of the effects on glycaemic control and beta-cell function in newly diagnosed type 2 diabetes patients of treatment with exenatide, insulin or pioglitazone: a multicentre randomized parallel-group trial (the CONFIDENCE Study). *J Intern Med*. 2015;277:137–150.
112. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, Hale PM, Zdravkovic M, Bode B. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet*. 2009;373:473–481.
113. Seino Y, Terauchi Y, Osonoi T, Yabe D, Abe N, Nishida T, Zacho J, Kaneko S. Safety and efficacy of semaglutide once weekly vs sitagliptin once daily, both as monotherapy in Japanese people with type 2 diabetes. *Diabetes Obes Metab*. 2018;20:378–388.
114. Weissman PN, Carr MC, Ye J, Cirkel DT, Stewart M, Perry C, Pratley R. Harmony 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. *Diabetologia*. 2014;57:2475–2484.
115. Dungan KM, Povedano ST, Forst T, Gonzalez JG, Atisso C, Sealls W, Fahrbach JL. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet*. 2014;384:1349–1357.
116. Araki E, Inagaki N, Tanizawa Y, Oura T, Takeuchi M, Imaoka T. Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open-label, phase III, non-inferiority study. *Diabetes Obes Metab*. 2015;17:994–1002.
117. Blonde L, Jendle J, Gross J, Woo V, Jiang H, Fahrbach JL, Milicevic Z. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. *Lancet*. 2015;385:2057–2066.
118. Wang W, Nevarez L, Filippova E, Song KH, Tao B, Gu L, Wang F, Li P, Yang J. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in mainly Asian patients with type 2 diabetes mellitus on metformin and/or a sulphonylurea: a 52-week open-label, randomized phase III trial. *Diabetes Obes Metab*. 2019;21:234–243.
119. Pratley RE, Aroda VR, Lingvay I, Ludemann J, Andreassen C, Navarria A, Viljoen A; SUSTAIN 7 investigators. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3B trial. *Lancet Diabetes Endocrinol*. 2018;6:275–286.
120. Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtner V. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). *Diabetes Care*. 2015;38:2241–2249.
121. Wysham CH, MacConell L, Hardy E. Efficacy and safety of multiple doses of exenatide once-monthly suspension in patients with type 2 diabetes: a phase II randomized clinical trial. *Diabetes Care*. 2016;39:1768–1776.
122. Blevins T, Pullman J, Malloy J, Yan P, Taylor K, Schulteis C, Trautmann M, Porter L. Duration-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2011;96:1301–1310.
123. Rosenstock J, Balas B, Charbonnel B, Bolli GB, Boldrin M, Ratner R, Balena R. The fate of taspoglutide, a weekly GLP-1 receptor agonist, versus twice-daily exenatide for type 2 diabetes: the T-emerge 2 trial. *Diabetes Care*. 2013;36:498–504.
124. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, Zychma M, Blonde L. Liraglutide once a day versus exenatide twice a

day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet*. 2009;374:39–47.
125. Davies MJ, Donnelly R, Barnett AH, Jones S, Nicolay C, Kilcoyne A. Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: results of the helping evaluate exenatide in patients with diabetes compared with long-acting insulin (HEELA) study. *Diabetes Obes Metab*. 2009;11:1153–1162.
126. Bergenstal RM, Wysham C, Macconell L, Malloy J, Walsh B, Yan P, Wilhelm K, Malone J, Porter LE. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet*. 2010;376:431–439.
127. Diamant M, Van Gaal L, Stranks S, Northrup J, Cao D, Taylor K, Trautmann M. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet*. 2010;375:2234–2243.
128. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, Hoogwerf BJ, Gao A, Boardman MK, Fineman M, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet*. 2013;381:117–124.
129. Davies M, Heller S, Sreenan S, Sapin H, Adetunji O, Tahbaz A, Vora J. Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. *Diabetes Care*. 2013;36:1368–1376.
130. Ji L, Onishi Y, Ahn CW, Agarwal P, Chou CW, Haber H, Guerrettaz K, Boardman MK. Efficacy and safety of exenatide once-weekly vs exenatide twice-daily in Asian patients with type 2 diabetes mellitus. *J Diabetes Invest*. 2013;4:53–61.
131. Wysham CH, Rosenstock J, Vetter ML, Dong F, Ohman P, Iqbal N. Efficacy and tolerability of the new autoinjected suspension of exenatide once weekly versus exenatide twice daily in patients with type 2 diabetes. *Diabetes Obes Metab*. 2018;20:165–172.
132. Diamant M, Nauck MA, Shaginian R, Malone JK, Cleall S, Reaney M, de Vries D, Hoogwerf BJ, MacConell L, Wolffenbuttel BH. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. *Diabetes Care*. 2014;37:2763–2773.
133. Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, Porter L. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet*. 2008;372:1240–1250.
134. Nauck MA, Duran S, Kim D, Johns D, Northrup J, Festa A, Brodows R, Trautmann M. A comparison of twice-daily exenatide and biphasic insulin as part in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia*. 2007;50:259–267.
135. Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, Holst AG, Annett MP, Aroda VR. Efficacy and safety of once-weekly semaglutide versus exenatide er in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care*. 2018;41:258–266.
136. Simo R, Guerci B, Schernthaner G, Gallwitz B, Rosas-Guzman J, Dotta F, Festa A, Zhou M, Kiljanski J. Long-term changes in cardiovascular risk markers during administration of exenatide twice daily or glimepiride: results from the European exenatide study. *Cardiovasc Diabetol*. 2015;14:116.
137. Meier JJ, Rosenstock J, Hincelin-Mery A, Roy-Duval C, Delfolie A, Coester HV, Menge BA, Forst T, Kapitza C. Contrasting effects of lixisenatide and liraglutide on postprandial glycemic control, gastric emptying, and safety parameters in patients with type 2 diabetes on optimized insulin glargine with or without metformin: a randomized, open-label trial. *Diabetes Care*. 2015;38:1263–1273.
138. Brady EM, Davies MJ, Gray LJ, Saeed MA, Smith D, Hanif W, Khunti K. A randomized controlled trial comparing the GLP-1 receptor agonist liraglutide to a sulphonylurea as add on to metformin in patients with established type 2 diabetes during ramadan: the treat 4 ramadan trial. *Diabetes Obes Metab*. 2014;16:527–536.
139. D'Alessio D, Haring HU, Charbonnel B, de Pablos-Velasco P, Candelas C, Dain MP, Vincent M, Pilorget V, Yki-Jarvinen H. Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes. *Diabetes Obes Metab*. 2015;17:170–178.
140. Abreu M, Tumyan A, Elhassan A, Peicher K, Papacostea O, Dimachkie P, Siddiqui MS, Pop LM, Gunasekaran U, Meneghini LF, et al. A randomized trial comparing the efficacy and safety of treating patients with type 2 diabetes and highly elevated HbA1c levels with basal-bolus insulin or a glucagon-like peptide-1 receptor agonist plus basal insulin: the SIMPLE study. *Diabetes Obes Metab*. 2019;21:2133-2141.
141. Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, Thomsen AB, Sondergaard RE, Davies M. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet*. 2010;375:1447–1456.
142. Charbonnel B, Steinberg H, Eymard E, Xu L, Thakkar P, Prabhu V, Davies MJ, Engel SS. Efficacy and safety over 26 weeks of an oral treatment strategy including sitagliptin compared with an injectable treatment strategy with liraglutide in patients with type 2 diabetes mellitus inadequately controlled on metformin: a randomised clinical trial. *Diabetologia*. 2013;56:1503–1511.
143. de Wit HM, Vervoort GM, Jansen HJ, de Grauw WJ, de Galan BE, Tack CJ. Liraglutide reverses pronounced insulin-associated weight gain, improves glycaemic control and decreases insulin dose in patients with type 2 diabetes: a 26 week, randomised clinical trial (ELEGANT). *Diabetologia*. 2014;57:1812–1819.
144. Bailey TS, Takacs R, Tinahones FJ, Rao PV, Tsoukas GM, Thomsen AB, Kaltoft MS, Maislos M. Efficacy and safety of switching from sitagliptin to liraglutide in subjects with type 2 diabetes (LIRA-SWITCH): a randomized, double-blind, double-dummy, active-controlled 26-week trial. *Diabetes Obes Metab*. 2016;18:1191–1198.
145. Nauck M, Rizzo M, Johnson A, Bosch-Traberg H, Madsen J, Cariou B. Once-daily liraglutide versus lixisenatide as add-on to metformin in type 2 diabetes: a 26-week randomized controlled clinical trial. *Diabetes Care*. 2016;39:1501–1509.
146. Zang L, Liu Y, Geng J, Luo Y, Bian F, Lv X, Yang J, Liu J, Peng Y, Li Y, et al. Efficacy and safety of liraglutide versus sitagliptin, both in combination with metformin, in Chinese patients with type 2 diabetes: a 26-week, open-label, randomized, active comparator clinical trial. *Diabetes Obes Metab*. 2016;18:803–811.
147. Kaku K, Kiyosue A, Ono Y, Shiraiwa T, Kaneko S, Nishijima K, Bosch-Traberg H, Seino Y. Liraglutide is effective and well tolerated in combination with an oral antidiabetic drug in Japanese patients with type 2 diabetes: a randomized, 52-week, open-label, parallel-group trial. *J Diabetes Invest*. 2016;7:76–84.
148. Rosenstock J, Allison D, Birkenfeld AL, Blicher TM, Deenadayalan S, Jacobsen JB, Serusclat P, Violante R, Watada H, Davies M, et al. Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: the PIONEER 3 randomized clinical trial. *JAMA*. 2019;321:1466–1480.
149. Aroda VR, Bain SC, Cariou B, Piletic M, Rose L, Axelsen M, Rowe E, DeVries JH. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5:355–366.
150. Ahren B, Masmiquel L, Kumar H, Sargin M, Karsbol JD, Jacobsen SH, Chow F. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol*. 2017;5:341–354.
151. Kaku K, Yamada Y, Watada H, Abiko A, Nishida T, Zacho J, Kiyosue A. Safety and efficacy of once-weekly semaglutide vs additional oral antidiabetic drugs in Japanese people with inadequately controlled type 2 diabetes: a randomized trial. *Diabetes Obes Metab*. 2018;20:1202–1212.
152. Nauck M, Horton E, Andjelkovic M, Ampudia-Blasco FJ, Parusel CT, Boldrin M, Balena R. Taspoglutide, a once-weekly glucagon-like peptide 1 analogue, vs. insulin glargine titrated to target in patients with type 2 diabetes: an open-label randomized trial. *Diabetic Med*. 2013;30:109–113.
153. Pratley RE, Urosevic D, Boldrin M, Balena R. Efficacy and tolerability of taspoglutide versus pioglitazone in subjects with type 2 diabetes uncontrolled with sulphonylurea or sulphonylurea-metformin therapy: a randomized, double-blind study (T-emerge 6). *Diabetes Obes Metab*. 2013;15:234–240.

154. Inagaki N, Kondo K, Yoshinari T, Maruyama N, Susuta Y, Kuki H. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. *Diabetes Obes Metab*. 2013;15:1136–1145.
155. Inagaki N, Kondo K, Yoshinari T, Takahashi N, Susuta Y, Kuki H. Efficacy and safety of canagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled with diet and exercise: a 24-week, randomized, double-blind, placebo-controlled, phase III study. *Expert Opin Pharmacother*. 2014;15:1501–1515.
156. Stenlof K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab*. 2013;15:372–382.
157. Kaku K, Inoue S, Matsuoka O, Kiyosue A, Azuma H, Hayashi N, Tokudome T, Langkilde AM, Parikh S. Efficacy and safety of dapagliflozin as a monotherapy for type 2 diabetes mellitus in Japanese patients with inadequate glycaemic control: a phase II multicentre, randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2013;15:432–440.
158. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care*. 2010;33:2217–2224.
159. Bailey CJ, Iqbal N, T'Joen C, List JF. Dapagliflozin monotherapy in drug-naive patients with diabetes: a randomized-controlled trial of low-dose range. *Diabetes Obes Metab*. 2012;14:951–959.
160. Ji L, Ma J, Li H, Mansfield TA, T'Joen CL, Iqbal N, Ptaszynska A, List JF. Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. *Clin Ther*. 2014;36:84–100.e109.
161. Kaku K, Kiyosue A, Inoue S, Ueda N, Tokudome T, Yang J, Langkilde AM. Efficacy and safety of dapagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise. *Diabetes Obes Metab*. 2014;16:1102–1110.
162. Kadowaki T, Haneda M, Inagaki N, Terauchi Y, Taniguchi A, Koiwai K, Rattunde H, Woerle HJ, Broedl UC. Empagliflozin monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, 12-week, double-blind, placebo-controlled, phase II trial. *Adv Ther*. 2014;31:621–638.
163. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ, Broedl UC. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol*. 2013;1:208–219.
164. Terra SG, Focht K, Davies M, Frias J, Derosa G, Darekar A, Golm G, Johnson J, Saur D, Lauring B, et al. Phase III, efficacy and safety study of ertugliflozin monotherapy in people with type 2 diabetes mellitus inadequately controlled with diet and exercise alone. *Diabetes Obes Metab*. 2017;19:721–728.
165. Fonseca VA, Ferrannini E, Wilding JP, Wilpshaar W, Dhanjal P, Ball G, Klasen S. Active- and placebo-controlled dose-finding study to assess the efficacy, safety, and tolerability of multiple doses of ipragliflozin in patients with type 2 diabetes mellitus. *J Diabetes Complications*. 2013;27:268–273.
166. Seino Y, Sasaki T, Fukatsu A, Sakai S, Samukawa Y. Efficacy and safety of luseogliflozin monotherapy in Japanese patients with type 2 diabetes mellitus: a 12-week, randomized, placebo-controlled, phase II study. *Curr Med Res Opin*. 2014;30:1219–1230.
167. Seino Y, Sasaki T, Fukatsu A, Ubukata M, Sakai S, Samukawa Y. Dose-finding study of luseogliflozin in Japanese patients with type 2 diabetes mellitus: a 12-week, randomized, double-blind, placebo-controlled, phase II study. *Curr Med Res Opin*. 2014;30:1231–1244.
168. Seino Y, Sasaki T, Fukatsu A, Ubukata M, Sakai S, Samukawa Y. Efficacy and safety of luseogliflozin as monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, phase 3 study. *Curr Med Res Opin*. 2014;30:1245–1255.
169. Kaku K, Watada H, Iwamoto Y, Utsunomiya K, Terauchi Y, Tobe K, Tanizawa Y, Araki E, Ueda M, Suganami H, et al. Efficacy and safety of monotherapy with the novel sodium/glucose cotransporter-2 inhibitor tofogliflozin in Japanese patients with type 2 diabetes mellitus: a combined phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group comparative study. *Cardiovasc Diabetol*. 2014;13:65.
170. Townsend RR, Machin I, Ren J, Trujillo A, Kawaguchi M, Vijapurkar U, Damaraju CV, Pfeifer M. Reductions in mean 24-hour ambulatory blood pressure after 6-week treatment with canagliflozin in patients with type 2 diabetes mellitus and hypertension. *J Clin Hypertens*. 2016;18:43–52.
171. Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, Capuano G, Canovatchel W. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care*. 2012;35:1232–1238.
172. Inagaki N, Harashima S, Maruyama N, Kawaguchi Y, Goda M, Iijima H. Efficacy and safety of canagliflozin in combination with insulin: a double-blind, randomized, placebo-controlled study in Japanese patients with type 2 diabetes mellitus. *Cardiovasc Diabetol*. 2016;15:89.
173. Qiu R, Capuano G, Meininger G. Efficacy and safety of twice-daily treatment with canagliflozin, a sodium glucose co-transporter 2 inhibitor, added on to metformin monotherapy in patients with type 2 diabetes mellitus. *J Clin Transl Endocrinol*. 2014;1:54–60.
174. Ji L, Han P, Liu Y, Yang G, Van Dieu NK, Vijapurkar U, Qiu R, Meininger G. Canagliflozin in Asian patients with type 2 diabetes on metformin alone or metformin in combination with sulphonylurea. *Diabetes Obes Metab*. 2015;17:23–31.
175. Bode B, Stenlof K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp Pract (1995)*. 2013;41:72–84.
176. Lavalle-Gonzalez FJ, Januszewicz A, Davidson J, Tong C, Qiu R, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia*. 2013;56:2582–2592.
177. Yale JF, Bakris G, Cariou B, Yue D, David-Neto E, Xi L, Figueroa K, Wajs E, Usiskin K, Meininger G. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab*. 2013;15:463–473.
178. Forst T, Guthrie R, Goldenberg R, Yee J, Vijapurkar U, Meininger G, Stein P. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. *Diabetes Obes Metab*. 2014;16:467–477.
179. Wilding JP, Charpentier G, Hollander P, Gonzalez-Galvez G, Mathieu C, Vercruysse F, Usiskin K, Law G, Black S, Canovatchel W, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. *Int J Clin Pract*. 2013;67:1267–1282.
180. Rosenstock J, Chuck L, Gonzalez-Ortiz M, Merton K, Craig J, Capuano G, Qiu R. Initial combination therapy with canagliflozin plus metformin versus each component as monotherapy for drug-naive type 2 diabetes. *Diabetes Care*. 2016;39:353–362.
181. Wilding JP, Norwood P, T'Joen C, Bastien A, List JF, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. *Diabetes Care*. 2009;32:1656–1662.
182. Weber MA, Mansfield TA, Alessi F, Iqbal N, Parikh S, Ptaszynska A. Effects of dapagliflozin on blood pressure in hypertensive diabetic patients on renin-angiotensin system blockade. *Blood Press*. 2016;25:93–103.
183. Schumm-Draeger PM, Burgess L, Koranyi L, Hruba V, Hamer-Maansson JE, de Bruin TW. Twice-daily dapagliflozin co-administered with metformin in type 2 diabetes: a 16-week randomized, placebo-controlled clinical trial. *Diabetes Obes Metab*. 2015;17:42–51.
184. Araki E, Onishi Y, Asano M, Kim H, Yajima T. Efficacy and safety of dapagliflozin over 1 year as add-on to insulin therapy in Japanese patients with type 2 diabetes: the daisy (Dapagliflozin Added to Patients Under InSulin therapY) trial. *Diabetes Obes Metab*. 2017;19:562–570.
185. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010;375:2223–2233.
186. Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2011;13:928–938.
187. Bolinder J, Ljunggren O, Kullberg J, Johansson L, Wilding J, Langkilde AM, Sugg J, Parikh S. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2

diabetes mellitus with inadequate glycemic control on metformin. *J Clin Endocrinol Metab*. 2012;97:1020–1031.
188. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin xr, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. *Int J Clin Pract*. 2012;66:446–456.
189. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. *Diabetes Care*. 2012;35:1473–1478.
190. Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K, Parikh S; Dapagliflozin 006 Study Group. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med*. 2012;156:405–415.
191. Jabbour SA, Hardy E, Sugg J, Parikh S. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. *Diabetes Care*. 2014;37:740–750.
192. Leiter LA, Cefalu WT, de Bruin TW, Gause-Nilsson I, Sugg J, Parikh SJ. Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. *J Am Geriatr Soc*. 2014;62:1252–1262.
193. Cefalu WT, Leiter LA, de Bruin TW, Gause-Nilsson I, Sugg J, Parikh SJ. Dapagliflozin's effects on glycemia and cardiovascular risk factors in high-risk patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. *Diabetes Care*. 2015;38:1218–1227.
194. Mathieu C, Ranetti AE, Li D, Ekholm E, Cook W, Hirshberg B, Chen H, Hansen L, Iqbal N. Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes. *Diabetes Care*. 2015;38:2009–2017.
195. Matthaei S, Bowering K, Rohwedder K, Grohl A, Parikh S. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. *Diabetes Care*. 2015;38:365–372.
196. Rosenstock J, Hansen L, Zee P, Li Y, Cook W, Hirshberg B, Iqbal N. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. *Diabetes Care*. 2015;38:376–383.
197. Yang W, Han P, Min KW, Wang B, Mansfield T, T'Joen C, Iqbal N, Johnsson E, Ptaszynska A. Efficacy and safety of dapagliflozin in Asian patients with type 2 diabetes after metformin failure: a randomized controlled trial. *J Diabetes*. 2016;8:796–808.
198. Fioretto P, Del Prato S, Buse JB, Goldenberg R, Giorgino F, Reyner D, Langkilde AM, Sjostrom CD, Sartipy P, Investigators DS. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): the DERIVE study. *Diabetes Obes Metab*. 2018;20:2532–2540.
199. Yang W, Ma J, Li Y, Li Y, Zhou Z, Kim JH, Zhao J, Ptaszynska A. Dapagliflozin as add-on therapy in Asian patients with type 2 diabetes inadequately controlled on insulin with or without oral antihyperglycemic drugs: a randomized controlled trial. *J Diabetes*. 2018;10:589–599.
200. Pollock C, Stefansson B, Reyner D, Rossing P, Sjostrom CD, Wheeler DC, Langkilde AM, Heerspink HJL. Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2019;7:429–441.
201. Rosenstock J, Perl S, Johnsson E, Garcia-Sanchez R, Jacob S. Triple therapy with low-dose dapagliflozin plus saxagliptin versus dual therapy with each monocomponent, all added to metformin, in uncontrolled type 2 diabetes. *Diabetes Obes Metab*. 2019;21:2152–2162.
202. Rosenstock J, Seman LJ, Jelaska A, Hantel S, Pinnetti S, Hach T, Woerle HJ. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. *Diabetes Obes Metab*. 2013;15:1154–1160.
203. Tikkanen I, Narko K, Zeller C, Green A, Salsali A, Broedl UC, Woerle HJ. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. *Diabetes Care*. 2015;38:420–428.
204. Ross S, Thamer C, Cescutti J, Meinicke T, Woerle HJ, Broedl UC. Efficacy and safety of empagliflozin twice daily versus once daily in patients with type 2 diabetes inadequately controlled on metformin: a 16-week, randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2015;17:699–702.
205. Rosenstock J, Jelaska A, Frappin G, Salsali A, Kim G, Woerle HJ, Broedl UC. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care*. 2014;37:1815–1823.
206. Rosenstock J, Jelaska A, Zeller C, Kim G, Broedl UC, Woerle HJ. Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2015;17:936–948.
207. Haring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Woerle HJ, Broedl UC. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care*. 2013;36:3396–3404.
208. Haring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl UC, Woerle HJ. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care*. 2014;37:1650–1659.
209. Kovacs CS, Seshiah V, Swallow R, Jones R, Rattunde H, Woerle HJ, Broedl UC. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2014;16:147–158.
210. Kawamori R, Haneda M, Suzaki K, Cheng G, Shiki K, Miyamoto Y, Solimando F, Lee C, Lee J, George J. Empagliflozin as add-on to linagliptin in a fixed-dose combination in Japanese patients with type 2 diabetes: glycaemic efficacy and safety profile in a 52-week, randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2018;20:2200–2209.
211. Ferdinand KC, Izzo JL, Lee J, Meng L, George J, Salsali A, Seman L. Antihyperglycemic and blood pressure effects of empagliflozin in black patients with type 2 diabetes mellitus and hypertension. *Circulation*. 2019;139:2098–2109.
212. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ, Broedl UC. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2014;2:369–384.
213. Softeland E, Meier JJ, Vangen B, Toorawa R, Maldonado-Lutomirsky M, Broedl UC. Empagliflozin as add-on therapy in patients with type 2 diabetes inadequately controlled with linagliptin and metformin: a 24-week randomized, double-blind, parallel-group trial. *Diabetes Care*. 2017;40:201–209.
214. Amin NB, Wang X, Mitchell JR, Lee DS, Nucci G, Rusnak JM. Blood pressure-lowering effect of the sodium glucose co-transporter-2 inhibitor ertugliflozin, assessed via ambulatory blood pressure monitoring in patients with type 2 diabetes and hypertension. *Diabetes Obes Metab*. 2015;17:805–808.
215. Amin NB, Wang X, Jain SM, Lee DS, Nucci G, Rusnak JM. Dose-ranging efficacy and safety study of ertugliflozin, a sodium-glucose co-transporter 2 inhibitor, in patients with type 2 diabetes on a background of metformin. *Diabetes Obes Metab*. 2015;17:591–598.
216. Dagogo-Jack S, Liu J, Eldor R, Amorin G, Johnson J, Hille D, Liao Y, Huyck S, Golm G, Terra SG, et al. Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: the vertis sita2 placebo-controlled randomized study. *Diabetes Obes Metab*. 2018;20:530–540.
217. Grunberger G, Camp S, Johnson J, Huyck S, Terra SG, Mancuso JP, Jiang ZW, Golm G, Engel SS, Lauring B. Ertugliflozin in patients with stage 3 chronic kidney disease and type 2 diabetes mellitus: the vertis renal randomized study. *Diabetes Ther*. 2018;9:49–66.
218. Pratley RE, Eldor R, Raji A, Golm G, Huyck SB, Qiu Y, Sunga S, Johnson J, Terra SG, Mancuso JP, et al. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: the vertis factorial randomized trial. *Diabetes Obes Metab*. 2018;20:1111–1120.

219. Rosenstock J, Frias J, Pall D, Charbonnel B, Pascu R, Saur D, Darekar A, Huyck S, Shi H, Lauring B, et al. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET). *Diabetes Obes Metab*. 2018;20:520–529.
220. Ji L, Liu Y, Miao H, Xie Y, Yang M, Wang W, Mu Y, Yan P, Pan S, Lauring B, et al. Safety and efficacy of ertugliflozin in Asian patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: vertis asia. *Diabetes Obes Metab*. 2019;21:1474–1482.
221. Wilding JP, Ferrannini E, Fonseca VA, Wilpshaar W, Dhanjal P, Houzer A. Efficacy and safety of ipragliflozin in patients with type 2 diabetes inadequately controlled on metformin: a dose-finding study. *Diabetes Obes Metab*. 2013;15:403–409.
222. Shestakova MV, Wilding JPH, Wilpshaar W, Tretter R, Orlova VL, Verbovoy AF. A phase 3 randomized placebo-controlled trial to assess the efficacy and safety of ipragliflozin as an add-on therapy to metformin in Russian patients with inadequately controlled type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2018;146:240–250.
223. Kashiwagi A, Takahashi H, Ishikawa H, Yoshida S, Kazuta K, Utsuno A, Ueyama E. A randomized, double-blind, placebo-controlled study on long-term efficacy and safety of ipragliflozin treatment in patients with type 2 diabetes mellitus and renal impairment: results of the long-term ASP1941 safety evaluation in patients with type 2 diabetes with renal impairment (LANTERN) study. *Diabetes Obes Metab*. 2015;17:152–160.
224. Kashiwagi A, Kazuta K, Goto K, Yoshida S, Ueyama E, Utsuno A. Ipragliflozin in combination with metformin for the treatment of Japanese patients with type 2 diabetes: illuminate, a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab*. 2015;17:304–308.
225. Lu CH, Min KW, Chuang LM, Kokubo S, Yoshida S, Cha BS. Efficacy, safety, and tolerability of ipragliflozin in Asian patients with type 2 diabetes mellitus and inadequate glycemic control with metformin: results of a phase 3 randomized, placebo-controlled, double-blind, multicenter trial. *J Diabetes Invest*. 2016;7:366–373.
226. Han KA, Chon S, Chung CH, Lim S, Lee KW, Baik S, Jung CH, Kim DS, Park KS, Yoon KH, et al. Efficacy and safety of ipragliflozin as an add-on therapy to sitagliptin and metformin in Korean patients with inadequately controlled type 2 diabetes mellitus: a randomized controlled trial. *Diabetes Obes Metab*. 2018;20:2408–2415.
227. Seino Y, Sasaki T, Fukatsu A, Imazeki H, Ochiai H, Sakai S. Efficacy and safety of luseogliflozin added to insulin therapy in Japanese patients with type 2 diabetes: a multicenter, 52-week, clinical study with a 16-week, double-blind period and a 36-week, open-label period. *Curr Med Res Opin*. 2018;34:981–994.
228. Haneda M, Seino Y, Inagaki N, Kaku K, Sasaki T, Fukatsu A, Kakiuchi H, Sato Y, Sakai S, Samukawa Y. Influence of renal function on the 52-week efficacy and safety of the sodium glucose cotransporter 2 inhibitor luseogliflozin in Japanese patients with type 2 diabetes mellitus. *Clin Ther*. 2016;38:66–88.e20.
229. Rosenstock J, Cefalu WT, Lapuerta P, Zambrowicz B, Ogbaa I, Banks P, Sands A. Greater dose-ranging effects on A1c levels than on glucosuria with LX4211, a dual inhibitor of SGLT1 and SGLT2, in patients with type 2 diabetes on metformin monotherapy. *Diabetes Care*. 2015;38:431–438.
230. Terauchi Y, Tamura M, Senda M, Gunji R, Kaku K. Efficacy and safety of tofogliflozin in Japanese patients with type 2 diabetes mellitus with inadequate glycaemic control on insulin therapy (J-STEP/INS): results of a 16-week randomized, double-blind, placebo-controlled multicentre trial. *Diabetes Obes Metab*. 2017;19:1397–1407.
231. Tanizawa Y, Kaku K, Araki E, Tobe K, Terauchi Y, Utsunomiya K, Iwamoto Y, Watada H, Ohtsuka W, Watanabe D, et al. Long-term safety and efficacy of tofogliflozin, a selective inhibitor of sodium-glucose cotransporter 2, as monotherapy or in combination with other oral antidiabetic agents in Japanese patients with type 2 diabetes mellitus: multicenter, open-label, randomized controlled trials. *Expert Opin Pharmacother*. 2014;15:749–766.
232. Kario K, Hoshide S, Okawara Y, Tomitani N, Yamauchi K, Ohbayashi H, Itabashi N, Matsumoto Y, Kanegae H. Effect of canagliflozin on nocturnal home blood pressure in Japanese patients with type 2 diabetes mellitus: the SHIFT-J study. *J Clin Hypertens*. 2018;20:1527–1535.
233. Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, Balis DA, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet*. 2013;382:941–950.
234. Schernthaner G, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, Kawaguchi M, Canovatchel W, Meininger G. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care*. 2013;36:2508–2515.
235. Nauck MA, Del Prato S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M, Parikh SJ. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care*. 2011;34:2015–2022.
236. Muller-Wieland D, Kellerer M, Cypryk K, Skripova D, Rohwedder K, Johnsson E, Garcia-Sanchez R, Kurlyandskaya R, Sjostrom CD, Jacob S, et al. Efficacy and safety of dapagliflozin or dapagliflozin plus saxagliptin versus glimepiride as add-on to metformin in patients with type 2 diabetes. *Diabetes Obes Metab*. 2018;20:2598–2607.
237. Araki E, Tanizawa Y, Tanaka Y, Taniguchi A, Koiwai K, Kim G, Salsali A, Woerle HJ, Broedl UC. Long-term treatment with empagliflozin as add-on to oral antidiabetes therapy in Japanese patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2015;17:665–674.
238. Terauchi Y, Utsunomiya K, Yasui A, Seki T, Cheng G, Shiki K, Lee J. Safety and efficacy of empagliflozin as add-on therapy to GLP-1 receptor agonist (LIRAGLUTIDE) in Japanese patients with type 2 diabetes mellitus: a randomised, double-blind, parallel-group phase 4 study. *Diabetes Ther*. 2019;10:951–963.
239. Ridderstrale M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endocrinol*. 2014;2:691–700.
240. Hollander P, Liu J, Hill J, Johnson J, Jiang ZW, Golm G, Huyck S, Terra SG, Mancuso JP, Engel SS, et al. Ertugliflozin compared with glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin: the vertis su randomized study. *Diabetes Ther*. 2018;9:193–207.

SUPPLEMENTAL MATERIAL

Data S1: Search Strategy

MEDLINE(via Pubmed)

GLP-1RA

((((((“diabetes mellitus, type 2”[MeSH Terms] OR “type 2 diabetes mellitus”[All Fields] OR “type 2 diabetes”[All Fields] OR “diabetes mellitus type 2”[All Fields] OR “T2DM”[All Fields])))) AND ((((((((((((((((((((((((((glp 1 receptor agonist[Title/Abstract]) OR glp 1 receptor agonists[Title/Abstract]) OR glucagon like peptide 1 receptor agonist[Title/Abstract]) OR glucagon like peptide 1 receptor agonists[Title/Abstract]) OR glucagon like peptide 1 agonist[Title/Abstract]) OR glucagon like peptide 1 agonists[Title/Abstract]) OR glp 1 agonist[Title/Abstract]) OR glp 1 agonists[Title/Abstract]) OR glp 1 ra[Title/Abstract]) OR glp 1 ras[Title/Abstract]) OR glp 1ra[Title/Abstract]) OR glp 1ras[Title/Abstract]) OR glp1 receptor agonist[Title/Abstract]) OR glp1 receptor agonists[Title/Abstract]) OR glp1 agonist[Title/Abstract]) OR glp1 agonists[Title/Abstract]) OR glp1 ra[Title/Abstract]) OR glp1 ras[Title/Abstract]) OR glp1ra[Title/Abstract]) OR glp1ras[Title/Abstract]) OR Albiglutide[Title/Abstract]) OR Dulaglutide[Title/Abstract]) OR Exenatide[Title/Abstract]) OR Liraglutide[Title/Abstract]) OR Lixisenatide[Title/Abstract]) OR Semaglutide[Title/Abstract]) OR Taspoglutide[Title/Abstract])) AND ((((((((((((Randomized controlled trial [pt]) OR Controlled clinical trial[pt]) OR Randomized [tiab]) OR Randomised [tiab]) OR Placebo [tiab]) OR Drug therapy [sh]) OR Randomly [tiab]) OR Trial [tiab]) OR Groups [tiab])) NOT (Animals [mh] NOT humans [mh])))))) NOT Review[ptyp])

SGLT2i

((((((((“diabetes mellitus, type 2”[MeSH Terms] OR “type 2 diabetes mellitus”[All Fields] OR “type 2 diabetes”[All Fields] OR “diabetes mellitus type 2”[All Fields] OR “T2DM”[All Fields])))) AND ((((((((((((SGLT*[Title/Abstract]) OR Sodium-Glucose Transporter*[Title/Abstract]) OR Sodium-Glucose co-Transporter*[Title/Abstract]) OR Sodium-Glucose cotransporter*[Title/Abstract]) OR dapagliflozin[Title/Abstract]) OR canagliflozin[Title/Abstract]) OR empagliflozin[Title/Abstract]) OR ertugliflozin[Title/Abstract]) OR ipragliflozin[Title/Abstract]) OR luseogliflozin[Title/Abstract]) OR remogliflozin[Title/Abstract]) OR sotagliflozin[Title/Abstract]) OR tofogliflozin[Title/Abstract])) AND ((((((((((((Randomized controlled trial [pt]) OR Controlled clinical trial[pt]) OR Randomized [tiab]) OR Randomised [tiab]) OR Placebo [tiab]) OR Drug therapy [sh]) OR Randomly [tiab]) OR Trial [tiab]) OR Groups [tiab])) NOT (Animals [mh] NOT humans [mh])))))))) NOT Review[ptyp])

EMBASE

GLP-1RA

#1 'non insulin dependent diabetes mellitus'
#2 'type 2 diabetes'
#3 't2dm'
#4 'glucagon-like peptide 1 receptor agonist*'
#5 'glucagon-like peptide 1 agonist*'
#6 'glp-1 receptor agonist*'
#7 'glp-1 agonist*'
#8 'glp-1 ra*'
#9 'glp-1ra*'
#10 'glp1 receptor agonist*'
#11 'glp1 agonist*'
#12 'glp1 ra*'
#13 'glp1ra*'
#14 albiglutide
#15 dulaglutide
#16 exenatide
#17 'exendin 4'
#18 liraglutide
#19 lixisenatide
#20 semaglutide
#21 taspoglutide
#22 #1 OR #2 OR #3
#23 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#24 'clinical trial'/de
#25 'randomized controlled trial'/de
#26 'randomization'/de
#27 'single blind procedure'/de
#28 'double blind procedure'/de
#29 'crossover procedure'/de
#30 'placebo'/de
#31 'prospective study'/de
#32 'randomi?ed controlled' NEXT/1 trial*
#33 rct
#34 'randomly allocated'
#35 'allocated randomly'
#36 'random allocation'
#37 allocated NEAR/2 random
#38 single NEXT/1 blind*
#39 double NEXT/1 blind*
#40 (treble OR triple) NEAR/1 blind*

#41 placebo*
#42 #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41
#43 #22 AND #23 AND #42
#44 #43 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'meta analysis'/de OR 'meta analysis (topic)'/de OR 'network meta-analysis'/de OR 'systematic review'/de OR 'systematic review (topic)'/de)
#46. #45 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'review'/it)

SGLT2i
#1 'non insulin dependent diabetes mellitus'
#2 'type 2 diabetes'
#3 't2dm'
#4 sglt*
#5 'sodium-glucose transporter*'
#6 'sodium-glucose co-transporter*'
#7 'sodium-glucose cotransporter*'
#8 dapagliflozin
#9 canagliflozin
#10 empagliflozin
#11 ertugliflozin
#12 ipragliflozin
#13 luseogliflozin
#14 Remogliflozin
#15 sotagliflozin
#16 tofogliflozin
#17 #1 OR #2 OR #3
#18 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#19 'clinical trial'/de
#20 'randomized controlled trial'/de
#21 'randomization'/de
#22 'single blind procedure'/de
#23 'double blind procedure'/de
#24 'crossover procedure'/de
#25 'placebo'/de
#26 'prospective study'/de
#27 'randomi?ed controlled' NEXT/1 trial*
#28 rct
#29 'randomly allocated'
#30 'allocated randomly'
#31 'random allocation'

#32 allocated NEAR/2 random
#33 single NEXT/1 blind*
#34 double NEXT/1 blind*
#35 (treble OR triple) NEAR/1 blind*
#36 placebo*
#37 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
#38 #17 AND #18 AND #37
#39 #38 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'meta analysis'/de OR 'meta analysis (topic)'/de OR 'network meta-analysis'/de OR 'systematic review'/de OR 'systematic review (topic)'/de)
#41 #40 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'review'/it)

Cochrane Central Register of Controlled Trials

GLP-1RA

#1 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#2 (type 2 diabetes):ti,ab,kw
#3 (T2DM):ti,ab,kw
#4 #1 or #2 or #3
#5 MeSH descriptor: [Glucagon-Like Peptide-1 Receptor] explode all trees
#6 (glucagon-like peptide 1 receptor agonist):ti,ab,kw
#7 (glucagon-like peptide 1 agonist):ti,ab,kw
#8 (GLP-1 receptor agonist):ti,ab,kw
#9 (GLP-1 agonist):ti,ab,kw
#10 (GLP-1 RA):ti,ab,kw
#11 (GLP-1RA):ti,ab,kw
#12 (glucagon-like peptide 1 receptor agonists):ti,ab,kw
#13 (glucagon-like peptide 1 agonists):ti,ab,kw
#14 (GLP-1 receptor agonists):ti,ab,kw
#15 (GLP-1 agonists):ti,ab,kw
#16 (GLP-1 RAs):ti,ab,kw
#17 (GLP-1RAs):ti,ab,kw
#18 (GLP1 receptor agonist):ti,ab,kw
#19 (GLP1 receptor agonists):ti,ab,kw
#20 (GLP1 agonist):ti,ab,kw
#21 (GLP1 agonists):ti,ab,kw
#22 (GLP1 RA):ti,ab,kw
#23 (GLP1 RAs):ti,ab,kw
#24 (GLP1RA):ti,ab,kw
#25 (GLP1RAs):ti,ab,kw
#26 (OR #5-#25)
#27 (Albiglutide):ti,ab,kw
#28 (Dulaglutide):ti,ab,kw
#29 (Exenatide):ti,ab,kw
#30 (Liraglutide):ti,ab,kw
#31 (Lixisenatide):ti,ab,kw
#32 (Semaglutide):ti,ab,kw
#33 (Taspoglutide):ti,ab,kw
#34 (OR #27-#33)
#35 #4 and (#26 or #34)

SGLT2i

#1 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#2 (type 2 diabetes):ti,ab,kw
#3 (T2DM):ti,ab,kw
#4 #1 or #2 or #3

#5 MeSH descriptor: [Sodium-Glucose Transport Proteins] explode all trees
#6 MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] explode all trees
#7 (sodium glucose transporter*):ti,ab,kw
#8 (sodium glucose cotransporter*):ti,ab,kw
#9 (sodium glucose co-transporter*):ti,ab,kw
#10 (SGLT*):ti,ab,kw
#11 (or #5-#10)
#12 (dapagliflozin):ti,ab,kw
#13 (canagliflozin):ti,ab,kw
#14 (empagliflozin):ti,ab,kw
#15 (ertugliflozin):ti,ab,kw
#16 (ipragliflozin):ti,ab,kw
#17 (luseogliflozin):ti,ab,kw
#18 (remogliflozin):ti,ab,kw
#19 (sotagliflozin):ti,ab,kw
#20 (tofogliflozin):ti,ab,kw
#21 (or #12-#20)
#22 #4 and (#11 or #21)

Table S1. Participant characteristics of studies included in this meta-analysis in GLP-1RA treatment and SGLT2i treatment

	GLP-1RA	SGLT2i
No. studies	90	95
Age (years)	57.92±3.88	57.91±3.53
Male (%)	57.21	56.72
Baseline BMI (kg/m^2)	32.11±2.09	30.30±2.79
Baseline HbA1c (%)	8.31±0.36	8.10±0.38
Baseline weight (kg)	90.58±7.11	83.79±9.10
DM duration (years)	9.04±3.38	7.55±3.50
Baseline SBP (mmHg)	132.30±2.78	131.90±4.92
Baseline DBP (mmHg)	78.66±1.73	78.89±2.58
Antihypertensive therapy (%)*	86.21	84.12

Data are presented as mean ± standard deviation.

GLP-1RA, Glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter-2 inhibitors; BMI, body mass index; HbA1c, hemoglobin A1c; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*Based on 9 studies for GLP-1RA and 17 studies for SGLT2i that reported background antihypertensive therapies.

Table S2. Clinical characteristics of included studies in GLP-1RA treatment (sorted by first duration of follow-up, second year of publication)

Author, year	Duration of follow-up	Treatment group	Number of participants(N)	Age (years)	Male (%)	BMI (kg/m^2)	DM duration (years)	Baseline HbA1c (%)	Baseline Weight (kg)
Placebo controlled, monotherapy									
Albiglutide									
Rosenstock, 2009[Ref.73]	16 weeks	Albiglutide 4mg qw	35	50.4±10.3	42.9	34.2±5.2	4.4±4.1	8.1±1.0	97.6±23.7
		Albiglutide 15mg qw	35	55.5±10.5	51.4	31.1±4.1	4.7±4.6	8.0±0.9	88.4±14.9
		Albiglutide 30mg qw	31	54.2±9.7	25.8	33.0±3.9	5.2±5.4	8.0±0.9	88.1±13.9
		Albiglutide 15mg biw	33	52.5±9.6	42.4	32.1±4.3	4.3±4.3	8.2±1.0	88.9±19.4
		Albiglutide 30mg biw	32	55.5±9.9	50.0	31.2±4.1	5.5±4.5	8.0±1.0	88.0±14.1
		Albiglutide 50mg biw	35	51.1±10.3	54.3	32.1±4.3	5.2±5.5	8.0±0.7	92.3±15.5
		Albiglutide 50mg monthly	35	54.1±11.3	48.6	31.6±4.9	5.3±3.7	7.9±0.8	91.3±15.3
		Albiglutide 100mg monthly	34	54.4±9.9	55.9	31.8±5.2	4.3±3.7	8.0±1.0	92.2±21.1
		PBO	51	54.0±10.6	54.9	31.8±5.4	3.9±3.0	7.9±0.9	91.1±18.8
Nauck, 2016[Ref.74]	52 weeks	Albiglutide 30mg qw	101	53.6±10.9	57.4	33.7±5.1	3.4±3.7	8.0±0.8	95.8±19.6
		Albiglutide 50mg qw	99	52.0±11.8	50.5	33.9±5.5	4.2±4.6	8.2±0.9	97.1±17.8
		PBO	101	53.1±11.7	57.4	33.0±5.4	4.3±4.0	8.0±0.9	95.4±19.9
Dulaglutide									
Grunberger, 2012[Ref.75]	12 weeks	Dulaglutide 0.1mg qw	35	56.3±9.2	31.4	32.9±4.8	3.9±3.2	7.1±0.6	87.1±17.3
		Dulaglutide 0.5mg qw	34	56.9±9.1	47.1	32.3±5.4	3.7±3.8	7.2±0.6	90.2±21.3
		Dulaglutide 1.0mg qw	34	57.2±8.8	47.1	32.2±4.5	3.3±2.5	7.3±0.7	86.9±17.0
		Dulaglutide 1.5mg qw	29	57.5±7.9	44.8	31.0±4.3	4.6±4.1	7.3±0.4	85.8±18.6
		PBO	32	55.0±9.3	56.3	32.1±5.2	3.9±4.7	7.4±0.6	90.9±18.9
Miyagawa, 2015[Ref.76]	26 weeks	Dulaglutide 0.75mg qw	280	57.2±9.6	81	25.6±3.6	6.8±5.6	8.15±0.77	71.3±12.5
		PBO	70	57.7±8.3	79	25.2±3.2	6.3±5.1	8.20±0.83	69.3±11.6
Exenatide									
Moretto, 2008[Ref.77]	24 weeks	Exenatide 5μg bid	77	54±10	52	32±5	2±3	7.9±1.0	85±15
		Exenatide 10μg bid	78	55±10	62	31±5	2±3	7.8±1.0	86±16
		PBO	77	53±9	55	32±5	1±2	7.8±0.9	86±16
Semaglutide									
Aroda, 2019[Ref.78]	26 weeks	Semaglutide 3mg qd	175	55±11	50.9	31.8±6.3	3.8±5.3	7.9±0.7	86.9±21.0
		Semaglutide 7mg qd	175	56±11	53.1	31.6±6.4	3.6±5.1	8.0±0.6	89.0±21.8
		Semaglutide 14mg qd	175	54±11	49.1	31.7±6.6	3.4±4.4	8.0±0.7	88.1±22.1
		PBO	175	54±11	50.0	32.2±6.9	3.4±4.6	7.9±0.7	88.6±23.4
Sorli, 2017[Ref.79]	30 weeks	Semaglutide 0.5mg qw	128	54.6±11.1	47	32.46±7.62	4.81±6.10	8.09±0.89	89.81±22.96
		Semaglutide 1.0mg qw	130	52.7±11.9	62	33.92±8.43	3.62±4.88	8.12±0.81	96.76±25.59
		PBO	129	53.9±11.0	54	32.40±6.86	4.06±5.48	7.95±0.85	89.05±22.16
Taspoglutide									
Raz, 2012[Ref.80]	24 weeks	Taspoglutide 10mg qw	112	53.4±9.6	37	33.2±5.0	2.8±2.9	7.5±1.0	88.4±17.8
		Taspoglutide 20mg qw	127	55.0±10.4	36	31.7±4.9	2.1±2.4	7.7±1.0	85.0±17.0
		PBO	115	55.8±8.5	37	32.1±5.3	2.3±1.9	7.6±1.0	87.4±19.3

Placebo controlled, add-on therapy									
Albiglutide									
Hernandez, 2018[7]	1.6 years (median)	Albiglutide 30-50mg qw+AHA	4731	64.1±8.7	70	32.3±5.9	14.1±8.6	8.76±1.5	/
		PBO+AHA	4732	64.2±8.7	69	32.3±5.9	14.2±8.9	8.72±1.5	/
Ahrén, 2014[Ref.81]	104 weeks	Albiglutide 30mg qw+met	302	54.3±10.1	44.7	32.7±5.6	6.0±4.3	8.1±0.8	89.6±18.4
		PBO+met	101	56.1±10.0	49.5	32.8±5.4	6.7±6.6	8.2±0.9	91.6±19.3
Dulaglutide									
Ferdinand, 2014[39]	16 weeks	Dulaglutide 0.75mg qw+OAD	254	57.1±10.2	51.6	32.6±5.9	9.0±6.4	7.9±0.7	90.45±18.74
		Dulaglutide 1.5mg qw+OAD	251	56.0±10.1	51.8	32.8±5.7	7.6±5.3	7.9±0.8	90.42±18.58
		PBO+OAD	250	56.4±10.5	52.4	33.5±6.5	8.4±5.8	7.9±0.8	93.90±21.26
Dungan, 2016[Ref.82]	24 weeks	Dulaglutide 1.5mg qw+SU	239	57.7±10.2	43.5	30.9±5.2	7.8±5.3	8.4±0.7	84.5±16.4
		PBO+SU	60	58.2±7.4	46.7	32.4±5.9	6.8±3.8	8.4±0.7	89.5±18.6
Ludvik, 2018[Ref.83]	24 weeks	Dulaglutide 0.75mg qw+SGLT2i±met	141	58.55±9.14	49	32.77±6.27	10.05±6.56	8.04±0.61	91.07±20.99
		Dulaglutide 1.5mg qw+SGLT2i±met	142	56.17±9.26	54	32.87±5.56	9.21±5.74	8.04±0.65	92.87±19.73
		PBO+SGLT2i±met	140	57.10±9.59	47	32.39±4.98	8.87±6.13	8.05±0.66	90.50±19.47
Wysham, 2014[Ref.84]	26 weeks	Dulaglutide 1.5mg qw+met+TZD	279	56±10	58	33±5	9±6	8.1±1.3	96±20
		Dulaglutide 0.75mg qw+met+TZD	280	56±9	60	33±6	9±5	8.1±1.2	96±21
		PBO+met+TZD	141	55±10	59	33±6	9±6	8.1±1.3	94±19
Nauck, 2014[Ref.85]	52 weeks	Dulaglutide 0.75mg qw+met	302	54±10	44	31±4	7±5	8.2±1.1	86±18
		Dulaglutide 1.5mg qw+met	304	54±10	48	31±5	7±6	8.1±1.1	87±17
		PBO+met	177	55±9	51	31±4	7±5	8.1±1.1	87±17
Gerstein, 2019[10]	5.4 years (median)	Dulaglutide 1.5mg qw+ AHA	4949	66.2±6.5	53.4	32.3±5.7	10.5±7.3	7.3±1.1	/
		PBO+ AHA	4952	66.2±6.5	53.9	32.3±5.8	10.6±7.2	7.4±1.1	/
Exenatide									
Gill, 2010[Ref.86]	12 weeks	Exenatide 10μg bid+met±TZD	28	57±11	68	29.5±3.4	7±4	7.5±0.9	91.6±15.2
		PBO+met±TZD	26	54±10	42	30.1±3.9	6±4	7.1±0.7	85.9±12.2
Apovian, 2010[Ref.87]	24 weeks	Exenatide 5μg bid±met±SU	96	54.5±10.0	37	33.6±3.7	5.7±5.5	7.7±0.9	94.9±16.5
		PBO±met±SU	98	55.1±9.0	38	33.9±4.3	5.3±5.1	7.5±0.8	96.2±15.6
Liutkus, 2010[Ref.88]	26 weeks	Exenatide 10μg bid+TZD±met	111	55±8	60	34±6	6.3±4.2	8.2±0.9	94.5±17.8
		PBO+TZD±met	54	54±9	57	33±5	6.4±4.6	8.3±0.9	92.6±18.0
Frías, 2016[33]	28 weeks	Exenatide 2mg qw+Dapagliflozin 10mg qd+met	228	54±10	45	33.2±6.8	7.6±6.0	9.3±1.1	91.8±22.2
		PBO+Dapagliflozin 10mg qd +met	230	55±9	48	33.0±6.1	7.1±5.5	9.3±1.0	91.1±20.2
Gadde, 2017[Ref.89]	28 weeks	Exenatide 2mg qw+met	181	53.4±9.8	49.2	32.1±5.4	8.5±6.3	8.4±1.0	89.2±21.4
		PBO+met	61	53.4±9.5	60.7	31.6±5.8	7.9±4.6	8.5±1.0	88.1±20.3
Guja, 2018[Ref.90]	28 weeks	Exenatide 2mg qw+insulin	231	57.8±9.0	49.4	33.3±6.1	11.5±6.6	8.53±0.91	93.3±20.0
		PBO+insulin	230	57.6±10.3	46.5	34.1±6.6	11.1±6.1	8.53±0.92	94.7±19.8
Buse, 2011[Ref.91]	30 weeks	Exenatide 10μg bid+background antihyperglycemic therapy	137	59±10	51	33.8±5.8	12±7	8.32±0.85	95.4±20.4
		PBO+background antihyperglycemic therapy	122	59±10	64	33.1±6.2	12±7	8.50±0.96	93.4±21.2

Holman, 2017[Ref.92]	3.2 years (median)	Exenatide 2mg qw+OAD+insulin	7356	62.0 (56.0, 68.0)	62	31.8 (28.2, 36.2)	12.0 (7.0, 17.0)	8.0 (7.3, 8.9)	/
		PBO+OAD+insulin	7396	62.0 (56.0, 68.0)	62	31.7 (28.2, 36.1)	12.0 (7.0, 18.0)	8.0 (7.3, 8.9)	/
Liraglutide									
Liakos, 2019[41]	5 weeks	Liraglutide 1.2mg qd+background antihyperglycemic therapy	31	60.5±12.0	61.3	33.6±7.9	8.0±6.0	7.8±1.7	94.4±4.8
		PBO+background antihyperglycemic therapy	31	59.9±9.7	71.0	34.1±8.8	10.0±8.0	7.9±1.3	101.7±21.9
Lind, 2015[Ref.93]	24 weeks	Liraglutide 1.8mg qd+insulin	64	63.7±8.2	62.5	33.7±4.3	17.3±7.6	9.0±1.0	98.9±14.0
		PBO+insulin	60	63.5±7.7	66.7	33.5±4.0	17.0±8.1	9.0±1.1	100.0±14.8
Vanderheiden, 2016[Ref.94]	24 weeks	Liraglutide 1.8mg qd+insulin	35	52.8±8.1	34	40.7±6.7	16 (12-23)	9.0±1.2	114.6±21.4
		PBO+insulin	36	55.5±6.6	39	41.6±10.4	18 (13-27)	8.9±1.0	116.1±26.6
Nauck, 2009[28]	26 weeks	Liraglutide 0.6mg qd+met	242	56±11	62	30.5±4.8	7±5	8.4±0.9	/
		Liraglutide 1.2mg qd+met	240	57±9	54	31.1±4.8	7±5	8.3±1.0	/
		Liraglutide 1.8mg qd+met	242	57±9	59	30.9±4.6	8±5	8.4±1.0	/
		PBO+met	121	56±9	60	31.6±4.4	8±6	8.4±1.1	/
Russell-Jones, 2009[29]	26 weeks	Liraglutide 1.8mg qd+met+SU	230	57.6±9.5	57	30.4±5.3	9.2±5.8	8.3±0.9	85.5±19.4
		PBO+met+SU	114	57.5±9.6	49	31.3±5.0	9.4±6.2	8.3±0.9	85.7±16.7
Zinman, 2009[Ref.95]	26 weeks	Liraglutide 1.2mg qd+met+TZD	178	55±10	57	33.2±5.4	9±6	8.5±1.2	/
		Liraglutide 1.8mg qd+met+TZD	178	55±11	51	33.5±5.1	9±6	8.6±1.2	/
		PBO+met+TZD	177	55±10	62	33.9±5.2	9±6	8.4±1.2	/
Ahmann, 2015[Ref.96]	26 weeks	Liraglutide 1.8mg qd+insulin±met	225	59.3±9.2	53.3	32.3±5.6	12.1±7.1	8.2±0.8	90.2±20.0
		PBO+insulin±met	225	57.5±11.1	60.4	32.2±5.7	12.1±6.8	8.3±0.9	91.9±19.3
Davies, 2016[Ref.97]	26 weeks	Liraglutide 1.8mg qd+OAD±insulin	140	68±8.3	53.6	33.4±5.4	15.9±8.9	8.08±0.792	93.63±17.41
		PBO+OAD±insulin	137	66.3±8	47.4	34.5±5.4	14.2±7.5	8.00±0.853	95.63±17.65
Davies, 2015[Ref.98]	56 weeks	Liraglutide 1.8mg qd+background antihyperglycemic therapy	211	54.9±10.7	51.2	37.0±6.9	7.4±5.16	8.0±0.8	105.8±21.0
		Liraglutide 3.0mg qd+background antihyperglycemic therapy	423	55.0±10.8	52.0	37.1±6.5	7.5±5.65	7.9±0.8	105.7±21.9
		PBO+background antihyperglycemic therapy	212	54.7±9.8	45.8	37.4±7.1	6.7±5.07	7.9±0.8	106.5±21.3
Marso, 2016[9]	3.8 years (median)	Liraglutide 1.8mg qd+AHA	4668	64.2±7.2	64.5	32.5±6.3	12.8±8.0	8.7±1.6	91.9±21.2
		PBO+AHA	4672	64.4±7.2	64.0	32.5±6.3	12.9±8.1	8.7±1.5	91.6±20.8
Semaglutide									
Nauck, 2016[Ref.99]	12 weeks	Semaglutide 0.1mg qw±met	47	55.2±10.1	66	31.5±4.6	3.6±5.0	8.2±0.9	89.5±14.2
		Semaglutide 0.2mg qw±met	43	54.7±10.0	70	30.4±3.9	2.3±2.7	8.2±0.9	86.3±15.1
		Semaglutide 0.4mg qw±met	48	53.8±10.2	77	29.7±4.5	2.0±2.3	8.1±0.9	87.0±14.0
		Semaglutide 0.8mg qw±met	42	55.0±9.7	52	30.7±4.5	3.0±3.0	8.2±0.9	85.9±15.1
		Semaglutide 0.8mg qw (dose escalation)±met	43	55.9±7.9	63	31.2±4.2	2.6±2.1	8.0±0.8	85.7±12.6
		Semaglutide 1.6mg qw (dose escalation)±met	47	56.4±10.5	55	30.9±4.7	1.8±2.0	8.0±0.7	84.5±14.0
		PBO±met	46	55.3±10.6	61	31.7±3.8	2.4±3.3	8.1±0.8	90.5±13.0

Davies, 2017[Ref.100]	26 weeks	Semaglutide 2.5mg qd (standard dose escalation)+met	70	56.7±9.9	64.3	31.7±4.1	6.1±6.0	8.0±0.7	93.6±15.6
		Semaglutide 5mg qd (standard dose escalation)+met	70	55.7±11.0	67.1	31.6±4.9	5.3±4.7	7.8±0.6	93.1±19.0
		Semaglutide 10mg qd (standard dose escalation)+met	69	56.5±10.1	62.3	31.9±4.4	5.8±4.8	7.8±0.7	91.8±14.0
		Semaglutide 20mg qd (standard dose escalation)+met	70	58.3±10.4	62.9	32.0±4.5	7.0±5.3	7.9±0.7	93.8±17.9
		Semaglutide 40mg qd (standard dose escalation)+met	71	56.5±10.2	60.6	31.1±4.1	7.7±5.9	8.0±0.7	90.8±16.5
		Semaglutide 40mg qd (slow dose Escalation)+met	70	57.1±10.5	58.6	32.3±4.5	6.6±4.9	8.0±0.7	93.3±18.8
		Semaglutide 40mg qd (fast dose Escalation)+met	70	57.7±10.8	62.9	31.7±3.8	5.6±4.7	7.8±0.8	92.0±15.4
		Semaglutide 1mg qw+met	69	56.8±11.8	69.6	30.7±4.0	5.6±5.0	7.8±0.7	88.8±15.4
		PBO+met	71	58.9±10.3	56.3	32.6±4.5	6.7±5.1	8.0±0.8	93.8±18.1
Lingvay, 2018[Ref.101]	26 weeks	Semaglutide 0.05mg qd±met	64	57.5±9.8	51.6	32.3±4.6	6.5±4.6	7.9±0.7	93.4±18.3
		Semaglutide 0.1mg qd±met	63	57.5±10.0	55.6	32.4±4.5	8.1±7.3	7.9±0.8	92.4±17.2
		Semaglutide 0.2mg qd±met	65	58.4±9.6	66.2	32.8±4.5	7.2±5.7	8.0±0.8	98.1±17.9
		Semaglutide 0.3mg qd±met	63	54.8±9.7	50.8	33.1±4.7	6.5±4.4	8.2±0.8	94.8±17.8
		Semaglutide flexible dose±met	64	54.8±9.7	56.3	33.2±4.4	8.0±7.1	8.1±0.9	95.3±15.4
		PBO±met	129	57.1±9.2	55.8	32.8±4.2	7.1±4.5	8.1±0.9	94.0±17.8
Pratley, 2019[Ref.102]	26 weeks	Semaglutide 14mg qd+met±SGLT2i	285	56±10	52	32.5±5.9	7.8±5.7	8.0±0.7	92.9±20.6
		PBO+met±SGLT2i	142	57±10	52	32.9±6.1	7.8±5.5	7.9±0.7	93.2±20.0
Rodbard, 2018[Ref.103]	30 weeks	Semaglutide 0.5mg qw+insulin±met	132	59.1±10.3	56.1	*32.8 (21.1–51.4)	*12.9 (0.4–37.1)	8.36±0.83	92.74±19.57
		Semaglutide 1.0mg qw+insulin±met	131	58.5±9.0	58.8	*32.0 (19.5–51.6)	*13.7 (0.6–36.9)	8.31±0.82	92.49±22.23
		PBO+insulin±met	133	58.8±10.9	53.4	*31.8 (21.0–48.8)	*13.3 (0.8–39.6)	8.42±0.88	89.88±21.06
Zinman, 2019[Ref.104]	30 weeks	Semaglutide 1.0mg qw+SGLT2i±met	151	57.5±8.9	58.9	31.1±6.2	9.8±6.3	8.0±0.8	89.6±19.5
		PBO+SGLT2i±met	151	56.6±10.1	57.6	32.7±6.9	9.6±5.9	8.1±0.8	93.8±22.3
Husain, 2019[Ref.105]	15.9 months (median)	Semaglutide 14mg qd+AHA	1591	66±7	68.1	32.3±6.6	14.7±8.5	8.2±1.6	91.0±21.4
		PBO+AHA	1592	66±7	68.6	32.3±6.4	15.1±8.5	8.2±1.6	90.8±21.0
Marso, 2016[8]	104 weeks	Semaglutide 0.5mg qw+OAD±insulin	826	64.6±7.3	59.9	32.7±6.29	14.3±8.2	8.7±1.4	91.8±20.3
		Semaglutide 1.0mg qw+OAD±insulin	822	64.7±7.1	63.0	32.9±6.18	14.1±8.2	8.7±1.5	92.9±21.1
		PBO 0.5mg qw+OAD±insulin	824	64.8±7.6	58.5	32.9±6.35	14.0±8.5	8.7±1.5	91.8±20.3
		PBO 1.0mg qw+OAD±insulin	825	64.4±7.5	61.5	32.7±5.97	13.2±7.4	8.7±1.5	92.1±20.6
Taspoglutide									
Bergenstal, 2012[Ref.106]	24 weeks	Taspoglutide 10mg qw+met	182	55.3±9.5	56	32.7±5.2	6.1±4.8	7.95±0.93	93.6±20.4
		Taspoglutide 20mg qw+met	187	56.8±8.8	52	32.3±5.0	5.7±4.7	7.97±0.86	91.8±18.0
		PBO+met	90	56.1±10.1	52	32.5±5.5	5.5±3.9	8.03±0.83	91.1±19.0
Henry, 2012[Ref.107]	24 weeks	Taspoglutide 10mg qw+met+TZD	106	52.5±10.3	59	32.8±5.3	7.3±4.6	8.2±1.0	94.0±22.3
		Taspoglutide 20mg qw+met+TZD	113	55.5±10.1	53	33.0±5.0	8.3±5.3	8.1±0.9	93.5±21.8

		PBO+met+TZD	94	54.3±9.6	50	32.0±5.3	7.5±5.8	8.1±0.9	88.5±20.6
Active controlled, monotherapy									
Albiglutide									
Rosenstock, 2009[Ref.73]	16 weeks	Albiglutide 4mg qw	35	50.4±10.3	42.9	34.2±5.2	4.4±4.1	8.1±1.0	97.6±23.7
		Albiglutide 15mg qw	35	55.5±10.5	51.4	31.1±4.1	4.7±4.6	8.0±0.9	88.4±14.9
		Albiglutide 30mg qw	31	54.2±9.7	25.8	33.0±3.9	5.2±5.4	8.0±0.9	88.1±13.9
		Albiglutide 15mg biw	33	52.5±9.6	42.4	32.1±4.3	4.3±4.3	8.2±1.0	88.9±19.4
		Albiglutide 30mg biw	32	55.5±9.9	50.0	31.2±4.1	5.5±4.5	8.0±1.0	88.0±14.1
		Albiglutide 50mg biw	35	51.1±10.3	54.3	32.1±4.3	5.2±5.5	8.0±0.7	92.3±15.5
		Albiglutide 50mg monthly	35	54.1±11.3	48.6	31.6±4.9	5.3±3.7	7.9±0.8	91.3±15.3
		Albiglutide 100mg monthly	34	54.4±9.9	55.9	31.8±5.2	4.3±3.7	8.0±1.0	92.2±21.1
		Exenatide 5-10μg bid	35	53.7±9.4	45.7	32.4±5.1	6.4±5.4	8.0±0.9	91.1±18.8
Dulaglutide									
Umpierrez, 2014[Ref.108]	26 weeks	Dulaglutide 0.75mg qw	270	56±11	44	33±6	3±2	7.6±0.9	92±19
		Dulaglutide 1.5mg qw	269	56±10	42	34±6	3±2	7.6±0.9	93±19
		Metformin 1500-2000mg/day	268	55±10	45	33±5	3±2	7.6±0.8	92±19
Miyagawa, 2015[Ref.76]	26 weeks	Dulaglutide 0.75mg qw	280	57.2±9.6	81	25.6±3.6	6.8±5.6	8.15±0.77	71.3±12.5
		Liraglutide 0.9mg qd	137	57.9±10.4	83	25.5±3.5	6.3±6.0	8.08±0.89	70.2±12.5
Chen, 2018[Ref.109]	52 weeks	Dulaglutide 1.5mg qw	239	52.7±10.75	56.1	25.8±3.43	4.0±4.44	8.0±0.95	/
		Dulaglutide 0.75mg qw	239	53.8±10.09	53.1	26.2±3.49	3.5±4.06	8.0±1.03	/
		Glimepiride 1-3mg qd	242	52.0±10.05	53.7	25.7±3.14	3.8±4.09	7.9±1.01	/
Exenatide									
Russell-Jones, 2012[Ref.110]	26 weeks	Exenatide 2mg qw	248	54±11	56.0	31.4±5.3	2.7±3.2	8.5±1.2	87.5±18.9
		Metformin 2000mg/day	246	55±11	62.6	30.7±5.5	2.6±3.6	8.6±1.2	85.9±19.6
		Pioglitazone 45mg qd	163	55±11	59.5	31.1±5.3	2.7±3.7	8.5±1.2	86.1±17.8
		Sitagliptin 100mg qd	163	52±11	57.7	31.8±5.4	2.7±3.7	8.5±1.3	88.7±18.7
Xu, 2015[Ref.111]	48 weeks	Exenatide 10μg bid	142	50±9.6	69.0	26.1±3.6	/	8.0±1.2	72.6±11.9
		Premixed insulin	138	51±9.7	61.6	25.6±3.5	/	8.1±1.2	70.3±11.8
		Pioglitazone 45mg qd	136	50±8.9	61.0	25.8±3.5	/	8.0±1.2	71.2±11.7
Liraglutide									
Garber, 2009[Ref.112]	52 weeks	Liraglutide 1.2mg qd	251	53.7±11.0	47	33.2±5.6	5.2±5.5	8.3±1.0	92.5±19.2
		Liraglutide 1.8mg qd	247	52.0±10.8	49	32.8±6.3	5.3±5.1	8.3±1.1	92.8±20.7
		Glimepiride 8mg qd	248	53.4±10.9	54	33.2±5.6	5.6±5.1	8.4±1.2	93.4±19.2
Semaglutide									
Seino, 2018[Ref.113]	30 weeks	Semaglutide 0.5mg qw	103	58.8±10.4	76.7	25.1±3.8	8.0±5.2	8.2±1.0	67.8±11.7
		Semaglutide 1mg qw	102	58.1±11.6	73.5	26.1±5.2	7.8±6.9	8.0±0.9	70.8±16.4
		Sitagliptin 100mg qd	103	57.9±10.1	78.6	25.1±3.6	8.1±6.7	8.2±0.9	69.4±12.9
Active controlled, add-on therapy									
Albiglutide									
Weissman, 2014[Ref.114]	52 weeks	Albiglutide 30mg qw+met±SU	504	55.8±9.3	56.7	33.2±5.6	8.9±6.5	8.28±0.90	95.1±19.7
		Insulin Glargine+met±SU	241	54.7±9.8	54.8	33.0±5.4	8.4±5.7	8.36±0.95	94.6±19.1

Ahrén, 2014[Ref.81]	104 weeks	Albiglutide 30mg qw+met	302	54.3±10.1	44.7	32.7±5.6	6.0±4.3	8.1±0.8	89.6±18.4
		Sitagliptin 100mg qd+met	302	54.3±9.8	46.0	32.5±5.4	5.8±4.8	8.1±0.8	90.3±19.1
		Glimepiride 2mg qd+met	307	54.4±10.0	51.5	32.5±5.5	6.0±4.8	8.1±0.8	91.8±20.4
Dulaglutide									
Dungan, 2014[Ref.115]	26 weeks	Dulaglutide 1.5mg qw+met	299	56.6±9.3	46	33.5±5.1	7.1±5.4	8.1±0.8	93.8±18.2
		Liraglutide 1.8mg qd+met	300	56.8±9.9	50	33.6±5.2	7.3±5.4	8.1±0.8	94.4±19.0
Wysham, 2014[Ref.84]	26 weeks	Dulaglutide 0.75mg qw+met+TZD	280	56±9	60	33±6	9±5	8.1±1.2	96±21
		Dulaglutide 1.5mg qw+met+TZD	279	56±10	58	33±5	9±6	8.1±1.3	96±20
		Exenatide 10μg bid+met+TZD	276	55±10	57	34±5	9±6	8.1±1.3	97±19
Araki, 2015[Ref.116]	26 weeks	Dulaglutide 0.75mg qw+SU±met	181	57.5±10.5	69	26.1±3.6	8.9±6.7	8.1±0.8	70.9±13.7
		Insulin Glargine+SU±met	180	56.1±11.3	74	25.9±3.9	8.8±6.1	8.0±0.9	71.1±13.8
Blonde, 2015[Ref.117]	26 weeks	Dulaglutide 0.75mg qw+insulin Lispro	293	59.3±9.0	50	33.1±5.2	12.4±6.9	8.40±1.03	91.7±18.0
		Dulaglutide1.5mg qw+insulin Lispro	295	58.9±9.6	54	32.0±5.1	12.8±7.2	8.46±1.08	91.0±18.2
		Insulin Glargine+insulin Lispro	296	59.9±9.1	56	32.4±5.3	13.0±6.8	8.53±1.03	90.8±18.9
Wang, 2019[Ref.118]	26 weeks	Dulaglutide 0.75mg qw±met±SU	252	54.5±10.0	56.7	27.0±3.8	8.1±5.3	8.3±1.1	74.6±12.7
		Dulaglutide 1.5mg qw±met±SU	253	55.0±9.6	53.4	26.6±3.7	7.9±4.8	8.5±1.2	73.6±13.0
		Insulin Glargine±met±SU	250	55.4±9.2	55.6	26.7±3.5	8.4±5.3	8.3±1.1	73.4±13.1
Pratley, 2018[Ref.119]	40 weeks	Dulaglutide 0.75mg qw+met	299	55±10·4	54	33.6±6.9	7.0±5.5	8.2±0.9	95.6±23.0
		Dulaglutide 1.5mg qw+met	299	56±10·6	57	33.1±6.6	7.6±5.6	8.2±0.9	93.4±21.8
		Semaglutide 0.5mg qw+met	301	56±10·9	56	33.7±7.1	7.7±5.9	8.3±0.9	96.4±24.4
		Semaglutide 1.0mg qw+met	300	55±10·6	54	33.6±6.5	7.3±5.7	8.2±0.9	95.5±20.9
Giorgino, 2015[Ref.120]	52 weeks	Dulaglutide 0.75mg qw+met+SU	272	57±9	50	32±5	9±6	8.1±1	86±18
		Dulaglutide 1.5mg qw+met+SU	273	54±10	53	31±5	9±6	8.2±1	85±18
		Insulin Glargine+met+SU	262	57±9	51	32±6	9±6	8.1±1	88±20
Nauck, 2014[Ref.85]	52 weeks	Dulaglutide 0.75mg qw+met	302	54±10	44	31±4	7±5	8.2±1.1	86±18
		Dulaglutide 1.5mg qw+met	304	54±10	48	31±5	7±6	8.1±1.1	87±17
		Sitagliptin 100mg qd+met	315	54±10	48	31±4	7±5	8.1±1.1	86±17
Exenatide									
Wysham, 2016[Ref.121]	20 weeks	Exenatide 2mg qw±met±TZDe	29	49.0±9.8	65.5	33.8±5.4	6.0±5.5	8.63±1.21	101.1±20.4
		Exenatide 5mg monthly±met±TZD	26	50.0±10.1	57.7	33.4±6.0	5.0±3.6	8.42±1.14	92.4±17.1
		Exenatide 8mg monthly±met±TZD	28	52.3±10.7	82.1	34.0±6.0	6.4±5.9	8.61±1.22	102.7±16.0
		Exenatide 11mg monthly±met±TZD	27	49.9±10.6	55.6	33.8±5.7	6.7±5.8	8.36±1.34	95.4±19.6
Blevins, 2011[Ref.122]	24 weeks	Exenatide 2mg qw+met/SU/TZD	129	56±11	60	33.6±5.5	7±5	8.5±1.1	97.0±20.7
		Exenatide 10μg bid+met/SU/TZD	123	55±10	55	33.0±5.3	7±5	8.4±1.2	94.3±18.9
Rosenstock, 2013[Ref.123]	24 weeks	Exenatide 10μg bid+met±TZD	373	55±9.9	49	33.8±5.2	6.5±5.4	8.1±0.9	94.5±18.6
		Taspoglutide 10mg qw+met±TZD	384	56±10.0	58	33.5±5.2	6.3±5.2	8.1±0.9	95.5±20.0
		Taspoglutide 20mg qw+met±TZD	392	56±9.6	52	33.1±5.3	7.0±5.7	8.1±0.9	93.2±18.9
Buse, 2009[Ref.124]	26 weeks	Exenatide 10μg bid±met±SU	231	57.1±10.8	55	32.9±5.7	7.9±5.9	8.1±1.0	93.0±19.5
		Liraglutide1.8mg qd±met±SU	233	56.3±9.8	49	32.9±5.5	8.5±6.2	8.2±1.0	93.1±20.1
Davies, 2009[Ref.125]	26 weeks	Exenatide 5-10μg bid+OAD	118	56.8±10.2	70.3	34.6±5.7	9.0±4.6	8.65±0.68	101.4±19.8
		Insulin Glargine+OAD	116	56.2±7.9	66.4	33.7±4.9	8.4±4.4	8.48±0.66	97.6±16.4

Bergenstal, 2010[Ref.126]	26 weeks	Exenatide 2mg qw+met	160	52±10	56	32±5	5±4	8.6±1.2	89±20
		Sitagliptin 100mg qd+met	166	52±11	52	32±5	6±5	8.5±1.2	87±20
		Pioglitazone 45mg qd+met	165	53±10	48	32±6	6±5	8.5±1.1	88±20
Diamant, 2010[Ref.127]	26 weeks	Exenatide 2mg qw+met±SU	233	58±10	52	32±5	8.0±6.0	8.3±1.1	91.2±18.6
		Insulin Glargine+met±SU	223	58±9	55	32±5	7.8±6.0	8.3±1.0	90.6±16.4
Buse, 2013[Ref.128]	26 weeks	Exenatide 2mg qw+OAD	461	57±9.4	55	32.3±5.6	8±6	8.5±1.0	90.9±19.5
		Liraglutide 1.8mg qd+OAD	450	57±9.6	54	32.3±5.4	9±6	8.4±1.0	91.1±19.1
Davies, 2013[Ref.129]	26 weeks	Exenatide 2mg qw+met±SU	111	59±10	64	33.7±4.7	8±6	8.37±0.85	96.7±17.0
		Insulin Detemir+met±SU	105	58±10	69	33.7±4.7	7±5	8.35±0.88	97.9±15.8
Ji, 2013[Ref.130]	26 weeks	Exenatide 2mg qw+OAD	340	55±11	53.8	26.4±3.7	7.7±5.1	8.7±1.0	69.6±12.4
		Exenatide 10μg bid+OAD	338	56±10	54.4	26.7±3.4	8.6±6.0	8.7±1.0	70.4±12.1
Gadde, 2017[Ref.89]	28 weeks	Exenatide 2mg qw+met	181	53.4±9.8	49.2	32.1±5.4	8.5±6.3	8.4±1.0	89.2±21.4
		Sitagliptin 100mg qd+met	122	54.3±9.0	54.1	31.5±5.1	8.7±5.8	8.5±1.0	89.0±20.1
Wysham, 2018[Ref.131]	28 weeks	Exenatide 2mg qw+background antihyperglycemic therapy	229	56±10	65	33±6	9±6	8.5±1.0	97±23
		Exenatide 10μg bid+background antihyperglycemic therapy	146	57±10	63	33±5	8±6	8.5±1.0	97±19
Diamant, 2014[Ref.132]	30 weeks	Exenatide 5-10μg bid+insulin Glargine+met	247	59.5±9.6	52	32.7±4.7	12 (8-17)	8.3±1.0	91.1±16.6
		Insulin Lispro+insulin Glargine+met	263	59.4±9.3	51	32.3±4.7	11 (8-15)	8.2±0.9	89.4±17.0
Drucker, 2008[Ref.133]	30 weeks	Exenatide 2mg qw+met/SU/TZD	148	55±10	55	35±5	6±5	8.3±1.0	102±21
		Exenatide10μg bid+met/SU/TZD	147	55±10	51	35±5	7±6	8.3±1.0	102±19
Nauck, 2007[Ref.134]	52 weeks	Exenatide 5-10μg bid+met+SU	253	59±9	53	30.6±4.0	9.8±6.3	8.6±1.0	85.5±15.7
		Insulin Aspart+met+SU	248	58±9	49	30.2±4.2	10.0±6.2	8.6±1.1	83.4±15.6
Ahmann, 2018[Ref.135]	56 weeks	Exenatide 2mg qw+met±TZD±SU	405	*56.7 (21–83)	56.3	*33.6 (21.2–55.8)	*9.4 (0.3–54.0)	*8.3 (6.5–11.2)	*95.4 (53.2–171.9)
		Semaglutide 1mg qw+met±TZD±SU	404	*56.4 (20–82)	54.2	*34.0 (21.0–72.8)	*9.0 (0.4–37.1)	*8.4 (6.7–11.1)	*96.2 (49.9–198.3)
Simo, 2015[Ref.136]	144 weeks	Exenatide 10μg bid+met	511	56±10	56	32.5±4.2	/	7.5±0.7	92.6±16.6
		Glimepiride 1mg qd+met	508	57±9	52	32.3±4.0	/	7.4±0.7	90.9±15.1
Liraglutide									
Meier, 2015[Ref.137]	8 weeks	Liraglutide 1.2mg qd+insulin ±met±SU±DPP-4i	47	61.4±7.9	83.0	30.5±4	10.5±15.2	7.8±0.8	91.4±14
		Liraglutide 1.8mg qd+insulin ±met±SU±DPP-4i	47	62.6±9.4	70.2	31.2±4.3	12.5±15.2	7.9±0.8	93.1±15.4
		Lixisenatide 20μg qd+insulin ±met±SU±DPP-4i	48	61.6±7.4	68.8	30.7±4.3	11.4±15.2	7.8±0.7	90.3±13.3
Brady, 2014[Ref.138]	12 weeks	Liraglutide 1.2mg qd +met	47	51.5±11.1	51.1	33.0±7.3	/	7.6±1.1	86.1±16.9
		SU+met	52	52.2±10.7	50.0	30.1±4.3	/	7.8±1.0	79.0±11.2
D'Alessio, 2015[Ref.139]	24 weeks	Liraglutide 1.8mg qd+OAD	470	57.4±8.9	56.0	31.8±4.1	8.4 (1.0, 33.5)	9.1±1.1	90.1±16.7
		Insulin Glargine+OAD	474	57.1±8.8	52.7	32.0±4.2	8.5 (0.9, 34.8)	9.0±1.0	90.8±16.6
Abreu, 2019[Ref.140]	24 weeks	Liraglutide 1.8mg qd+insulin Detemir	59	46.7±9.0	32.2	36.1±9.5	10 (6,15)	12.1±1.4	96.7±31.2
		Insulin Aspart+insulin Detemir	61	48.1±10.0	26.2	38.3±11.0	10 (4,16)	12.0±1.5	105.5±32.5

Buse, 2009[Ref.124]	26 weeks	Liraglutide 1.8mg qd±met±SU	233	56.3±9.8	49	32.9±5.5	8.5±6.2	8.2±1.0	93.1±20.1
		Exenatide 10μg bid±met±SU	231	57.1±10.8	55	32.9±5.7	7.9±5.9	8.1±1.0	93.0±19.5
Nauck, 2009[28]	26 weeks	Liraglutide 0.6mg qd+met	242	56±11	62	30.5±4.8	7±5	8.4±0.9	/
		Liraglutide 1.2mg qd+met	240	57±9	54	31.1±4.8	7±5	8.3±1.0	/
		Liraglutide 1.8mg qd+met	242	57±9	59	30.9±4.6	8±5	8.4±1.0	/
		Glimepiride 4mg qd+met	242	57±9	57	31.2±4.6	8±5	8.4±1.0	/
Russell-Jones, 2009[29]	26 weeks	Liraglutide 1.8mg qd+met+SU	230	57.6±9.5	57	30.4±5.3	9.2±5.8	8.3±0.9	85.5±19.4
		Insulin Glargine+met+SU	232	57.5±10.5	60	30.3±5.3	9.7±6.4	8.2±0.9	85.0±17.9
Pratley, 2010[Ref.141]	26 weeks	Liraglutide 1.2mg qd+met	225	55.9±9.6	52	93.7±18.4	6.0±4.5	8.4±0.8	93.7±18.4
		Liraglutide 1.8mg qd+met	221	55.0±9.1	52	94.6±18.1	6.4±5.4	8.4±0.7	94.6±18.1
		Sitagliptin 100mg qd+met	219	55.0±9.0	55	93.1±18.9	6.3±5.4	8.5±0.7	93.1±18.9
Buse, 2013[Ref.128]	26 weeks	Liraglutide 1.8mg qd+OAD	450	57±9.6	54	32.3±5.4	9±6	8.4±1.0	91.1±19.1
		Exenatide 2mg qw+OAD	461	57±9.4	55	32.3±5.6	8±6	8.5±1.0	90.9±19.5
Charbonnel, 2013[Ref.142]	26 weeks	Liraglutide 0.6-1.2mg qd+met	327	57.6±10.8	55	32.7±6.1	8.2±6.2	8.1±0.9	92.1±20.4
		Sitagliptin 100mg qd+met	326	56.9±10	55	32.6±5.9	7.6±4.8	8.2±1.1	91.0±20.5
De Wit, 2014[Ref.143]	26 weeks	Liraglutide 0.6-1.8mg qd±insulin±OAD	26	57±10	61.5	34±7	8.3±5.9	7.2±0.6	102.3±20.1
		Continuation and intensification of insulin therapy±OAD	24	59±8	62.5	32±5	7.6±6.2	7.5±0.7	97.7±18.5
Dungan, 2014[Ref.115]	26 weeks	Liraglutide 1.8mg qd+met	300	56.8±9.9	50	33.6±5.2	7.3±5.4	8.1±0.8	94.4±19.0
		Dulaglutide 1.5mg qw+met	299	56.6±9.3	46	33.5±5.1	7.1±5.4	8.1±0.8	93.8±18.2
Bailey, 2016[Ref.144]	26 weeks	Liraglutide 1.8mg qd+met	202	56.3±10.6	58	31.7±6	7.9±5.7	8.3±0.6	88.9±19.8
		Sitagliptin 100mg qd+met	204	56.5±9.7	61	32.2±6.2	7.6±6.2	8.2±0.6	91.2±19.6
Nauck, 2016[Ref.145]	26 weeks	Liraglutide 1.8mg qd+met	202	56.3±10.6	65	34.5±6.8	6.5±5.3	8.4±0.7	101.9±23.3
		Lixisenatide 20μg qd+met	202	56.1±10.0	55	34.9±6.6	6.3±5.0	8.4±0.8	100.6±19.9
Zang, 2016[Ref.146]	26 weeks	Liraglutide 1.8mg qd+met	183	51.7±10.7	55.7	27.3±3.4	5.3±4.4	8.14±0.83	76.2±13.6
		Sitagliptin 100mg qd+met	184	51.4±11.0	63.6	27.2±4.0	5.2±5.4	8.11±0.78	75.8±15.1
Kaku, 2016[Ref.147]	52 weeks	Liraglutide 0.9mg qd+ glinide/met/AGI/TZD	240	59.6±11.6	75.8	25.7±4.2	7.80±5.77	8.1±0.8	69.4±14.2
		One additional OAD (DPP4/ SU/glinide/met/AGI/TZD)+glinide/met/ AGI/TZD	120	59.2±10.2	66.7	25.5±3.7	8.47±6.55	8.1±0.8	68.2±13.6
Lixisenatide									
Meier, 2015[Ref.137]	8 weeks	Lixisenatide 20μg qd+insulin ±met±SU±DPP-4i	48	61.6±7.4	68.8	30.7±4.3	11.4±15.2	7.8±0.7	90.3±13.3
		Liraglutide 1.2mg qd+insulin ±met±SU±DPP-4i	47	61.4±7.9	83.0	30.5±4	10.5±15.2	7.8±0.8	91.4±14
		Liraglutide 1.8mg qd+insulin ±met±SU±DPP-4i	47	62.6±9.4	70.2	31.2±4.3	12.5±15.2	7.9±0.8	93.1±15.4
Nauck, 2016[Ref.145]	26 weeks	Lixisenatide 20μg qd+met	202	56.1±10.0	55	34.9±6.6	6.3±5.0	8.4±0.8	100.6±19.9
		Liraglutide 1.8mg qd+met	202	56.3±10.6	65	34.5±6.8	6.5±5.3	8.4±0.7	101.9±23.3
Semaglutide									

Nauck, 2016[Ref.99]	12 weeks	Semaglutide 0.1mg qw±met	47	55.2±10.1	66	31.5±4.6	3.6±5.0	8.2±0.9	89.5±14.2
		Semaglutide 0.2mg qw±met	43	54.7±10.0	70	30.4±3.9	2.3±2.7	8.2±0.9	86.3±15.1
		Semaglutide 0.4mg qw±met	48	53.8±10.2	77	29.7±4.5	2.0±2.3	8.1±0.9	87.0±14.0
		Semaglutide 0.8mg qw±met	42	55.0±9.7	52	30.7±4.5	3.0±3.0	8.2±0.9	85.9±15.1
		Semaglutide 0.8mg qw (dose escalation)±met	43	55.9±7.9	63	31.2±4.2	2.6±2.1	8.0±0.8	85.7±12.6
		Semaglutide 1.6mg qw (dose escalation)±met	47	56.4±10.5	55	30.9±4.7	1.8±2.0	8.0±0.7	84.5±14.0
		Liraglutide 1.2mg qd±met	45	54.8±9.2	69	31.0±4.6	3.3±3.4	8.0±0.8	90.5±13.5
		Liraglutide 1.8mg qd±met	50	54.3±10.1	70	30.9±4.6	2.5±2.6	8.1±0.7	87.2±13.1
Lingvay, 2018[Ref.101]	26 weeks	Semaglutide 0.05mg qd±met	64	57.5±9.8	51.6	32.3±4.6	6.5±4.6	7.9±0.7	93.4±18.3
		Semaglutide 0.1mg qd±met	63	57.5±10.0	55.6	32.4±4.5	8.1±7.3	7.9±0.8	92.4±17.2
		Semaglutide 0.2mg qd±met	65	58.4±9.6	66.2	32.8±4.5	7.2±5.7	8.0±0.8	98.1±17.9
		Semaglutide 0.3mg qd±met	63	54.8±9.7	50.8	33.1±4.7	6.5±4.4	8.2±0.8	94.8±17.8
		Semaglutide flexible dose±met	64	54.8±9.7	56.3	33.2±4.4	8.0±7.1	8.1±0.9	95.3±15.4
		Liraglutide 0.3mg qd±met	64	57.2±10.8	45.3	32.9±3.9	8.1±7.1	8.1±0.9	92.3±17.5
		Liraglutide 0.6mg qd±met	64	59.5±9.8	50.0	33.0±4.3	6.8±4.6	8.1±0.8	92.7±16.5
		Liraglutide 1.2mg qd±met	64	53.7±11.4	53.1	33.3±4.3	6.9±4.9	8.1±0.9	96.7±18.3
		Liraglutide 1.8mg qd±met	65	55.8±9.2	50.8	32.1±4.5	6.6±5.2	8.1±0.8	93.4±19.3
Pratley, 2019[Ref.102]	26 weeks	Semaglutide 14mg qd+met±SGLT2i	285	56±10	52	32.5±5.9	7.8±5.7	8.0±0.7	92.9±20.6
		Liraglutide 1.8mg qd+met±SGLT2i	284	56±10	52	33.4±6.7	7.3±5.3	8.0±0.7	95.5±21.9
Rosenstock, 2019[Ref.148]	26 weeks	Semaglutide 3mg qd+met±SU	466	58±10	54.5	32.6±6.7	8.4±6.1	8.3±1.0	91.6±22.0
		Semaglutide 7mg qd+met±SU	465	58±10	52.7	32.6±6.4	8.3±5.8	8.4±1.0	91.3±20.8
		Semaglutide 14mg qd+met±SU	465	57±10	53.1	32.6±6.3	8.7±6.1	8.3±0.9	91.2±21.7
		Sitagliptin 100mg qd+met±SU	467	58±10	51.0	32.5±6.2	8.8±6.0	8.3±0.9	90.9±21.0
Aroda, 2017[Ref.149]	30 weeks	Semaglutide 0.5mg qw+met±SU	362	56.5±10.3	54	33.1±6.5	7.8±5.1	8.1±0.8	93.7±21.4
		Semaglutide 1.0mg qw+met±SU	360	56.7±10.4	51	33.0±6.5	9.3±7.2	8.3±0.9	94.0±22.5
		Insulin Glargine+met±SU	360	56.2±10.6	54	33.0±6.5	8.6±6.3	8.1±0.9	92.6±21.5
Pratley, 2018[Ref.119]	40 weeks	Semaglutide 0.5mg qw+met	301	56±10·9	56	33.7±7.1	7.7±5.9	8.3±0.9	96.4±24.4
		Semaglutide 1.0mg qw+met	300	55±10·6	54	33.6±6.5	7.3±5.7	8.2±0.9	95.5±20.9
		Dulaglutide 0.75mg qw+met	299	55±10·4	54	33.6±6.9	7.0±5.5	8.2±0.9	95.6±23.0
		Dulaglutide 1.5mg qw+met	299	56±10·6	57	33.1±6.6	7.6±5.6	8.2±0.9	93.4±21.8
Ahrén 2017[Ref.150]	56 weeks	Semaglutide 0.5mg qw±met±TZD	409	54.8±10.2	51	32.4±6.2	6.4±4.7	8.0±0.9	89.9±20.4
		Semaglutide 1.0mg qw±met±TZD	409	56.0±9.4	50	32.5±6.6	6.7±5.6	8.0±0.9	89.2±20.7
		Sitagliptin 100mg qd±met±TZD	407	54.6±10.4	51	32.5±5.8	6.6±5.1	8.2±0.9	89.3±19.7
Ahmann, 2018[Ref.135]	56 weeks	Semaglutide 1mg qw+met±TZD±SU	404	*56.4 (20–82)	54.2	*34.0 (21.0–72.8)	*9.0 (0.4–37.1)	*8.4 (6.7–11.1)	*96.2 (49.9–198.3)
		Exenatide 2mg qw+met±TZD±SU	405	*56.7 (21–83)	56.3	*33.6 (21.2–55.8)	*9.4 (0.3–54.0)	*8.3 (6.5–11.2)	*95.4 (53.2–171.9)
Kaku, 2018[Ref.151]	56 weeks	Semaglutide 0.5mg qw+background antihyperglycemic therapy	239	58.0±10.6	69.5	26.2±4.8	8.1±6.0	8.0±0.9	71.0±15.4
		Semaglutide 1.0mg qw+background antihyperglycemic therapy	241	58.7±10.2	72.2	26.4±4.7	9.4±6.5	8.1±1.0	71.7±15.9

		One additional OAD (DPP4/met/SU/glinide/AGI/TZD)+back ground antihyperglycemic therapy	120	59.2±10.1	74.2	26.7±4.6	9.3±7.0	8.1±0.9	72.2±14.9
Taspoglutide									
Bergenstal, 2012[Ref.106]	24 weeks	Taspoglutide 10mg qw+met	182	55.3±9.5	56	32.7±5.2	6.1±4.8	7.95±0.93	93.6±20.4
		Taspoglutide 20mg qw+met	187	56.8±8.8	52	32.3±5.0	5.7±4.7	7.97±0.86	91.8±18.0
		Sitagliptin 100mg qd+met	177	55.5±9.9	59	32.4±5.0	6.0±5.0	7.94±0.85	92.5±19.7
Nauck, 2013[Ref.152]	24 weeks	Taspoglutide 10mg qw+met	361	58±10	56	32.1±5.3	9±6	8.24±0.9	90.2±19.2
		Taspoglutide 20mg qw+met	348	57±9	57	32.4±5.3	9±6	8.26±0.9	91.5±19.8
		Insulin Glargine+met	319	58±9	46	32.7±5.2	10±6	8.35±0.9	90.6±19.5
Pratley,2013[Ref.153]	24 weeks	Taspoglutide 10 mg qw+SU±met	240	57.1±9.7	50	32.4±5.2	9.4±6.9	8.3±0.9	90.6±19.8
		Taspoglutide 20 mg qw+SU±met	245	55.8±9.8	51	32.7±5.1	8.5±5.8	8.3±0.9	89.8±19.5
		Pioglitazone 45mg qd+SU±met	255	56.4±9.8	45	33.1±5.2	8.6±6.1	8.3±0.8	90.0±17.8
Rosenstock, 2013[Ref.123]	24 weeks	Taspoglutide 10mg qw+met±TZD	384	56±10.0	58	33.5±5.2	6.3±5.2	8.1±0.9	95.5±20.0
		Taspoglutide 20mg qw+met±TZD	392	56±9.6	52	33.1±5.3	7.0±5.7	8.1±0.9	93.2±18.9
		Exenatide 10μg bid+met±TZD	373	55±9.9	49	33.8±5.2	6.5±5.4	8.1±0.9	94.5±18.6

Data are presented as mean ± standard deviation or median (interquartile range) unless otherwise specified.

GLP-1RA, Glucagon-like peptide-1 receptor agonists; BMI, body mass index; DM, diabetes mellitus; HbA1c, hemoglobin A1c; PBO, placebo; AHA, antihyperglycemic agents; OAD, oral antidiabetes drug; MET, metformin; SU, sulfonylurea; DPP-4i, dipeptidyl-peptidase-4 inhibitors; AGI, alpha-glucosidase inhibitors; TZD, thiazolidinedione; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

*Data are presented as mean (range).

Table S3. Clinical characteristics of included studies in SGLT2i treatment (sorted by first duration of follow-up, second year of publication)

Author, year	Duration of follow-up	Treatment group	Number of participants(N)	Age (years)	Male (%)	BMI (kg/m^2)	DM duration (years)	Baseline HbA1c (%)	Baseline Weight (kg)
Placebo controlled, monotherapy									
Canagliflozin									
Inagaki, 2013[Ref.154]	12 weeks	Canagliflozin 50mg qd	82	57.4±10.8	61.0	25.11±4.13	/	8.13±0.78	65.77±13.56
		Canagliflozin 100mg qd	74	57.7±10.5	70.3	25.61±4.64	/	8.05±0.86	68.61±14.86
		Canagliflozin 200mg qd	76	57.0±10.7	64.5	25.51±4.30	/	8.11±0.88	68.97±14.5
		Canagliflozin 300mg qd	75	57.1±10.1	73.3	25.89±3.68	/	8.17±0.81	71.30±12.19
		PBO	75	57.7±11.0	72.0	26.41±4.34	/	7.99±0.77	72.56±15.36
Inagaki, 2014[Ref.155]	24 weeks	Canagliflozin 100mg qd	90	58.4±10.4	65.6	25.59±4.20	4.72±4.59	7.98±0.73	69.10±14.48
		Canagliflozin 200mg qd	88	57.4±11.1	81.8	25.43±4.18	5.88±5.93	8.04±0.77	69.88±14.22
		PBO	93	58.2±11.0	64.5	25.85±4.39	5.63±5.76	8.04±0.70	68.57±15.15
Stenlöf, 2013[Ref.156]	26 weeks	Canagliflozin 100mg qd	195	55.1±10.8	41.5	31.3±6.6	4.5±4.4	8.1±1.0	85.8±21.4
		Canagliflozin 300mg qd	197	55.3±10.2	45.2	31.7±6.0	4.3±4.7	8.0±1.0	86.9±20.5
		PBO	192	55.7±10.9	45.8	31.8±6.2	4.2±4.1	8.0±1.0	87.6±19.5
Dapagliflozin									
List, 2009[63]	12 weeks	Dapagliflozin 2.5mg qd	59	55±11	49	32±5	/	7.6±0.7	90±20
		Dapagliflozin 5mg qd	58	55±12	48	32±5	/	8.0±0.9	89±17
		Dapagliflozin 10mg qd	47	54±9	53	31±5	/	8.0±0.8	86±17
		Dapagliflozin 20mg qd	59	55±10	54	31±5	/	7.7±0.9	88±18
		Dapagliflozin 50mg qd	56	53±10	45	32±4	/	7.8±1.0	92±19
		PBO	54	53±11	56	32±5	/	7.9±0.9	89±18
Kaku, 2013[Ref.157]	12 weeks	Dapagliflozin 1mg qd	59	55.9±9.7	79.7	/	4.89±4.37	8.10±0.79	68.40±11.04
		Dapagliflozin 2.5mg qd	56	57.7±9.3	69.6	/	4.41±3.97	7.92±0.74	66.61±14.29
		Dapagliflozin 5mg qd	58	58.0±9.5	81.0	/	5.34±4.51	8.05±0.66	68.92±12.43
		Dapagliflozin 10mg qd	52	56.5±11.5	75.0	/	4.73±4.73	8.18±0.69	70.35±17.48
		PBO	54	58.4±10.0	79.6	/	4.74±3.82	8.12±0.71	68.88±14.94
Ferrannini, 2010[Ref.158]	24 weeks	Dapagliflozin 2.5mg qd	65	53.0±11.7	55.4	32.6±5.5	0.50 (0.10,2.90)	7.92±0.90	90.8±22.8
		Dapagliflozin 5.0mg qd	64	52.6±10.9	48.4	31.9±4.8	0.25 (0.10,1.40)	7.86±0.94	87.6±17.1
		Dapagliflozin 10mg qd	70	50.6±9.97	48.6	33.6±5.4	0.45 (0.10, 3.40)	8.01±0.96	94.2±18.7
		PBO	75	52.7±10.3	41.3	32.3±5.5	0.50 (0.10,3.40)	7.84±0.87	88.8±19
Bailey, 2012[Ref.159]	24 weeks	Dapagliflozin 1mg qd	72	53.7±9.04	52.8	32.53±5.68	1.6±2.55	7.8±0.98	88.2±18.49
		Dapagliflozin 2.5mg qd	74	53.5±10.61	45.9	31.13±5.47	1.5±2.19	8.1±1.07	84.3±18.18
		Dapagliflozin 5mg qd	68	51.3±11.51	47.1	30.97±5.68	1.4±3.24	7.9±1.03	85.4±19.43
		PBO	68	53.5±11.08	54.4	32.47±4.91	1.1±1.95	7.8±1.12	90±17.98
Ji, 2014[Ref.160]	24 weeks	Dapagliflozin 5mg qd	128	53.0±11.07	65.6	25.17±3.29	1.15±2.3	8.14±0.74	68.89±11.43
		Dapagliflozin 10mg qd	133	51.2±9.89	64.7	25.76±3.43	1.67±2.8	8.28±0.95	70.92±11.64
		PBO	132	49.9±10.87	65.9	25.93±3.64	1.30±2.0	8.35±0.95	72.18±13.23
Kaku, 2014[Ref.161]	24 weeks	Dapagliflozin 5 mg qd	86	58.6±10.4	58.1	24.88±3.91	4.59±5.56	7.50±0.72	65.81±14.37

		Dapagliflozin 10 mg qd	88	57.5±9.3	60.2	26.06±4.52	4.93±4.52	7.46±0.61	69.70±13.82
		PBO	87	60.4±9.7	59.8	25.22±4.39	5.29±6.17	7.50±0.63	65.96±12.91
Empagliflozin									
Kadowaki, 2014[Ref.162]	12 weeks	Empagliflozin 5mg qd	110	57.3±11.2	76.4	26.3±4.2	/	7.92±0.70	72.3±14.7
		Empagliflozin 10mg qd	109	57.9±9.4	70.6	25.3±4.4	/	7.93±0.71	68.1±14.6
		Empagliflozin 25mg qd	109	57.2±9.7	77.1	25.1±3.8	/	7.93±0.78	68.3±14.1
		Empagliflozin 50mg qd	110	56.6±10.3	77.3	25.0±3.6	/	8.02±0.65	68.2±12.3
		PBO	109	58.7±8.7	73.4	25.6±3.4	/	7.94±0.74	69.0±12.2
Roden, 2013[Ref.163]	24 weeks	Empagliflozin 10mg qd	224	56.2±11.6	63	28.3±5.5	/	7.87±0.88	78.4±18.7
		Empagliflozin 25mg qd	224	53.8±11.6	65	28.2±5.5	/	7.86±0.85	77.8±18.0
		PBO	228	54.9±10.9	54	28.7±6.2	/	7.91±0.78	78.2±19.9
Ertugliflozin									
Terra, 2017[Ref.164]	26 weeks	Ertugliflozin 5mg qd	156	56.8±11.4	57.1	33.2±7.4	5.11±5.09	8.16±0.88	94.0±25.4
		Ertugliflozin 15mg qd	152	56.2±10.8	59.2	32.5±5.7	5.22±5.55	8.35±1.12	90.6±18.3
		PBO	153	56.1±10.9	53.6	33.3±6.8	4.63±4.52	8.11±0.92	94.2±25.2
Ipragliflozin									
Fonseca, 2013[Ref.165]	12 weeks	Ipragliflozin 12.5mg qd	70	53.9±9.6	55.7	31.0±5.9	4.08±3.24	7.95±0.78	86.0±22.3
		Ipragliflozin 50mg qd	67	52.6±10.7	50.7	32.2±5.9	4.61±4.65	8.05±0.81	90.7±20.8
		Ipragliflozin 150mg qd	68	54.2±10.3	42.6	30.9±6.3	5.11±6.46	7.83±0.65	83.3±21.6
		Ipragliflozin 300mg qd	68	54.2±10.7	54.4	30.7±5.0	4.48±4.91	7.90±0.67	86.7±19.6
		PBO	69	53.4±9.7	46.4	30.9±5.5	4.64±5.93	7.84±0.78	81.8±17.4
Luseogliflozin									
Seino, 2014[Ref.166]	12 weeks	Luseogliflozin 0.5mg qd	60	55.2±10.1	68.3	25.4±3.54	4.90±4.49	8.16±0.93	69.7±13.7
		Luseogliflozin 2.5mg qd	61	58.3±9.4	57.4	24.8±3.56	6.15±6.50	8.07±0.90	65.5±12.2
		Luseogliflozin 5mg qd	61	56.8±9.3	72.1	24.5±3.21	5.77±5.55	8.16±0.96	66.3±12.4
		PBO	54	57.6±11.0	74.1	25.2±4.26	7.30±6.43	7.88±0.72	68.3±13.4
Seino, 2014[Ref.167]	12 weeks	Luseogliflozin 1mg qd	55	58.5±9.1	72.7	24.51±4.00	4.7±4.1	7.77±0.79	66.93±12.76
		Luseogliflozin 2.5mg qd	56	57.4±9.3	67.9	24.79±3.81	4.6±4.4	8.05±0.75	66.67±11.25
		Luseogliflozin 5mg qd	54	57.3±11.4	75.9	26.43±4.26	4.5±4.2	7.86±0.69	72.56±13.94
		Luseogliflozin 10mg qd	58	59.6±7.8	63.8	23.36±3.22	6.2±5.4	7.95±0.67	60.97±12.74
		PBO	57	57.1±10.0	71.9	25.15±3.62	5.1±4.6	7.92±0.84	67.32±13.14
Seino, 2014[Ref.168]	24 weeks	Luseogliflozin 2.5mg qd	79	58.9±10.1	75.9	25.98±4.88	6.5±5.9	8.14±0.91	70.19±13.65
		PBO	79	59.6±9.3	70.9	25.34±4.19	6.1±5.4	8.17±0.8	66.67±11.23
Tofogliflozin									
Kaku, 2014[Ref.169]	24 weeks	Tofogliflozin 10mg	57	58.6±9.8	66.7	25.07±3.53	6.3±7.1	8.45±0.75	67.26±12.67
		Tofogliflozin 20mg	58	56.6±10.2	67.2	24.99±4.55	6.4±5.1	8.34±0.81	68.06±15.82
		Tofogliflozin 40mg	58	57.0±9.1	67.2	25.78±4.10	6.7±5.5	8.37±0.77	68.72±11.91
		PBO	56	56.8±9.9	66.1	26.00±4.11	6.0±6.1	8.41±0.78	71.20±12.64
PBO controlled, add-on therapy									
Canagliflozin									
Townsend,	6 weeks	Canagliflozin 100mg	57	57.8±8.7	59.6	33.0±6.0	/	8.1±0.9	95.3±22.2

2016[Ref.170]		qd+met±SU/TZD/DPP4							
		Canagliflozin 300mg qd+met±SU/TZD/DPP4	56	58.3±6.9	55.4	34.1±6.8	/	8.0±0.8	96.1±20.2
		PBO+met±SU/TZD/DPP4	56	59.6±9.5	58.9	32.9±5.7	/	8.2±0.9	91.7±17.5
Rosenstock, 2012[Ref.171]	12 weeks	Canagliflozin 50mg qd+met	64	53.3±8.5	53	31.7±4.6	5.6±5.0	8.00±0.99	87.6±16.3
		Canagliflozin 100mg qd+met	64	51.7±8.0	56	31.7±5.0	6.1±4.7	7.83±0.96	87.7±15.5
		Canagliflozin 200mg qd+met	65	52.9±9.6	51	31.4±5.2	6.4±5.7	7.61±0.80	87.7±17.0
		Canagliflozin 300mg qd+met	64	52.3±6.9	56	31.6±4.9	5.9±5.2	7.69±1.02	87.3±15.9
		Canagliflozin 300mg bid+met	64	55.2±7.1	44	31.8±5.2	5.8±4.6	7.73±0.89	86.0±19.7
		PBO+met	65	53.3±7.8	48	30.6±4.6	6.4±5.0	7.75±0.83	85.9±19.5
Inagaki, 2016[Ref.172]	16 weeks	Canagliflozin 100mg qd+insulin	76	59.7±9.4	57.9	26.88±4.82	15.18±8.61	8.89±0.81	69.95±13.93
		PBO+insulin	70	56.1±10.9	70.0	25.99±4.40	12.34±8.21	8.85±0.84	69.68±13.13
Qiu, 2014[Ref.173]	18 weeks	Canagliflozin 50mg bid+met	93	58.6±8.9	43.0	33.0±7.0	6.7±4.9	7.6±0.9	91.2±23.9
		Canagliflozin 100mg bid+met	93	56.7±10.3	47.3	32.3±6.8	7.3±6.0	7.6±0.9	90.2±19.1
		PBO+met	93	57.0±9.3	49.5	32.3±5.7	7.0±6.4	7.7±0.9	90.5±18.1
Ji, 2015[Ref.174]	18 weeks	Canagliflozin 100mg qd+met±SU	223	56.5±8.3	55.5	25.6±3.4	6.8±4.5	8.0±0.9	69.1±11.8
		Canagliflozin 300mg qd+met±SU	227	56.4±9.2	49.8	26.0±3.4	6.9±4.9	8.0±0.9	69.6±11.9
		PBO+met±SU	226	55.8±9.4	55.3	25.5±3.6	6.4±4.6	7.9±0.9	68.6±11.9
Bode, 2013[Ref.175]	26 weeks	Canagliflozin 100mg qd+AHA	241	64.3±6.5	51.5	31.4±4.4	12.3±7.8	7.8±0.8	88.4±15.6
		Canagliflozin 200mg qd+AHA	236	63.4±6.0	54.7	31.5±4.6	11.3±7.2	7.7±0.8	88.8±17.1
		Canagliflozin 300mg qd+AHA	236	63.4±6.0	54.7	31.5±4.6	11.3±7.2	7.7±0.8	88.8±17.1
		PBO+AHA	237	63.2±6.2	60.3	31.8±4.8	11.4±7.3	7.8±0.8	91.1±17.5
Lavalle-González, 2013[Ref.176]	26 weeks	Canagliflozin 100mg qd+met	368	55.5±9.4	47.3	32.4±6.4	6.7±5.4	7.9±0.9	88.8±22.2
		Canagliflozin 300mg qd+met	367	55.3±9.2	45.0	31.4±6.3	7.1±5.4	7.9±0.9	85.4±20.9
		PBO+met	183	55.3±9.8	51.4	31.1±6.1	6.8±5.3	8.0±0.9	86.6±22.4
Yale, 2013[Ref.177]	26 weeks	Canagliflozin 100mg qd+AHA	90	69.5±8.2	64.4	32.4±5.5	15.6±7.4	7.9±0.9	90.5±18.4
		Canagliflozin 300mg qd+AHA	89	67.9±8.2	53.9	33.4±6.5	17.0±7.8	8.0±0.8	90.2±18.1
		PBO+AHA	90	68.2±8.4	63.3	33.1±6.5	16.4±10.1	8.0±0.9	92.8±17.4
Forst, 2014[Ref.178]	26 weeks	Canagliflozin 100mg qd+met+TZD	113	56.7±10.4	68.1	32.3±6.2	10.5±6.6	8.0±0.9	94.2±22.2
		Canagliflozin 300mg qd+met+TZD	114	57.0±10.2	55.3	32.8±7.7	11.0±7.6	7.9±0.9	94.4±25.9
		PBO+met+TZD	115	58.3±9.6	66.1	32.5±6.4	10.1±6.6	8.0±1.0	93.8±22.4
Wilding, 2013[Ref.179]	26 weeks	Canagliflozin 100mg qd+met+SU	157	57.4±10.5	51.6	33.3±6.3	9.0±5.7	8.1±0.9	93.8±22.6
		Canagliflozin 300mg qd+met+SU	156	56.1±8.9	44.2	33.2±6.3	9.4±6.4	8.1±0.9	93.5±22.0
		PBO+met+SU	156	56.8±8.3	51.3	32.7±6.8	10.3±6.7	8.1±0.9	91.2±22.6
Rosenstock, 2016[Ref.180]	26 weeks	Canagliflozin 100mg qd+met	237	54.2±9.6	45.6	31.9±5.3	2.9±3.3	8.8±1.1	88.3±17.6
		Canagliflozin 300mg qd+met	237	55.4±9.8	48.5	32.8±6.5	3.3±3.9	8.9±1.2	91.4±21.4
		PBO+met	237	55.2±9.8	48.9	33.0±6.0	3.3±4.5	8.8±1.2	92.1±20.1
Neal, 2017[11]	126.1 weeks (median)	Canagliflozin 100/300mg qd+background antihyperglycemic therapy	5795	63.2±8.3	64.9	31.9±5.9	13.5±7.7	8.2±0.9	/
		PBO+background antihyperglycemic therapy	4347	63.4±8.2	63.3	32.0±6.0	13.7±7.8	8.2±0.9	/
Dapagliflozin									
Wilding, 2009[Ref.181]	12 weeks	Dapagliflozin 10mg qd+OAD+insulin	24	55.7±9.2	54.2	35.5±3.6	11.8±5.8	8.4±0.7	103.4±10.2

		Dapagliflozin 20mg qd+OAD+insulin	24	56.1±10.6	54.2	36.2±4.6	11.3±5.6	8.5±0.9	101.2±15.3
		PBO+OAD+insulin	23	58.4±6.5	69.6	34.8±4.6	13.8±7.3	8.4±0.9	101.8±16.5
Lambers Heerspink, 2013[64]	12 weeks	Dapagliflozin 10mg qd+met±SU	24	53.7±9.4	66.7	/	6.5±4.4	7.7±0.6	93.2±18.0
		PBO+met±SU	25	58.0±9.5	72.0	/	6.5±5.0	7.5±1.0	96.2±19.5
Weber, 2016[38]	12 weeks	Dapagliflozin 10mg qd +OAD/insulin	225	56.0 (50.0-62.0)	52	/	7.7±5.9	8.1±0.9	88.0±20.5
		PBO+OAD/insulin	224	57.0 (51.0-62.0)	58	/	7.3±5.0	8.0±1.0	89.9±18.4
Weber, 2016[Ref.182]	12 weeks	Dapagliflozin 10mg qd+ACEI/ARB+AHA	302	55.6±8.4	59.3	/	8.2±6.4	8.1±1.0	84.1±17.5
		PBO+ACEI/ARB+AHA	311	56.2±8.9	55	/	7.6±6.2	8.0±0.9	86.0±18.4
Schumm-Draeger, 2015[Ref.183]	16 weeks	Dapagliflozin 2.5mg bid+met	100	58.3±9.0	37.0	33.16±5.16	4.80±3.87	7.77±0.75	92.49±18.632
		Dapagliflozin 5mg bid+met	99	55.3±9.3	46.5	33.09±4.94	5.12±4.2	7.78±0.76	93.62±16.641
		Dapagliflozin 10mg qd+met	99	58.5±9.8	49.5	32.25±5.01	5.45±4.05	7.71±0.71	90.58±15.929
		PBO+met	101	58.5±9.4	46.5	31.74±4.69	5.53±4.23	7.94±0.85	88.82±15.327
Araki, 2017[Ref.184]	16 weeks	Dapagliflozin5/10mg qd+insulin	122	58.3±9.8	73.0	26.9±4.9	15.3±9.0	8.3±0.8	73.9±15.7
		PBO+insulin	60	57.6±9.9	66.7	26.1±3.5	14.2±8.9	8.5±0.9	71.9±13.4
Bailey, 2010[Ref.185]	24 weeks	Dapagliflozin 2.5mg qd+met	137	55.0±9.3	51	31.6±4.8	6.0±6.2	7.99±0.90	84.9±17.8
		Dapagliflozin 5mg qd+met	137	54.3±9.4	50	31.4±5.0	6·4±5.8	8.17±0.96	84.7±16.3
		Dapagliflozin 10mg qd+met	135	52·7±9.9	57	31.2±5.1	6.1±5.4	7.92±0.82	86.3±17.5
		PBO+met	137	53.7±10.3	55	31.8±5.3	5.8±5.1	8.11±0.96	87.7±19.2
Strojek, 2011[Ref.186]	24 weeks	Dapagliflozin 2.5mg qd+SU	154	59.9±10.14	50.0	30.01±5.12	7.7±6.0	8.11±0.75	81.89
		Dapagliflozin 5mg qd+SU	142	60.2±9.73	50.0	29.84±5.18	7.4±5.7	8.12±0.78	81
		Dapagliflozin 10mg qd+SU	151	58.9±8.32	43.7	29.75±5.64	7.2±5.5	8.07±0.79	80.56
		PBO+SU	145	60.3±10.16	49.0	29.74±4.57	7.4±5.7	8.15±0.74	80.94
Bolinder, 2012[Ref.187]	24 weeks	Dapagliflozin 10mg qd+met	89	60.6±8.2	55.1	32.1±3.9	6.0±4.5	7.19±0.44	92.1±14.1
		PBO+met	91	60.8±6.9	56.0	31.7±3.9	5.5±5.3	7.16±0.53	90.9±13.7
Henry, 2012[Ref.188]	24 weeks	Dapagliflozin 5mg qd+met	194	51.7±9.3	40.2	/	1.6±2.4	9.2±1.3	84.1±19.5
		PBO+met	201	51.8±9.8	47.3	/	1.6±2.6	9.2±1.3	85.6±20.0
Henry, 2012[Ref.188]	24 weeks	Dapagliflozin 10mg qd+met	211	51.0±10.1	50.2	/	2.2±3.3	9.1±1.3	88.4±19.7
		PBO+met	208	52.7±10.4	46.6	/	1.9±4.0	9.1±1.3	87.2±19.4
Rosenstock, 2012[Ref.189]	24 weeks	Dapagliflozin 5mg qd+TZD	141	53.2±10.9	55.3	/	5.64±5.36	8.40±1.03	87.8±20.7
		Dapagliflozin 10mg qd+TZD	140	53.8±10.4	42.1	/	5.75±6.44	8.37±0.96	84.8±22.2
		PBO+TZD	139	53.5±11.4	51.1	/	5.07±5.05	8.34±1.00	86.4±21.3
Wilding, 2012[Ref.190]	24 weeks	Dapagliflozin 2.5mg qd+insulin	202	59.8±7.6	49.5	33.0±5.0	13.6±6.6	8.46±0.78	93.0±16.7
		Dapagliflozin 5mg qd+insulin	211	59.3±7.9	47.4	33.0±5.3	13.1±7.8	8.62±0.89	93.3±17.4
		Dapagliflozin 10mg qd+insulin	194	59.3±8.8	44.8	33.4±5.1	14.2±7.3	8.57±0.82	94.5±16.8
		PBO+insulin	193	58.8±8.6	49.2	33.1±5.9	13.5±7.3	8.47±0.77	94.5±19.8
Jabbour, 2014[Ref.191]	24 weeks	Dapagliflozin 10mg qd+DPP-4i±met	223	54.8±10.4	57.0	/	5.70±4.87	7.9±0.8	91.0±21.6
		PBO+DPP-4i±met	224	55.0±10.2	52.7	/	5.64±5.40	8.0±0.8	89.2±20.9
Leiter, 2014[Ref.192]	24 weeks	Dapagliflozin 10mg qd+background antihyperglycemic therapy	480	63.9±7.6	66.9	33.0±5.3	13.5±8.2	8.0±0.8	94.5±17.8
		PBO+background antihyperglycemic therapy	482	63.6±7.0	67.0	32.7±5.7	13.0±8.4	8.1±0.8	93.2±16.8

Cefalu, 2015[Ref.193]	24 weeks	Dapagliflozin 10mg qd+background antihyperglycemic therapy	455	62.8±7.0	67.9	32.6±5.9	12.6±8.7	8.18±0.84	92.6±20.5
		PBO+background antihyperglycemic therapy	459	63.0±7.0	68.6	32.9±6.1	12.3±8.2	8.08±0.80	93.6±19.5
Mathieu, 2015[Ref.194]	24 weeks	Dapagliflozin 10mg qd+DPP-4i+met	158	55.2±8.6	43.7	31.2±4.7	7.2±5.7	8.24±0.96	85.8±18.4
		PBO+DPP-4i+met	158	55.0±9.6	47.5	32.2±5.3	8.0±5.6	8.17±0.98	88.2±18.1
Matthaei, 2015[Ref.195]	24 weeks	Dapagliflozin 10mg qd+met+SU	108	61.1±9.7	42.6	31.9±4.8	9.3±6.5	8.08±0.91	88.6±17.6
		PBO+met+SU	108	60.2±9.2	55.6	32.0±4.6	9.6±6.2	8.24±0.87	90.1±16.2
Rosenstock, 2015[Ref.196]	24 weeks	Dapagliflozin 10mg qd+Saxagliptin 5mg qd+met	179	53±10	47.0	31.8±4.8	7.1±5.0	8.92±1.18	87.1±18.0
		PBO+Saxagliptin 5mg qd+met	176	55±10	53.0	31.8±5.1	8.2±5.5	9.03±1.05	88.0±18.7
Yang, 2016[Ref.197]	24 weeks	Dapagliflozin 5mg qd+met	147	53.1±9.1	45.6	26.4±3.5	4.2±3.8	8.09±0.72	70.8±12.2
		Dapagliflozin 10mg qd+met	152	54.6±9.5	57.9	26.2±3.5	5.3±4.6	8.17±0.84	71.4±12.0
		PBO+met	145	53.5±9.2	59.3	25.7±2.9	5.3±4.4	8.13±0.85	70.9±11.4
Fioretto, 2018[Ref.198]	24 weeks	Dapagliflozin 10mg qd+OAD/insulin	160	65.3±6.22	56.9	32.6±4.7	14.3±8.1	8.33±1.08	92.4±16.8
		PBO+OAD/insulin	161	66.2±6.49	56.5	31.6±5.0	14.5±8.1	8.03±1.08	88.3±16.2
Yang, 2018[Ref.199]	24 weeks	Dapagliflozin 10mg qd+insulin±OAD	133	56.5±8.4	47.5	26.4±3.8	12.7±7.2	8.52±0.76	71.1±12.0
		PBO+insulin±OAD	139	58.6±8.9	48.1	26.7±3.3	12.2±6.7	8.58±0.81	72.4±13.1
Pollock, 2019[Ref.200]	24 weeks	Dapagliflozin 10mg qd+antihyperglycemic therapy	145	64.7±8.6	70	30.19±5.3	17.55±7.7	8.44±1.0	/
		PBO+antihyperglycemic therapy	148	64.7±8.6	71	30.34±5.6	17.71±9.5	8.57±1.2	/
Rosenstock, 2019[Ref.201]	24weeks	Dapagliflozin 5mg qd+DPP-4i+met	290	57.2±10.7	49.0	31.5±5.5	7.5±6.3	8.1±0.9	87.2±18.7
		PBO+DPP-4i+met	291	57.0±9.9	54.0	32.4±5.5	7.8±5.8	8.3±1.0	92.3±18.7
Frías, 2016[33]	28 weeks	Dapagliflozin 10mg qd+Exenatide 2mg qw+met	228	54±10	45	33.2±6.8	7.6±6.0	9.3±1.1	91.8±22.2
		PBO+Exenatide 2mg qw+met	227	54±10	51	32.0±5.9	7.4±5.5	9.3±1.1	89.8±20.2
Empagliflozin									
Rosenstock, 2013[Ref.202]	12 weeks	Empagliflozin 1mg qd+met	71	57±8.8	58	31.1±4.8	/	7.8±0.7	90.6±18.9
		Empagliflozin 5mg qd+met	71	60±7.3	41	31.6±4.4	/	8.0±0.7	87.0±14.8
		Empagliflozin 10mg qd+met	71	59±9.0	47	31.4±4.0	/	7.9±0.7	87.9±14.4
		Empagliflozin 25mg qd+met	70	59±8.1	53	31.5±4.8	/	8.1±0.7	90.5±16.9
		Empagliflozin 50mg qd+met	70	56±9.4	56	31.8±4.4	/	7.9±0.7	91.6±15.8
		PBO+met	71	60±8.5	47	31.1±4.5	/	8.0±0.7	87.7±15.7
Tikkanen, 2015[Ref.203]	12 weeks	Empagliflozin 10mg qd+background antihyperglycemic therapy	276	60.6±8.5	62.0	32.4±5.3	/	7.87±0.77	/
		Empagliflozin 25mg qd+background antihyperglycemic therapy	276	59.9±9.7	56.5	33.0±5.0	/	7.92±0.72	/
		PBO+background antihyperglycemic therapy	271	60.3±8.8	62.0	32.4±4.9	/	7.90±0.72	/
Mancia, 2016[42]	12 weeks	Empagliflozin 10mg qd+background antihyperglycemic therapy	276	60.6±8.5	62.0	32.4±5.3	/	7.87±0.77	/
		Empagliflozin 25mg qd+background antihyperglycemic therapy	276	59.9±9.7	56.5	33.0±5.0	/	7.92±0.72	/
		PBO+background antihyperglycemic	271	60.3±8.8	62.0	32.4±4.9	/	7.90±0.72	/

		therapy							
Kario, 2018[40]	12 weeks	Empagliflozin 10mg qd+OAD	68	70.9±8.7	52.9	26.1±3.8	10.6±7.9	6.6±0.8	65.4±11.4
		PBO+OAD	63	69.3±7.8	52.4	26.0±4.9	9.6±8.2	6.6±0.8	64.6±14.3
Ross, 2015[Ref.204]	16 weeks	Empagliflozin 5mg bid+met	215	58.8 ± 9.8	55.8	31.5±5.2	/	7.79±0.88	88.3±17.4
		Empagliflozin 12.5mg bid +met	215	57.6 ± 9.9	57.2	31.6±5.1	/	7.78±0.79	89.4±19.0
		Empagliflozin 10mg qd+met	214	58.5 ± 10.8	50.5	31.9±5.4	/	7.84±0.75	89.2±19.0
		Empagliflozin 25mg qd+met	214	58.2 ± 10.2	53.3	32.1±5.3	/	7.73±0.79	88.7±18.6
		PBO+met	207	57.9 ± 11.2	51.4	32.0± .0	/	7.69±0.72	90.1±18.4
Rosenstock, 2014[Ref.205]	18 weeks	Empagliflozin 10mg qd+insulin	186	56.7±8.7	52	34.7±3.8	/	8.39±0.74	96.7±17.9
		Empagliflozin 25mg qd+insulin	189	58.0±9.4	44	35.0±4.0	/	8.29±0.72	95.9±17.3
		PBO+insulin	188	55.3±10.1	40	34.7±4.3	/	8.33±0.72	95.5±17.5
Rosenstock, 2015[Ref.206]	18 weeks	Empagliflozin 10mg qd+insulin±met±SU	169	58.6±9.8	55	32.1±5.8	/	8.3±0.8	91.6±20.1
		Empagliflozin 25mg qd+insulin±met±SU	155	59.9±10.5	60	32.7±5.9	/	8.3±0.8	94.7±20.7
		PBO+insulin±met±SU	170	58.1±9.4	53	31.8±6.0	/	8.2±0.8	90.5±22.5
Häring, 2013[Ref.207]	24 weeks	Empagliflozin 10mg qd+met+SU	225	57.0±9.2	50	28.3±5.4	/	8.07±0.81	77.1±18.3
		Empagliflozin 25mg qd+met+SU	216	57.4±9.3	53	28.3±5.5	/	8.10±0.83	77.5±18.8
		PBO+met+SU	225	56.9±9.2	50	27.9±4.9	/	8.15±0.83	76.2±16.9
Häring, 2014[Ref.208]	24 weeks	Empagliflozin 10mg qd+met	217	55.5±9.9	58	29.1±5.5	/	7.94±0.79	81.6±18.5
		Empagliflozin 25mg qd+met	213	55.6±10.2	56	29.7±5.7	/	7.86±0.87	82.2±19.3
		PBO+met	207	56.0±9.7	56	28.7±5.2	/	7.90±0.88	79.7±18.6
Kovacs, 2014[Ref.209]	24 weeks	Empagliflozin 10mg qd+TZD±met	165	54.7±9.9	50.3	29.2±5.6	/	8.1±0.89	78.0±19.1
		Empagliflozin 25mg qd+TZD±met	168	54.2±8.9	50.6	29.1±5.5	/	8.1±0.82	78.9±19.9
		PBO+TZD±met	165	54.6±0.5	44.2	29.3±5.4	/	8.2±0.92	78.1±20.1
Kawamori, 2018[Ref.210]	24 weeks	Empagliflozin 10mg+DPP-4i	182	60.0±9.9	78.0	26.0±3.8	9.0±7.2	8.27±0.65	71.2±12.6
		PBO+DPP-4i	93	59.8±10.8	77.4	26.6±4.5	8.7±6.1	8.36±0.74	73.1±15.9
Ferdinand, 2019[Ref.211]	24 weeks	Empagliflozin 10-25mg qd+OAD	78	56.5±9.3	55.1	36.04±12.83	9.3±6.2	8.66±0.97	105.05±24.29
		PBO+OAD	72	57.2±9.3	50.0	35.12±8.29	9.3±7.9	8.51±1.1	101.35±20.96
Barnett, 2014[Ref.212] (patients with stage 2 CKD)	52 weeks	Empagliflozin 10mg qd+background antihyperglycemic therapy	98	63.2±8.5	61.2	32.4±5.4	/	8.02±0.84	92.1±21.4
		Empagliflozin 25mg qd+background antihyperglycemic therapy	97	62.0±8.4	62.9	31.3±5.8	/	7.96±0.73	88.1±21.7
		PBO+background antihyperglycemic therapy	95	62.6±8.1	58.9	30.8±5.6	/	8.09±0.80	86.0±20.0
Barnett, 2014[Ref.212] (patients with stage 3 CKD)	52 weeks	Empagliflozin 25mg qd+background antihyperglycemic therapy	187	64.6±8.9	57.2	30.2±5.3	/	8.02±0.84	83.2±19.5
		PBO+background antihyperglycemic therapy	187	65.1±8.2	56.7	30.3±5.3	/	8.09±0.80	82.5±18.0
Barnett, 2014[Ref.212] (patients with stage	52 weeks	Empagliflozin 25mg qd+background antihyperglycemic therapy	37	65.4±10.2	56.8	29.0±4.9	/	8.06±1.05	77.9±16.4

4 CKD)		PBO+background antihyperglycemic therapy	37	62.9±11.9	51.4	31.8±6.0	/	8.16±0.99	84.1±21.1
Søfteland, 2017[Ref.213]	52 weeks	Empagliflozin 10mg qd+DPP-4i+met	109	54.3±9.6	60.6	31.2±5.9	/	7.97±0.84	88.4±20.8
		Empagliflozin 25mg qd+DPP-4i+met	110	55.4±9.9	64.5	29.9±5.3	/	7.97±0.82	84.4±19.2
		PBO+DPP-4i+met	108	55.9±9.7	55.6	29.6±5.7	/	7.97±0.85	82.3±19.8
Zinman, 2015[13]	3.1 years (median observation time)	Empagliflozin 10mg qd+background antihyperglycemic therapy	2345	63.0±8.6	70.5	30.6±5.2	/	8.07±0.86	85.9±18.8
		Empagliflozin 25mg qd+background antihyperglycemic therapy	2342	63.2±8.6	71.9	30.6±5.3	/	8.06±0.84	86.5±19.0
		PBO+background antihyperglycemic therapy	2333	63.2±8.8	72.0	30.7±5.2	/	8.08±0.84	86.6±19.1
Ertugliflozin									
Amin, 2015[Ref.214]	4 weeks	Ertugliflozin 1mg qd+OAD	39	54.4±7.0	50.0	/	7.54±6.74	8.38±0.81	85.3±19.3
		Ertugliflozin 5mg qd+OAD	38	53.8±9.9	45.5	/	5.48±3.79	8.05±0.68	87.8±18.8
		Ertugliflozin 25mg qd+OAD	39	52.5±6.6	49.0	/	5.83±4.18	8.31±0.87	82.7±18.5
		PBO+OAD	38	55.1±6.7	63.2	/	6.38±5.55	8.21±0.68	83.5±17.5
Amin, 2015[Ref.215]	12 weeks	Ertugliflozin 1mg qd+met	54	53.1±9.1	63.0	29.8±4.92	6.3	8.01±1.25	83.44±18.89
		Ertugliflozin 5mg qd+met	55	54.7±7.7	74.5	31.1±6.30	6.7	7.88±0.96	85.74±20.91
		Ertugliflozin 10mg qd+met	55	57.3±6.5	56.4	30.7±5.93	6.1	8.13±1.26	82.28±21.73
		Ertugliflozin 25mg qd+met	55	54.2±8.8	67.3	29.8±4.97	6.0	8.30±1.19	81.81±17.35
		PBO+met	54	54.0±8.1	55.6	30.6±4.48	6.4	8.08±1.03	83.78±17.42
Dagogo-Jack, 2017[Ref.216]	26 weeks	Ertugliflozin 5mg qd +met+DPP-4i	156	59.2±9.3	51.9	31.2±5.5	9.9±6.1	8.1±0.9	87.6±18.6
		Ertugliflozin15mg qd +met+DPP-4i	153	59.7±9.3	53.6	30.9±6.1	9.2±5.3	8.0±0.8	86.6±19.5
		PBO+met+DPP-4i	153	58.3±9.2	65.4	30.3±6.4	9.4±5.6	8.0±0.9	86.4±20.8
Grunberger, 2017[Ref.217]	26 weeks	Ertugliflozin 5mg qd+background antihyperglycemic therapy	158	66.7±8.3	53.2	32.6±6.8	14.9±9.0	8.2±1.0	89.4±22.5
		Ertugliflozin 15mg qd+background antihyperglycemic therapy	155	67.5±8.5	48.4	31.7±5.3	14.5±8.5	8.2±0.9	85.8±17.4
		PBO+background antihyperglycemic therapy	154	67.5±8.9	46.8	33.2±6.1	13.1±8.1	8.1±0.9	90.4±18.9
Pratley, 2018[Ref.218]	26 weeks	Ertugliflozin 5mg qd+sitagliptin100mg qd+met	243	55.2±10.4	50.6	32.5±6.7	7.0±5.6	8.6±1.0	89.5±20.8
		Ertugliflozin 15mg qd+sitagliptin100mg qd+met	244	55.1±9.8	51.6	31.8±6.5	6.9±5.2	8.6±1.0	87.5±20.5
		PBO+sitagliptin 100mg qd+met	247	54.8±10.7	62.3	31.7±6.5	6.2±5.2	8.5±1.0	89.8±23.5
Rosenstock, 2018[Ref.219]	26 weeks	Ertugliflozin 5mg qd +met	207	56.6±8.1	46.9	30.8±4.8	7.9±6.1	8.1±0.9	84.8±17.2
		Ertugliflozin 15mg qd +met	205	56.9±9.4	45.4	31.1±4.5	8.1±5.5	8.1±0.9	85.3±16.5

		PBO+met	209	56.5±8.7	46.9	30.7±4.7	8.0±6.3	8.2±0.9	84.5±17.1
Ji, 2019[Ref.220]	26 weeks	Ertugliflozin 5mg qd+met	170	56.1±9.0	55.9	26.0±2.8	7.0±5.0	8.1±0.9	71.4±11.1
		Ertugliflozin 15mg qd+met	169	56.3±9.3	58.0	25.7±3.2	7.5±5.1	8.1±0.9	69.5±10.9
		PBO+met	167	56.9±9.0	52.7	26.1±3.4	6.4±5.1	8.1±1.0	70.1±12.4
Ipragliflozin									
Wilding, 2013[Ref.221]	12 weeks	Ipragliflozin 12.5mg qd+met	69	56.6±8.5	47.8	31.9±4.9	6.8±6.4	7.78±0.64	89.5±13.6
		Ipragliflozin 50mg qd+met	68	58.6±7.6	47.1	31.1±4.9	6.0±5.3	7.76±0.66	86.7±13.7
		Ipragliflozin 150mg qd+met	67	58.1±8.2	56.7	31.8±5.2	5.7±4.8	7.73±0.69	89.3±17.0
		Ipragliflozin 300mg qd+met	72	56.6±8.9	50.0	31.8±4.6	5.5±4.8	7.87±0.82	89.3±15.0
		PBO+met	66	57.3±8.6	54.5	32.0±4.8	5.7±3.2	7.68±0.60	89.0±14.5
Shestakova, 2018[Ref.222]	12 weeks	Ipragliflozin 50mg qd+met	110	58.9±9.3	43.6	32.80±4.76	6.65±5.22	8.39±0.93	92.74±16.24
		PBO+met	55	58.0±9.5	40.0	31.95±4.18	6.56±4.66	8.46±0.96	89.54±15.60
Kashiwagi, 2015[Ref.223]	24 weeks	Ipragliflozin 50mg qd+OAD	118	63.9±6.59	78.0	25.84±3.450	9.5±7.7	7.53±0.538	69.16±11.571
		PBO+OAD	46	65.7±6.93	78.3	24.96±3.362	9.4±8.3	7.55±0.526	66.70±10.940
Kashiwagi, 2015[Ref.224]	24 weeks	Ipragliflozin 50mg qd+met	112	56.2±10.67	58.9	25.96±4.410	7.5±5.7	8.25±0.719	68.52±13.864
		PBO+met	56	57.7±9.24	58.9	25.47±3.092	8.1±5.2	8.38±0.738	67.51±11.365
Lu, 2016[Ref.225]	24 weeks	Ipragliflozin 50mg qd+met	87	53.9±11.3	50.6	26.57±4.30	6.5±5.7	7.74±0.78	70.36±14.75
		PBO+met	83	53.4±11.3	39.8	27.04±4.60	5.8±4.2	7.75±0.71	70.45±12.44
Han, 2018[Ref.226]	24 weeks	Ipragliflozin 50mg qd+met+DPP4-i	73	57.62±8.26	50.7	25.50±3.07	11.6±5.9	7.90±0.69	67.50±12.50
		PBO+met+DPP4-i	66	57.44±7.88	48.5	26.05±3.79	11.3±6.6	7.92±0.79	67.90±10.98
Luseogliflozin									
Seino, 2018[Ref.227]	16 weeks	Luseogliflozin 2.5mg qd+insulin	159	57.4±10.3	70.4	25.42±3.53	11.7±7.6	8.70±0.83	68.10±11.32
		PBO+insulin	74	57.1±10.9	68.9	25.15±3.44	12.1±6.8	8.84±0.83	69.13±12.16
Haneda, 2016[Ref.228]	24 weeks	Luseogliflozin 2.5mg qd+OAD	95	67.9±8.9	75.8	25.45±4.18	10.4±6.9	7.72±0.68	66.9±13.60
		PBO+OAD	50	68.4±8.9	78.0	25.81±3.95	12.6±10.4	7.69±0.65	67.77±11.79
Sotagliflozin									
Rosenstock, 2015[Ref.229]	12 weeks	Sotagliflozin 75mg qd+met	59	56.1±9.6	57.6	33.4±5.2	/	8.0±0.9	96.2±19.3
		Sotagliflozin 200mg qd+met	60	55.6±9.3	28.3	34.2±5.8	/	8.3±1.0	95.6±19.4
		Sotagliflozin 400mg qd+met	60	56.1±9.5	48.3	32.7±5.8	/	8.1±1.0	91.4±18.6
		Sotagliflozin200mg bid+met	60	56.4±8.8	48.3	32.9±5.6	/	8.4±0.9	95.0±22.2
		PBO+met	60	55.1±9.8	43.3	32.2±5.8	/	7.9±0.9	90.6±20.7
Tofogliflozin									
Terauchi, 2017[Ref.230]	16 weeks	Tofogliflozin 20mg qd+insulin	141	59.1±10.8	63.8	25.8±3.5	15.02±9.36	8.53±0.75	68.87±13.20
		PBO+insulin	70	56.4±10.0	68.6	26.9±3.9	12.39±7.34	8.40±0.65	72.24±11.12
Active controlled, monotherapy									
Canagliflozin									
Rosenstock, 2016[Ref.180]	26 weeks	Canagliflozin 100mg qd	237	54.0±10.7	44.3	32.4±5.4	3.5±4.4	8.8±1.2	90.2±18.6
		Canagliflozin 300mg qd	238	55.8±9.6	52.5	32.6±5.8	3.3±4.4	8.8±1.2	93.0±19.9
		Metformin 2000mg/day	237	55.2±9.8	48.9	33.0±6.0	3.3±4.5	8.8±1.2	92.1±20.1
Dapagliflozin									
List, 2009[63]	12 weeks	Dapagliflozin 2.5mg qd	59	55±11	49	32±5	/	7.6±0.7	90±20

		Dapagliflozin 5mg qd	58	55±12	48	32±5	/	8.0±0.9	89±17
		Dapagliflozin 10mg qd	47	54±9	53	31±5	/	8.0±0.8	86±17
		Dapagliflozin 20mg qd	59	55±10	54	31±5	/	7.7±0.9	88±18
		Dapagliflozin 50mg qd	56	53±10	45	32±4	/	7.8±1.0	92±19
		Metformin 1500mg/day	56	55±11	48	32±5	/	7.6±0.8	88±20
Henry, 2012[Ref.189]	24 weeks	Dapagliflozin 5mg qd	203	52.3±10.2	45.3	/	1.6±3.1	9.1±1.4	86.2±21.1
		Metformin 2000mg/day	201	51.8±9.8	47.3	/	1.6±2.6	9.2±1.3	85.6±20.0
Henry, 2012[Ref.189]	24 weeks	Dapagliflozin 10mg qd	219	51.1±11.5	47.9	/	2.1±3.8	9.1±1.3	88.5±19.3
		Metformin 2000mg/day	208	52.7±10.4	46.6	/	1.9±4.0	9.1±1.3	87.2±19.4
Empagliflozin									
Roden, 2013[Ref.163]	24 weeks	Empagliflozin 10mg qd	224	56.2±11.6	63	28.3±5.5	/	7.87±0.88	78.4±18.7
		Empagliflozin 25mg qd	224	53.8±11.6	65	28.2±5.5	/	7.86±0.85	77.8±18.0
		Sitagliptin 100mg qd	223	55.1±9.9	63	28.2±5.2	/	7.85±0.79	79.3±20.4
Ipragliflozin									
Fonseca, 2013[Ref.165]	12 weeks	Ipragliflozin 12.5mg qd	70	53.9±9.6	55.7	31.0±5.9	4.08±3.24	7.95±0.78	86.0±22.3
		Ipragliflozin 50mg qd	67	52.6±10.7	50.7	32.2±5.9	4.61±4.65	8.05±0.81	90.7±20.8
		Ipragliflozin 150mg qd	68	54.2±10.3	42.6	30.9±6.3	5.11±6.46	7.83±0.65	83.3±21.6
		Ipragliflozin 300mg qd	68	54.2±10.7	54.4	30.7±5.0	4.48±4.91	7.90±0.67	86.7±19.6
		Metformin 1500mg/day	69	53.1±11.7	58.0	29.8±5.5	4.13±4.71	8.03±0.90	84.1±21.8
Tofogliflozin									
Tanizawa, 2014[Ref.231]	52 weeks	Tofogliflozin 20mg qd	63	58.7±10.36	66.7	25.88±4.263	5.630±4.3275	7.83±0.96	68.95±13.351
		Tofogliflozin 40mg qd	127	57.8±11.07	66.1	25.39±4.652	5.361±5.2704	7.83±0.88	68.57±15.810
Active controlled, add-on therapy									
Canagliflozin									
Kario, 2018[Ref.232]	8 weeks	Canagliflozin 100mg qd +OAD	41	70.4 ± 9.5	65.9	25.5 ± 3.3	/	7.4 ± 0.7	/
		Increased hypoglycemic dosage/Addition of another hypoglycemic agent	37	67.8 ± 9.8	51.4	26.3 ± 4.1	/	7.2 ± 0.6	/
Rosenstock, 2012[Ref.171]	12 weeks	Canagliflozin 50mg qd+met	64	53.3±8.5	53	31.7±4.6	5.6±5.0	8.00±0.99	87.6±16.3
		Canagliflozin 100mg qd+met	64	51.7±8.0	56	31.7±5.0	6.1±4.7	7.83±0.96	87.7±15.5
		Canagliflozin 200mg qd+met	65	52.9±9.6	51	31.4±5.2	6.4±5.7	7.61±0.80	87.7±17.0
		Canagliflozin 300mg qd+met	64	52.3±6.9	56	31.6±4.9	5.9±5.2	7.69±1.02	87.3±15.9
		Canagliflozin 300mg bid+met	64	55.2±7.1	44	31.8±5.2	5.8±4.6	7.73±0.89	86.0±19.7
		Sitagliptin 100mg qd+met	65	51.7±8.1	58	31.6±5.0	5.6±4.7	7.64±0.95	87.2±18.0
Lavalle-González, 2013[Ref.176]	26 weeks	Canagliflozin 100mg qd+met	368	55.5±9.4	47.3	32.4±6.4	6.7±5.4	7.9±0.9	88.8±22.2
		Canagliflozin 300mg qd+met	367	55.3±9.2	45.0	31.4±6.3	7.1±5.4	7.9±0.9	85.4±20.9
		Sitagliptin 100mg qd+met	366	55.5±9.6	47.0	32.0±6.1	6.8±5.2	7.9±0.9	87.7±21.6
Cefalu, 2013[Ref.233]	52 weeks	Canagliflozin 100mg qd +met	483	56.4±9.5	52	31.0±5.3	6.5±5.5	7.8±0.8	86.9±20.1
		Canagliflozin 300mg qd	485	55.8±9.2	50	31.2±5.4	6.7±5.5	7.8±0.8	86.6±19.5

		+met							
		glimepiride 6mg qd +met	482	56.3±9.0	55	30.9±5.5	6.6±5.0	7.8±0.8	86.5±19.8
Schernthaner, 2013[Ref.234]	52weeks	Canagliflozin 300mg qd+met+SU	377	56.6±9.6	54.9	31.5±6.9	9.4±6.1	8.1±0.9	87.4±23.2
		Sitagliptin 100mg qd+met+SU	378	56.7±9.3	56.9	31.7±6.9	9.7±6.3	8.1±0.9	89.1±23.2
Dapagliflozin									
Rosenstock, 2019[Ref.201]	24 weeks	Dapagliflozin 5mg qd+met	289	55.9±10.9	52.6	31.8±5.2	7.6±6.3	8.2±0.9	89.5±17.8
		Saxagliptin 5mg qd+met	291	57.0±9.9	54.0	32.4±5.5	7.8±5.8	8.3±1.0	92.3±18.7
Nauck, 2011[Ref.235]	52 weeks	Dapagliflozin 10mg qd +met	400	58±9	55.3	31.7±5.1	6±5	7.7±0.9	88.4±16.3
		Glipizide 20mg/day +met	401	59±10	54.9	31.2±5.1	7±6	7.7±0.9	87.6±17.0
Müller-Wieland, 2018[Ref.236]	52 weeks	Dapagliflozin 10mg qd+met	314	57.4±9.4	64.3	33.1±5.2	6.9±5.2	8.3±0.7	97.7±18.9
		Glimepiride 1-4mg/day+met	313	58.6±8.4	66.5	33.0±5.1	6.7±5.1	8.3±0.8	97.3±17.9
Empagliflozin									
Rosenstock, 2013[Ref.202]	12 weeks	Empagliflozin 1mg qd+met	71	57±8.8	58	31.1±4.8	/	7.8±0.7	90.6±18.9
		Empagliflozin 5mg qd+met	71	60±7.3	41	31.6±4.4	/	8.0±0.7	87.0±14.8
		Empagliflozin 10mg qd+met	71	59±9.0	47	31.4±4.0	/	7.9±0.7	87.9±14.4
		Empagliflozin 25mg qd+met	70	59±8.1	53	31.5±4.8	/	8.1±0.7	90.5±16.9
		Empagliflozin 50mg qd+met	70	56±9.4	56	31.8±4.4	/	7.9±0.7	91.6±15.8
		Sitagliptin 100mg met+met	71	58±10.1	54	31.0±4.5	/	8.1±0.9	88.0±15.0
Araki, 2015[Ref.237]	52 weeks	Empagliflozin 10mg qd+SU	136	61.3±9.9	78.2	24.6 ± 3.8	/	7.99 ± 0.73	65.8 ± 12.2
		Empagliflozin 25mg qd+SU	137	61.8±9.6	70.1	25.2 ± 4.2	/	8.06 ± 0.76	67.0 ± 13.7
		Metformin 500-2250mg/day+SU	63	60.0±10.2	74.6	25.2 ± 3.6	/	7.93 ± 0.79	68.2 ± 12.2
		Empagliflozin 10mg qd+met	68	56.9±9.5	55.9	26.4 ± 4.4	/	7.68 ± 0.74	70.7 ± 15.6
		Empagliflozin 25mg qd+met	65	57.3±11.4	66.2	26.4 ± 3.5	/	7.51 ± 0.73	70.4 ± 11.4
		Empagliflozin 10mg qd+TZD	137	60.4±10.1	83.2	26.7 ± 4.2	/	7.85 ± 0.74	73.8 ± 14.2
		Empagliflozin 25mg qd+TZD	136	59.7±9.9	75.0	26.8 ± 4.2	/	7.95 ± 0.84	72.9 ± 12.7
		Empagliflozin 10mg qd+AGI	69	63.5±8.8	73.9	24.3 ± 3.6	/	7.78 ± 0.80	63.9 ± 10.9
		Empagliflozin 25mg qd+AGI	70	61.9±11.7	74.3	25.7 ± 4.1	/	7.56 ± 0.59	68.6 ± 13.1
		Empagliflozin 10mg qd+DPP4	68	63.3±9.9	60.3	24.7 ± 3.7	/	7.78 ± 0.68	64.1 ± 12.1
		Empagliflozin 25mg qd+DPP4	71	59.1±10.3	67.6	26.0 ± 4.2	/	7.82 ± 0.74	70.0 ± 13.2
		Empagliflozin 10mg qd+Glinide	70	59.2±12.1	67.1	25.4 ± 3.9	/	8.01 ± 0.85	67.8 ± 14.1
		Empagliflozin 25mg qd+Glinide	70	57.7±11.8	81.4	26.2 ± 4.6	/	7.98 ± 0.84	73.2 ± 17.3
Terauchi, 2019[Ref.238]	52 weeks	Empagliflozin 10mg qd+GLP-1RA	32	55.6±9.8	81.3	28.0±4.9	/	8.83±0.80	78.6±18.4
		Empagliflozin 25mg qd+GLP-1RA	33	58.9±9.3	66.7	27.7±5.5	/	8.68±0.87	76.5±14.6
Ridderstråle 2014[Ref.239]	104 weeks	Empagliflozin 25mg qd+met	765	56.2±10.3	56	29.9±5.3	/	7.92±0.81	82.5±19.2
		Glimepiride 1-4mg qd+met	780	55.7±10.4	54	30.3±5.3	/	7.92±0.82	83.0±19.2
Ertugliflozin									
Amin, 2015[Ref.215]	12 weeks	Ertugliflozin 1mg qd+met	54	53.1±9.1	63.0	29.8±4.92	6.3	8.01±1.25	83.44±18.89
		Ertugliflozin 5mg qd+met	55	54.7±7.7	74.5	31.1±6.30	6.7	7.88±0.96	85.74±20.91

		Ertugliflozin 10mg qd+met	55	57.3±6.5	56.4	30.7±5.93	6.1	8.13±1.26	82.28±21.73
		Ertugliflozin 25mg qd+met	55	54.2±8.8	67.3	29.8±4.97	6.0	8.30±1.19	81.81±17.35
		Sitagliptin 100mg qd+met	55	53.3±10.7	72.7	30.4±5.71	6.3	8.24±1.11	85.52±18.61
Pratley, 2018[Ref.218]	26 weeks	Ertugliflozin 5mg qd+met	250	55.1±10.1	50.8	31.8±6.2	7.1±5.4	8.6±1.0	88.6±22.2
		Ertugliflozin 15mg qd+met	248	55.3±9.5	54.0	31.5±5.8	7.3±5.4	8.6±1.0	88.0±20.3
		Sitagliptin 100mg qd+met	247	54.8±10.7	62.3	31.7±6.5	6.2±5.2	8.5±1.0	89.8±23.5
Hollander, 2018[Ref.240]	52 weeks	Ertugliflozin 5mg qd+met	448	58.8±9.7	50.7	31.7±5.5	7.4±5.7	7.8±0.6	87.9±18.9
		Ertugliflozin 15mg qd+met	440	58.0±9.9	43.4	31.3±6.2	7.5±5.7	7.8±0.6	85.6±19.1
		Glimepiride 8mg qd+met	437	57.8±9.2	51.3	31.2±6.4	7.5±5.6	7.8±0.6	86.8±20.7
Tofogliflozin									
Tanizawa, 2014[Ref.231]	52 weeks	Tofogliflozin 20mg qd+OAD	172	58.2±10.03	65.7	25.53±3.95	7.62±5.89	8.13±0.93	68.10±13.45
		Tofogliflozin 40mg qd+OAD	413	58.7±10.53	66.1	25.68±4.42	7.71±6.18	8.12±0.89	68.46±14.18

Data are presented as mean ± standard deviation or median (interquartile range) unless otherwise specified.

SGLT2i, sodium-glucose cotransporter-2 inhibitors; BMI, body mass index; DM, diabetes mellitus; HbA1c, hemoglobin A1c; PBO, placebo; AHA, antihyperglycemic agents; OAD, oral antidiabetes drug; MET, metformin; SU, sulfonylurea; DPP-4i, dipeptidyl-peptidase-4 inhibitors; AGI, alpha-glucosidase inhibitors; TZD, thiazolidinedione; GLP-1RA, Glucagon-like peptide-1 receptor agonists; ACEI, angiotension converting enzyme inhibitors; ARB, angiotensin receptor blocker; CKD, chronic kidney disease.

Table S4. Summary of bias risk of included studies in GLP-1RA treatment

	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other bias
Rosenstock, 2009[Ref.73]	U	U	L	L	H	L	L
Nauck, 2016[Ref.74]	L	L	L	L	H	L	L
Grunberger, 2012[Ref.75]	L	L	L	L	L	U	L
Miyagawa, 2015[Ref.76]	L	L	L	L	L	L	L
Moretto, 2008[Ref.77]	L	L	L	L	L	L	L
Aroda, 2019[Ref.78]	L	L	L	L	L	L	L
Sorli, 2017[Ref.79]	L	L	L	L	L	L	L
Raz, 2012[Ref.80]	L	U	L	L	L	L	L
Hernandez, 2018[7]	L	L	L	L	L	L	L
Ahrén, 2014[Ref.81]	U	U	L	L	H	L	L
Ferdinand, 2014[39]	L	U	L	L	L	L	L
Dungan, 2016[Ref.82]	L	U	L	L	L	L	L
Ludvik, 2018[Ref.83]	L	L	L	L	L	L	L
Wysham, 2014[Ref.84]	L	L	L	L	L	L	L
Nauck, 2014[Ref.85]	L	L	L	L	H	L	L
Gerstein, 2019[10]	L	L	L	L	L	L	L
Gill, 2010[Ref.86]	U	U	L	L	H	L	L
Apovian, 2010[Ref.87]	L	L	L	L	H	U	L
Liutkus, 2010[Ref.88]	L	L	L	L	L	U	L
Frías, 2016[33]	L	L	L	L	L	L	L
Gadde, 2017[Ref.89]	L	L	L	L	H	L	L
Guja, 2018[Ref.90]	L	L	L	L	L	L	L
Buse, 2011[Ref.91]	L	L	L	L	L	L	L

Holman, 2017[Ref.92]	L	L	L	L	L	L	L
Liakos, 2019[41]	L	L	L	L	L	L	L
Lind, 2015[Ref.93]	L	L	L	L	L	L	L
Vanderheiden, 2016[Ref.94]	L	L	L	L	L	L	L
Nauck, 2009[28]	L	L	L	L	L	L	L
Russell-Jones, 2009[29]	L	L	L	L	L	L	L
Zinman, 2009[Ref.95]	L	L	L	L	U	L	L
Ahmann, 2015[Ref.96]	L	L	L	L	H	L	L
Davies, 2016[Ref.97]	L	L	L	L	H	L	L
Davies, 2015[Ref.98]	L	L	L	L	H	L	L
Marso, 2016[9]	L	L	L	L	L	L	L
Nauck, 2016[Ref.99]	L	L	L	L	H	L	L
Davies, 2017[Ref.100]	L	L	L	L	H	L	L
Lingvay, 2018[Ref.101]	L	L	L	L	L	L	L
Pratley, 2019[Ref.102]	L	L	L	L	L	L	L
Rodbard, 2018[Ref.103]	L	L	L	L	L	L	L
Zinman, 2019[Ref.104]	L	L	L	L	L	L	L
Husain, 2019[Ref.105]	L	L	L	L	L	L	L
Marso, 2016[8]	L	L	L	L	L	L	L
Bergenstal, 2012[Ref.106]	L	L	L	L	H	L	L
Henry, 2012[Ref.107]	L	L	L	L	L	L	L
Umpierrez, 2014[Ref.108]	L	L	L	L	L	L	L
Chen, 2018[Ref.109]	L	L	L	L	L	L	L
Russell-Jones, 2012[Ref.110]	L	L	L	L	L	L	L
Xu, 2015[Ref.111]	L	L	H	H	L	L	L
Garber, 2009[Ref.112]	L	L	L	L	L	L	L
Seino, 2018[Ref.113]	L	L	H	H	L	L	L
Weissman, 2014[Ref.114]	L	L	H	H	L	L	L

Dungan, 2014[Ref.115]	L	L	H	L	L	L	L
Araki, 2015[Ref.116]	L	L	H	H	L	L	L
Blonde, 2015[Ref.117]	L	L	H	H	H	L	L
Wang, 2019[Ref.118]	L	L	H	H	L	L	L
Pratley, 2018[Ref.119]	L	L	H	H	L	L	L
Giorgino, 2015[Ref.120]	L	L	H	H	L	L	L
Wysham, 2016[Ref.121]	L	L	L	L	L	L	L
Blevins, 2011[Ref.122]	L	L	H	H	L	L	L
Rosenstock, 2013[Ref.123]	L	L	H	H	L	L	L
Buse, 2009[Ref.124]	L	L	H	H	L	L	L
Davies, 2009[Ref.125]	U	U	H	H	L	U	L
Bergenstal, 2010[Ref.126]	L	L	L	L	L	L	L
Diamant, 2010[Ref.127]	L	L	H	L	L	L	L
Buse, 2013[Ref.128]	L	L	H	H	L	L	L
Davies, 2013[Ref.129]	L	L	H	H	H	L	L
Ji, 2013[Ref.130]	L	U	H	H	H	L	L
Wysham, 2018[Ref.131]	L	L	H	H	L	L	L
Diamant, 2014[Ref.132]	L	U	H	H	L	L	L
Drucker, 2008[Ref.133]	L	U	H	H	L	L	L
Nauck, 2007[Ref.134]	L	L	H	H	H	L	L
Ahmann, 2018[Ref.135]	L	L	H	H	H	L	L
Simo, 2015[Ref.136]	L	U	H	L	H	L	L
Meier, 2015[Ref.137]	L	L	H	H	L	L	L
Brady, 2014[Ref.138]	L	U	H	H	H	U	L
D'Alessio, 2015[Ref.139]	L	L	H	H	L	L	L
Abreu, 2019[Ref.140]	L	L	H	H	H	L	L
Pratley, 2010[Ref.141]	L	L	H	L	L	L	L
Charbonnel, 2013[Ref.142]	L	L	H	H	H	L	L

De Wit, 2014[Ref.143]	L	U	H	H	L	L	L
Bailey, 2016[Ref.144]	L	L	L	L	H	L	L
Nauck, 2016[Ref.145]	L	L	H	H	L	L	L
Zang, 2016[Ref.146]	L	L	H	H	L	L	L
Kaku, 2016[Ref.147]	L	L	H	H	L	L	L
Rosenstock, 2019[Ref.148]	L	L	L	L	L	L	L
Aroda, 2017[Ref.149]	L	L	L	L	L	L	L
Ahrén, 2017[Ref.150]	L	L	L	L	L	L	L
Kaku, 2018[Ref.151]	L	U	H	H	L	L	L
Nauck, 2013[Ref.152]	U	U	H	H	H	L	L
Pratley, 2013[Ref.153]	L	L	L	L	L	L	L

L, low risk of bias; U, unclear risk of bias; H, high risk of bias.

Table S5. Summary of bias risk of included studies in SGLT2i treatment

	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other bias
Inagaki, 2013[Ref.154]	L	L	L	L	L	L	L
Inagaki, 2014[Ref.155]	L	L	L	L	H	L	L
Stenlöf, 2013[Ref.156]	U	U	L	L	L	L	L
List, 2009[63]	U	U	L	L	L	L	L
Kaku, 2013[Ref.157]	L	L	L	L	H	L	L
Ferrannini, 2010[Ref.158]	U	U	L	L	L	L	L
Bailey, 2012[Ref.159]	L	L	L	L	L	L	L
Ji, 2014[Ref.160]	L	L	L	L	L	L	L
Kaku, 2014[Ref.161]	U	U	L	L	L	U	L
Kadowaki, 2014[Ref.162]	L	L	L	L	L	L	L
Roden, 2013[Ref.163]	L	L	L	L	L	L	L
Terra, 2017[Ref.164]	L	U	L	L	H	L	L
Fonseca, 2013[Ref.165]	L	U	L	L	L	L	L
Seino, 2014[Ref.166]	L	L	L	L	L	L	L
Seino, 2014[Ref.167]	L	L	L	L	L	L	L
Seino, 2014[Ref.168]	L	L	L	L	L	L	L
Kaku, 2014[Ref.169]	L	L	L	L	L	L	L
Townsend, 2016[Ref.170]	U	U	L	L	L	U	L
Rosenstock, 2012[Ref.171]	U	U	L	L	L	L	L
Inagaki, 2016[Ref.172]	L	L	L	L	L	L	L
Qiu, 2014[Ref.173]	L	U	L	L	L	L	L
Ji, 2015[Ref.174]	L	L	L	L	L	L	L

Bode, 2013[Ref.175]	L	U	L	L	H	L	L
Lavalle-González, 2013[Ref.176]	L	U	L	L	L	L	L
Yale, 2013[Ref.177]	L	L	L	L	L	U	L
Forst, 2014[Ref.178]	L	L	L	L	L	L	L
Wilding, 2013[Ref.179]	L	L	L	L	L	L	L
Rosenstock, 2016[Ref.180]	L	U	L	L	L	L	L
Neal, 2017[11]	L	L	L	L	L	L	L
Wilding, 2009[Ref.181]	U	U	L	L	H	L	L
Lambers Heerspink, 2013[64]	L	L	L	L	L	L	L
Weber, 2016[38]	L	L	L	L	L	L	L
Weber, 2016[Ref.182]	L	L	L	L	L	L	L
Schumm-Draeger, 2015[Ref.183]	L	L	L	L	L	L	L
Araki, 2017[Ref.184]	L	L	L	L	L	L	L
Bailey, 2010[Ref.185]	L	L	L	L	L	L	L
Strojek, 2011[Ref.186]	L	L	L	L	L	L	L
Bolinder, 2012[Ref.187]	L	L	L	L	L	L	L
Henry, 2012[Ref.188]	L	L	L	L	L	L	L
Rosenstock, 2012[Ref.189]	U	U	L	L	L	L	L
Wilding, 2012[Ref.190]	L	L	L	L	L	L	L
Jabbour, 2014[Ref.191]	L	U	L	L	L	L	L
Leiter, 2014[Ref.192]	L	L	L	L	L	L	L
Cefalu, 2015[Ref.193]	L	U	L	L	L	L	L
Mathieu, 2015[Ref.194]	L	L	L	L	L	L	L
Matthaei, 2015[Ref.195]	L	L	L	L	L	L	L
Rosenstock, 2015[Ref.196]	L	L	L	L	L	L	L
Yang, 2016[Ref.197]	L	L	L	L	L	L	L
Fioretto, 2018[Ref.198]	L	L	L	L	L	L	L
Yang, 2018[Ref.199]	L	L	L	L	L	L	L

Pollock, 2019[Ref.200]	L	L	L	L	L	L	L
Rosenstock, 2019[Ref.201]	L	L	L	L	L	L	L
Frías, 2016[33]	L	L	L	L	L	L	L
Rosenstock, 2013[Ref.202]	L	L	L	L	L	L	L
Tikkanen, 2015[Ref.203]	L	L	L	L	L	L	L
Mancia, 2016[42]	U	U	L	L	L	L	L
Kario, 2018[40]	L	U	L	L	L	L	L
Ross, 2015[Ref.204]	L	U	U	U	L	L	L
Rosenstock, 2014[Ref.205]	L	L	L	L	L	L	L
Rosenstock, 2015[Ref.206]	L	L	L	L	L	L	L
Häring, 2013[Ref.207]	L	L	L	L	L	L	L
Häring, 2014[Ref.208]	L	L	L	L	L	L	L
Kovacs, 2014[Ref.209]	L	L	L	L	L	L	L
Kawamori, 2018[Ref.210]	L	L	L	L	L	L	L
Ferdinand, 2019[Ref.211]	L	L	L	L	L	L	L
Barnett, 2014[Ref.212]	L	L	L	L	L	L	L
Søfteland, 2017[Ref.213]	L	L	L	L	L	L	L
Zinman, 2015[13]	L	L	L	L	L	L	L
Amin, 2015[Ref.214]	U	U	L	L	L	L	L
Amin, 2015[Ref.215]	L	U	L	L	L	L	L
Dagogo-Jack, 2017[Ref.216]	L	U	L	L	L	L	L
Grunberger, 2017[Ref.217]	L	L	L	L	L	L	H
Pratley, 2018[Ref.218]	L	L	L	L	L	L	L
Rosenstock, 2018[Ref.219]	L	L	L	L	L	L	L
Ji, 2019[Ref.220]	L	U	L	L	L	L	L
Wilding, 2013[Ref.221]	U	U	L	L	L	L	L
Shestakova, 2018[Ref.222]	L	L	L	L	L	L	L
Kashiwagi, 2015[Ref.223]	L	U	L	L	L	L	L

Kashiwagi, 2015[Ref.224]	U	U	L	L	H	L	L
Lu, 2016[Ref.225]	L	L	L	L	L	L	L
Han, 2018[Ref.226]	L	L	L	L	H	L	L
Seino, 2018[Ref.227]	U	L	L	L	L	L	L
Haneda, 2016[Ref.228]	U	U	L	L	L	L	L
Rosenstock, 2015[Ref.229]	U	U	L	L	L	L	L
Terauchi, 2017[Ref.230]	L	L	L	L	L	L	L
Tanizawa, 2014[Ref.231]	L	L	H	H	L	L	L
Kario, 2018[Ref.232]	U	U	H	H	L	L	L
Cefalu, 2013[Ref.233]	L	L	L	L	L	L	L
Schernthaner, 2013[Ref.234]	L	L	L	L	H	L	L
Nauck, 2011[Ref.235]	L	L	L	L	H	L	L
Müller-Wieland, 2018[Ref.236]	L	U	L	L	L	L	L
Araki, 2015[Ref.237]	L	L	L	L	L	L	L
Terauchi, 2019[Ref.238]	L	L	L	L	L	L	L
Ridderstråle, 2014[Ref.239]	L	L	L	L	L	L	L
Hollander, 2018[Ref.240]	L	L	L	L	H	L	L

L, low risk of bias; U, unclear risk of bias; H, high risk of bias.

Table S6. SBP and DBP changes in GLP-1RA and SGLT2i treatment

	SBP changes					DBP changes				
	Observations	**WMD**	**95%CI**	***P* value**	**I^2**	**Observations**	**WMD**	**95%CI**	***P* value**	**I^2**
GLP-1RA										
Total	164	-2.856	-3.017, -2.695	<0.001	78.0%	156	-0.898	-1.007, -0.789	<0.001	63.3%
Placebo controlled	61	-1.724	-2.043, -1.404	<0.001	51.2%	54	0.199	-0.016, 0.415	0.070	28.9%
Active controlled	100	-2.913	-3.123, -2.703	<0.001	77.5%	96	-0.984	-1.128, -0.841	<0.001	67.4%
Insulin	22	-2.763	-3.306, -2.220	<0.001	17.0%	21	-0.083	-0.424, 0.259	0.635	16.6%
Sulfonylurea	10	-2.721	-3.459, -1.983	<0.001	50.0%	5	-1.318	-1.944, -0.693	<0.001	61.4%
DPP-4i	20	-1.150	-1.657, -0.644	<0.001	49.2%	20	-0.332	-0.730, 0.067	0.103	13.6%
Monotherapy	34	-2.499	-2.947, -2.052	<0.001	67.2%	32	-0.727	-1.120, -0.334	<0.001	54.6%
Add-on therapy	130	-2.899	-3.071, -2.727	<0.001	79.6%	124	-0.917	-1.030, -0.804	<0.001	64.9%
Individual										
Albiglutide	13	-1.110	-1.543, -0.677	<0.001	50.4%	13	-0.538	-0.795, -0.282	<0.001	9.0%
Dulaglutide	28	-1.514	-1.832, -1.196	<0.001	72.9%	28	-0.061	-0.267, 0.144	0.559	28.3%
Exenatide	34	-3.021	-3.404, -2.637	<0.001	71.5%	33	-1.236	-1.484, -0.987	<0.001	66.8%
Liraglutide	31	-3.107	-3.508, -2.706	<0.001	61.0%	24	-0.799	-1.049, -0.549	<0.001	72.3%
Semaglutide	44	-4.346	-4.674, -4.019	<0.001	67.4%	44	-1.278	-1.528, -1.029	<0.001	28.8%

Taspoglutide	12	-3.164	-3.823, -2.505	<0.001	45.0%	12	-1.471	-1.883, -1.060	<0.001	0.0%
SGLT2i										
Total	208	-4.331	-4.476, -4.185	<0.001	67.6%	186	-2.279	-2.376, -2.182	<0.001	67.8%
Placebo controlled	179	-3.612	-3.844, -3.379	<0.001	20.8%	160	-1.559	-1.713, -1.406	<0.001	7.1%
Active controlled	59	-4.122	-4.378, -3.867	<0.001	61.7%	56	-1.995	-2.165, -1.824	<0.001	60.6%
Metformin	15	-3.600	-4.383, -2.818	<0.001	35.3%	15	-1.532	-2.020, -1.045	<0.001	42.4%
Sulfonylurea	7	-4.536	-5.245, -3.826	<0.001	15.0%	6	-1.896	-2.372, -1.420	<0.001	32.9%
DPP-4i	22	-2.995	-3.571, -2.418	<0.001	28.2%	20	-1.583	-1.995, -1.171	<0.001	54.2%
Monotherapy	53	-4.315	-4.655, -3.976	<0.001	65.0%	48	-2.113	-2.344, -1.882	<0.001	58.4%
Add-on therapy	155	-4.334	-4.495, -4.173	<0.001	68.6%	138	-2.311	-2.417, -2.204	<0.001	70.2%
Individual										
Canagliflozin	40	-4.754	-5.030, -4.478	<0.001	80.6%	40	-2.855	-3.026, -2.684	<0.001	81.0%
Dapagliflozin	61	-4.245	-4.561, -3.930	<0.001	72.1%	46	-1.986	-2.226, -1.745	<0.001	56.7%
Empagliflozin	54	-4.266	-4.534, -3.998	<0.001	49.2%	54	-2.044	-2.209, -1.879	<0.001	55.6%
Ertugliflozin	23	-3.838	-4.203, -3.473	<0.001	19.4%	17	-1.611	-1.883, -1.339	<0.001	43.4%
Ipragliflozin	9	-3.235	-4.096, -2.374	<0.001	51.0%	8	-2.317	-2.975, -1.659	<0.001	37.8%
Luseogliflozin	10	-3.838	-4.753, -2.923	<0.001	68.4%	10	-1.948	-2.528, -1.368	<0.001	27.1%

Tofogliflozin	8	-5.076	-5.909, -4.244	<0.001	60.1%	8	-2.471	-3.053, -1.890	<0.001	55.8%

SBP, systolic blood pressure; DBP, diastolic blood pressure; WMD, weighted mean difference; CI, confidence interval; DPP-4i, dipeptidyl-peptidase-4 inhibitors.

Table S7. SBP and DBP changes stratified by study primary endpoint and study duration

	SBP changes					DBP changes				
	Observations	**WMD**	**95%CI**	***P* value**	**I^2**	**Observations**	**WMD**	**95%CI**	***P* value**	**I^2**
GLP-1RA	164	-2.856	-3.017, -2.695	<0.001	78.0%	156	-0.898	-1.007, -0.789	<0.001	63.3%
Study primary endpoint and study duration										
HbA1c changes	153	-2.975	-3.157, -2.793	<0.001	76.0%	145	-0.933	-1.062, -0.805	<0.001	62.5%
≤12weeks	14	-2.497	-3.485, -1.510	<0.001	72.0%	14	-0.528	-1.162, 0.105	0.102	76.6%
12-<26weeks	37	-2.965	-3.422, -2.507	<0.001	60.0%	37	-1.208	-1.498, -0.918	<0.001	38.7%
26-<52weeks	84	-3.106	-3.344, -2.867	<0.001	77.6%	78	-0.883	-1.058, -0.708	<0.001	64.8%
≥52 weeks	18	-2.600	-2.962, -2.238	<0.001	85.2%	16	-0.857	-1.107, -0.607	<0.001	56.9%
Weight changes	2	/	/	/	/	2	/	/	/	/
Blood pressure changes	4	-1.904	-2.865, -0.943	<0.001	42.0%	4	0.187*	-0.471, 0.845	0.577	0.0%
Cardiovascular outcomes	5	-2.502	-2.877, -2.127	<0.001	95.8%	5	-0.853	-1.075, -0.631	<0.001	85.2%
SGLT2i	208	-4.331	-4.476, -4.185	<0.001	67.6%	186	-2.279	-2.376, -2.182	<0.001	67.8%
Study primary endpoint and study duration										

HbA1c changes	191	-4.047	-4.204, -3.889	<0.001	57.3%	170	-2.050	-2.157, -1.944	<0.001	45.8%
≤12weeks	50	-4.145	-4.566, -3.725	<0.001	60.0%	48	-2.083	-2.362, -1.803	<0.001	53.3%
12-<26weeks	79	-3.835	-4.086, -3.585	<0.001	53.5%	68	-1.981	-2.151, -1.812	<0.001	33.8%
26-<52weeks	31	-4.054	-4.351, -3.757	<0.001	58.4%	24	-2.057	-2.270, -1.843	<0.001	39.4%
≥52 weeks	31	-4.410	-4.758, -4.061	<0.001	57.1%	30	-2.148	-2.375, -1.921	<0.001	57.9%
Weight changes	1	/	/	/	/	1	/	/	/	/
Blood pressure changes	14	-6.331*	-6.853, -5.809	<0.001	91.5%	13	-2.434	-2.740, -2.128	<0.001	88.2%
Cardiovascular outcomes	2	/	/	/	/	2	/	/	/	85.0%
Total	372	-3.536	-3.645, -3.426	<0.001	75.8%	342	-1.501	-1.576, -1.427	<0.001	76.0%

SBP, systolic blood pressure; DBP, diastolic blood pressure; WMD, weighted mean difference; CI, confidence interval; GLP-1RA, Glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

*P<0.05 compared with the total group.

Table S8. Comparisons of the effect sizes among subgroups

	SBP		DBP	
	Adjusted *P**	***P* for subgroup differences**	**Adjusted *P****	***P* for subgroup differences**
GLP-1RA				
Study duration		0.2111		0.0597
≤12weeks vs 12-<26weeks	0.6315		0.0534	
≤12weeks vs 26-<52weeks	0.3331		0.4689	
≤12weeks vs ≥52 weeks	0.9956		0.7097	
12-<26weeks vs 26-<52weeks	0.9402		0.2187	
12-<26weeks vs ≥52 weeks	0.7398		0.5057	
26-<52weeks vs ≥52 weeks	0.4048		0.9995	
Primary endpoint		0.1212		0.0187
HbA1c vs blood pressure	0.1490		0.0135	
HbA1c vs CVOT	0.6263		0.9719	
blood pressure vs CVOT	0.7091		0.1148	
Treatment strategy		0.0554		0.2196
SGLT2i				

Study duration		0.1286		0.7711
≤12weeks vs 12-<26weeks	0.4741		0.8956	
≤12weeks vs 26-<52weeks	0.9870		0.9991	
≤12weeks vs ≥52 weeks	0.7637		0.9836	
12-<26weeks vs 26-<52weeks	0.8207		0.9756	
12-<26weeks vs ≥52 weeks	0.1058		0.7549	
26-<52weeks vs ≥52 weeks	0.6407		0.9729	
Primary endpoint		<0.001		0.0571
HbA1c vs blood pressure	<0.001		0.0571	
HbA1c vs CVOT	/		/	
blood pressure vs CVOT	/		/	
Treatment strategy		0.9127		0.0877

SBP, systolic blood pressure; DBP, diastolic blood pressure; GLP-1RA, Glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter-2 inhibitors; HbA1c, hemoglobin A1c; CVOT, cardiovascular outcomes trials.

*P values were adjusted by Bonferroni correction for multiple comparisons.

Table S9. HbA1c and weight changes in GLP-1RA treatment

	HbA1c changes					Weight changes				
	Observations	**WMD**	**95%CI**	***P* value**	**I^2**	**Observations**	**WMD**	**95%CI**	***P* value**	**I^2**
Total	163	-1.202	-1.216, -1.189	<0.001	96.1%	163	-2.521	-2.571, -2.470	<0.001	96.7%
Placebo controlled	60	-0.687	-0.715, -0.659	<0.001	92.4%	60	-1.701	-1.825, -1.577	<0.001	92.8%
Active controlled	100	-1.247	-1.263, -1.230	<0.001	96.5%	100	-2.735	-2.803, -2.666	<0.001	96.3%
Insulin	22	-0.244	-0.284, -0.204	<0.001	91.5%	22	-3.683	-3.831, -3.535	<0.001	94.4%
Sulfonylurea	10	-0.221	-0.278, -0.164	<0.001	86.5%	10	-3.343	-3.555, -3.130	<0.001	92.1%
DPP-4i	20	-0.478	-0.528, -0.428	<0.001	94.2%	20	-1.808	-2.007, -1.609	<0.001	86.6%
Monotherapy	34	-1.155	-1.198, -1.112	<0.001	95.6%	34	-1.952	-2.086, -1.817	<0.001	93.2%
Add-on therapy	129	-1.208	-1.222, -1.194	<0.001	96.3%	129	-2.594	-2.648, -2.539	<0.001	97.0%
Individual										
Albiglutide	13	-0.867	-0.900, -0.834	<0.001	83.1%	13	-1.031	-1.134, -0.929	<0.001	0.0%
Dulaglutide	28	-1.232	-1.259, -1.206	<0.001	94.6%	28	-1.504	-1.596, -1.411	<0.001	94.7%
Exenatide	34	-1.174	-1.203, -1.144	<0.001	95.8%	34	-2.472	-2.588, -2.355	<0.001	87.5%
Liraglutide	31	-1.310	-1.340, -1.280	<0.001	95.7%	31	-3.038	-3.149, -2.928	<0.001	93.9%
Semaglutide	43	-1.368	-1.402, -1.335	<0.001	95.5%	43	-4.030	-4.163, -3.897	<0.001	95.8%

Taspoglutide	12	-1.164	-1.209, -1.119	<0.001	89.8%	12	-2.152	-2.350, -1.953	<0.001	94.6%

HbA1c, hemoglobin A1c; WMD, weighted mean difference; CI, confidence interval; DPP-4i, dipeptidyl-peptidase-4 inhibitors.

Table S10. HbA1c and weight changes in SGLT2i treatment

	HbA1c changes					Weight changes				
	Observations	**WMD**	**95%CI**	***P* value**	**I^2**	**Observations**	**WMD**	**95%CI**	***P* value**	**I^2**
Total	208	-0.745	-0.755, -0.735	<0.001	95.4%	201	-2.644	-2.685, -2.603	<0.001	93.1%
Placebo controlled	176	-0.561	-0.576, -0.546	<0.001	82.7%	175	-1.816	-1.876, -1.756	<0.001	64.9%
Active controlled	63	-0.821	-0.839, -0.804	<0.001	92.0%	58	-2.989	-3.056, -2.922	<0.001	83.0%
Metformin	15	0.002	-0.070, 0.074	0.951	0.0%	15	-1.448	-1.672, -1.223	<0.001	52.5%
Sulfonylurea	7	0.009	-0.033, 0.052	0.668	78.4%	7	-4.338	-4.525, -4.150	<0.001	83.9%
DPP-4i	22	-0.018	-0.058, 0.023	0.386	71.9%	21	-2.327	-2.492, -2.161	<0.001	55.8%
Monotherapy	57	-0.768	-0.793, -0.744	<0.001	93.6%	53	-2.646	-2.723, -2.570	<0.001	91.9%
Add-on therapy	151	-0.740	-0.751, -0.730	<0.001	95.9%	148	-2.643	-2.690, -2.597	<0.001	93.5%
Individual										
Canagliflozin	38	-0.742	-0.763, -0.720	<0.001	97.1%	40	-3.197	-3.297, -3.097	<0.001	92.5%
Dapagliflozin	61	-0.776	-0.795, -0.757	<0.001	96.6%	59	-2.389	-2.465, -2.313	<0.001	93.0%
Empagliflozin	54	-0.689	-0.706, -0.672	<0.001	90.4%	52	-2.362	-2.426, -2.297	<0.001	89.1%
Ertugliflozin	20	-0.859	-0.889, -0.829	<0.001	95.3%	20	-2.788	-2.893, -2.683	<0.001	84.9%
Ipragliflozin	13	-0.662	-0.736, -0.587	<0.001	85.1%	9	-2.061	-2.220, -1.902	<0.001	74.5%

Luseogliflozin	10	-0.502	-0.546, -0.458	<0.001	92.0%	10	-1.597	-1.708, -1.485	<0.001	91.1%
Tofogliflozin	8	-0.803	-0.847, -0.758	<0.001	64.5%	8	-2.705	-2.852, -2.559	<0.001	94.0%

HbA1c, hemoglobin A1c; WMD, weighted mean difference; CI, confidence interval; DPP-4i, dipeptidyl-peptidase-4 inhibitors.

Table S11. Effects of sex on the association between weight reduction and blood pressure changes

		Model 1* (unadjusted by sex)			Model 2† (adjusted by sex)		
		Coefficient	**95%CI**	***P* value**	**Coefficient**	**95%CI**	***P* value**
GLP-1RA	SBP	0.821	0.630, 1.012	<0.001	0.821	0.631, 1.011	<0.001
	DBP	0.288	0.172, 0.403	<0.001	0.287	0.172, 0.403	<0.001
SGLT2i	SBP	0.829	0.350, 1.309	0.001	0.820	0.332, 1.307	0.001
	DBP	0.282	-0.007, 0.572	0.055	0.268	-0.019, 0.556	0.067

Coefficient indicates change in mmHg of blood pressure associated with 1 kg change in weight.

GLP-1RA, Glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter-2 inhibitors; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval.

*Model 1: multivariable meta-regression model adjusted for age, BMI, duration of diabetes and HbA1c change from baseline.

†Model 2: Model 1 plus adjustment for sex.

Table S12. Effects of hypertensive therapy on the association between weight reduction and blood pressure changes

		Model 1* (unadjusted by hypertensive therapy)			Model 2† (adjusted by hypertensive therapy)		
		Coefficient	**95%CI**	***P* value**	**Coefficient**	**95%CI**	***P* value**
GLP-1RA	SBP	0.873	-2.703, 4.449	0.494	0.881	-5.131, 6.893	0.593
	DBP	-0.272	-1.456, 0.913	0.518	-0.297	-1.906, 1.311	0.510
SGLT2i	SBP	0.320	-0.679, 1.320	0.507	0.182	-0.594, 0.959	0.625
	DBP	0.164	-0.485, 0.814	0.595	0.157	-0.561, 0.875	0.642

Coefficient indicates change in mmHg of blood pressure associated with 1 kg change in weight.

GLP-1RA, Glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter-2 inhibitors; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval.

*Model 1: multivariable meta-regression model adjusted for age, sex, BMI and HbA1c change from baseline.

†Model 2: Model 1 plus adjustment for hypertensive therapy.

Figure S1. Meta-regression analysis of the associations between HbA1c reduction or body weight reduction and blood pressure changes in placebo-controlled trials in GLP-1RA treatment.

A. Association between HbA1c change from baseline and placebo-corrected SBP change from baseline.

B. Association between HbA1c change from baseline and placebo-corrected DBP change from baseline.

C. Association between weight change from baseline and placebo-corrected SBP change from baseline.

D. Association between weight change from baseline and placebo-corrected DBP change from baseline.

The size of circles is proportional to the weight of each study in the meta-regression.

*Analyses were adjusted for age, sex, BMI and duration of diabetes.

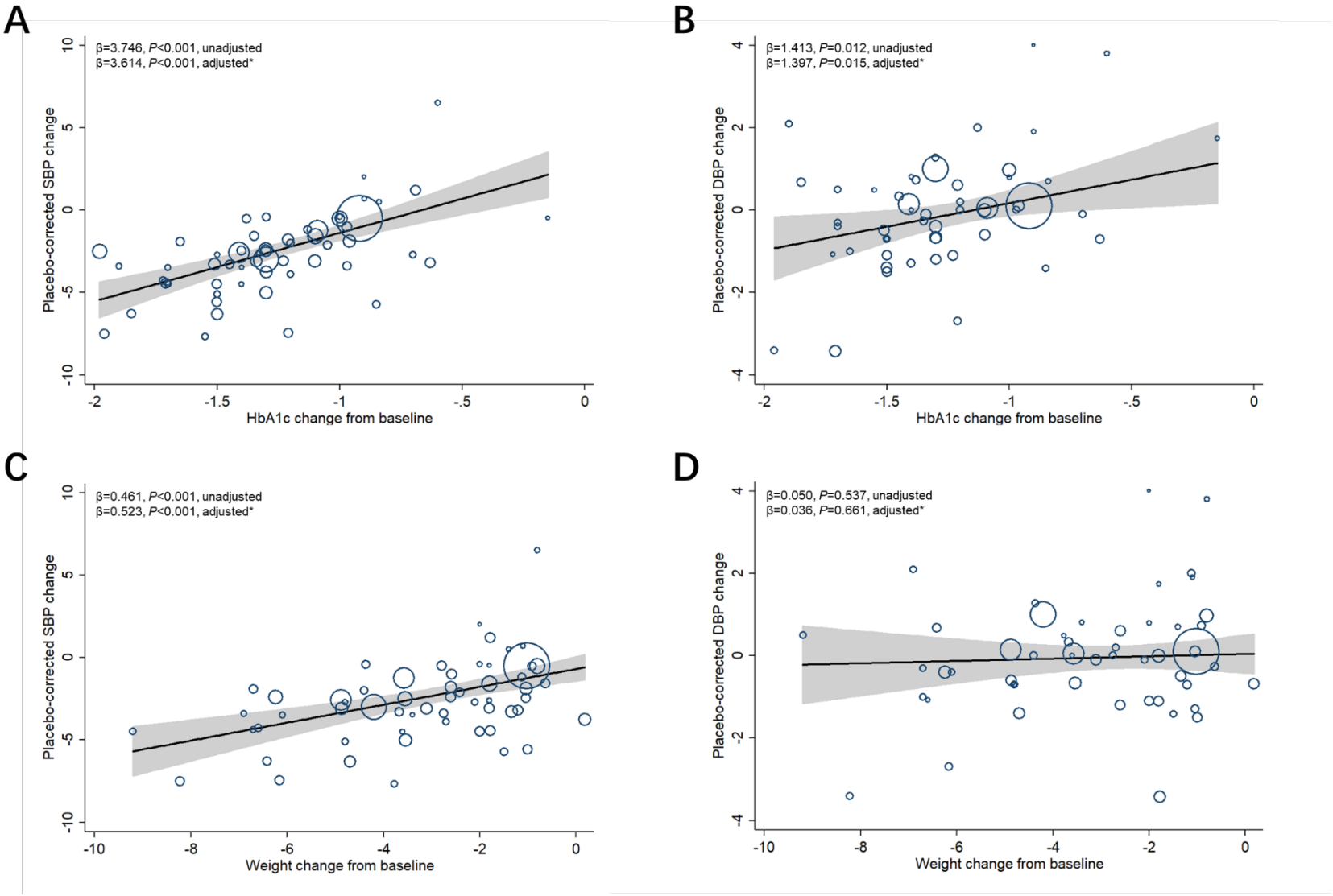
A
β=3.746, P<0.001, unadjusted
β=3.614, P<0.001, adjusted*
Placebo-corrected SBP change
HbA1c change from baseline
B
β=1.413, P=0.012, unadjusted
β=1.397, P=0.015, adjusted*
Placebo-corrected DBP change
HbA1c change from baseline
C
β=0.461, P<0.001, unadjusted
β=0.523, P<0.001, adjusted*
Placebo-corrected SBP change
Weight change from baseline
D
β=0.050, P=0.537, unadjusted
β=0.036, P=0.661, adjusted*
Placebo-corrected DBP change
Weight change from baseline

Figure S2. Meta-regression analysis of the associations between HbA1c reduction or body weight reduction and blood pressure changes in GLP-1RA monotherapy.

A. Association between HbA1c change from baseline and SBP change from baseline.

B. Association between HbA1c change from baseline and DBP change from baseline.

C. Association between weight change from baseline and SBP change from baseline.

D. Association between weight change from baseline and DBP change from baseline.

The size of circles is proportional to the weight of each study in the meta-regression.

*Analyses were adjusted for age, sex, BMI and duration of diabetes.

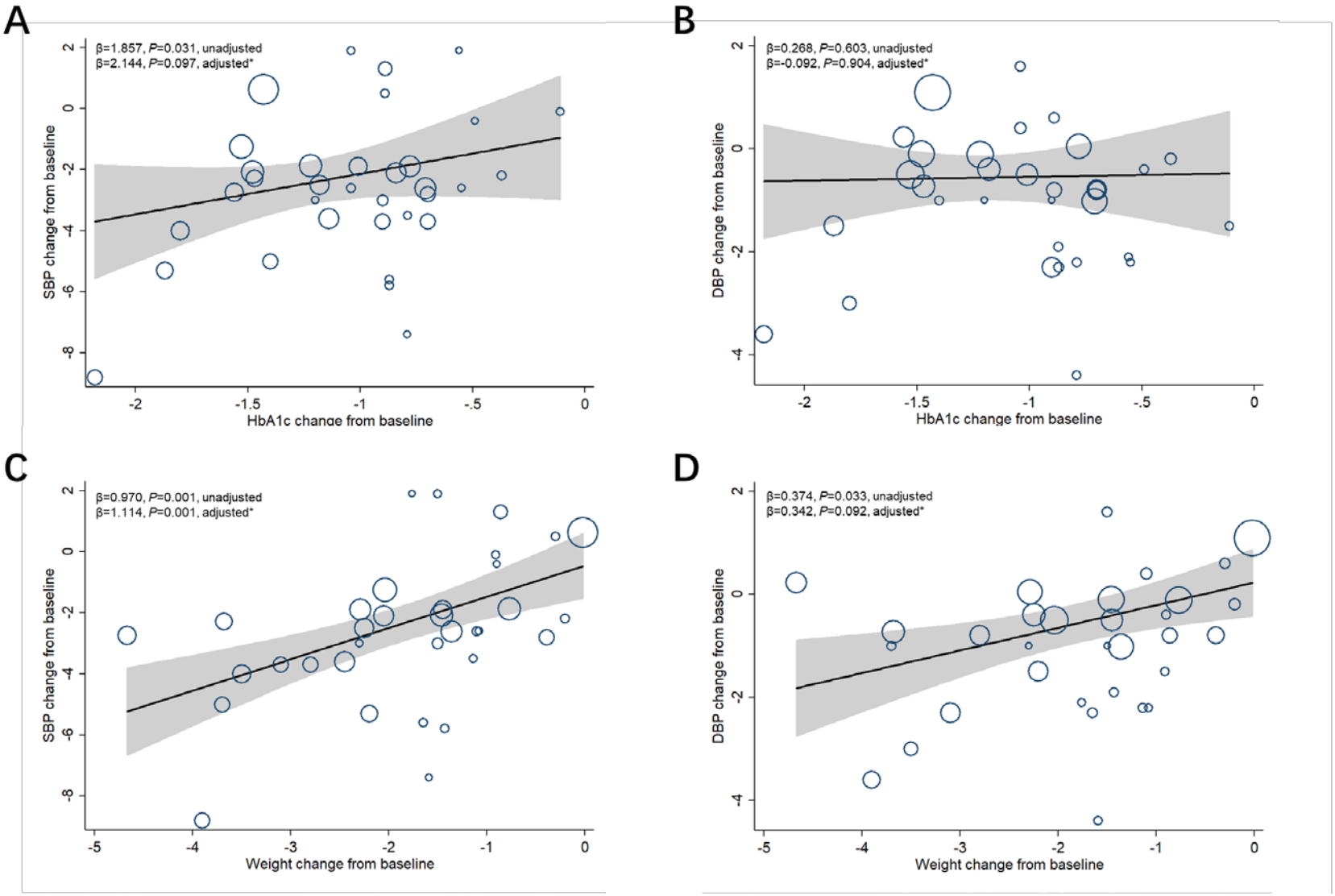
A
β=1.857, P=0.031, unadjusted
β=2.144, P=0.097, adjusted*
SBP change from baseline
HbA1c change from baseline
B
β=0.268, P=0.603, unadjusted
β=-0.092, P=0.904, adjusted*
DBP change from baseline
HbA1c change from baseline
C
β=0.970, P=0.001, unadjusted
β=1.114, P=0.001, adjusted*
SBP change from baseline
Weight change from baseline
D
β=0.374, P=0.033, unadjusted
β=0.342, P=0.092, adjusted*
DBP change from baseline
Weight change from baseline

Figure S3. Meta-regression analysis of the associations between HbA1c reduction or body weight reduction and blood pressure changes in GLP-1RA add-on therapy.

A. Association between HbA1c change from baseline and SBP change from baseline.

B. Association between HbA1c change from baseline and DBP change from baseline.

C. Association between weight change from baseline and SBP change from baseline.

D. Association between weight change from baseline and DBP change from baseline.

The size of circles is proportional to the weight of each study in the meta-regression.

*Analyses were adjusted for age, sex, BMI and duration of diabetes.

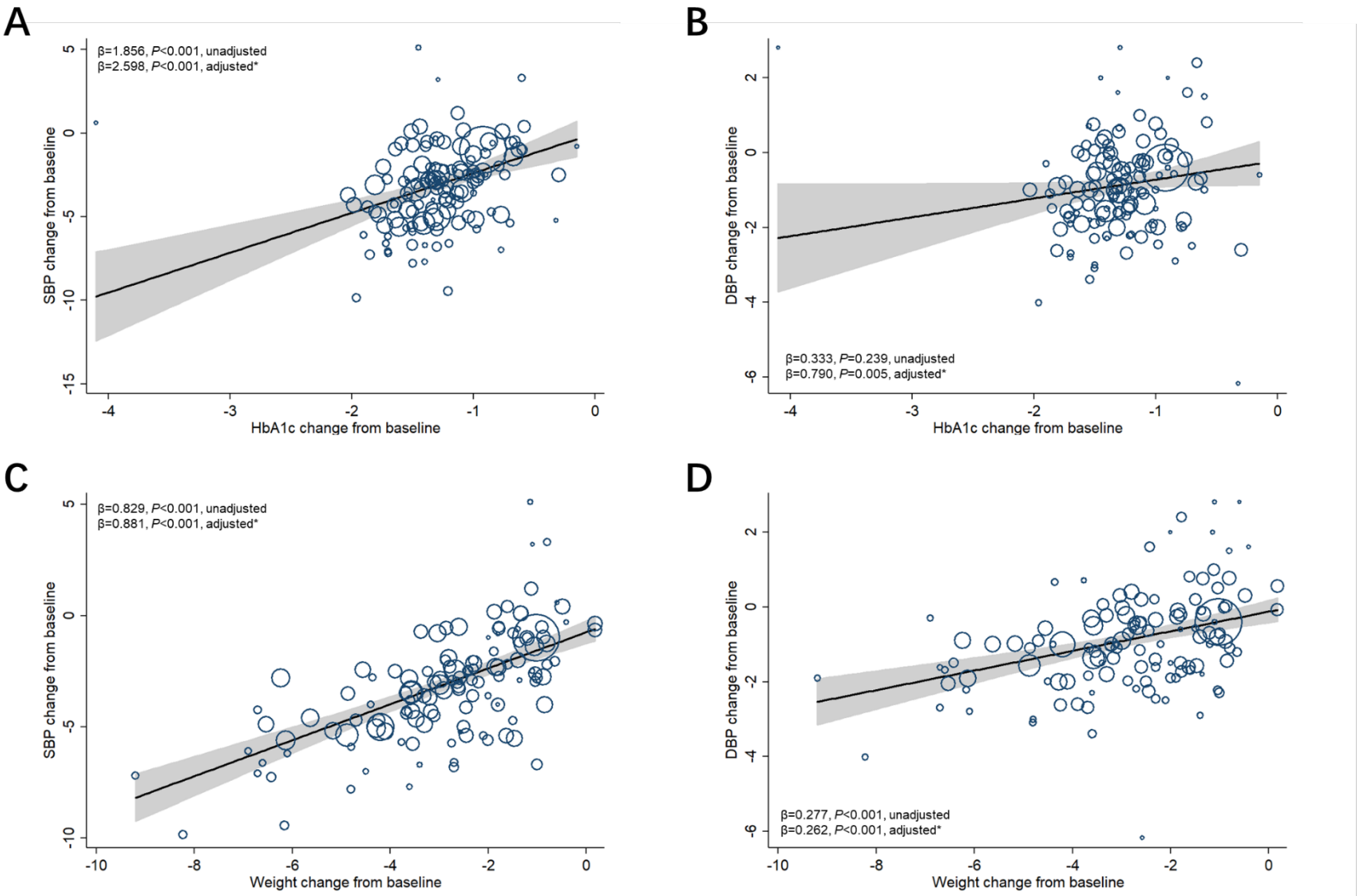
A
β=1.856, P<0.001, unadjusted
β=2.598, P<0.001, adjusted*
SBP change from baseline
HbA1c change from baseline
B
β=0.333, P=0.239, unadjusted
β=0.790, P=0.005, adjusted*
DBP change from baseline
HbA1c change from baseline
C
β=0.829, P<0.001, unadjusted
β=0.881, P<0.001, adjusted*
SBP change from baseline
Weight change from baseline
D
β=0.277, P<0.001, unadjusted
β=0.262, P<0.001, adjusted*
DBP change from baseline
Weight change from baseline

Figure S4. Meta-regression analysis of the associations between HbA1c reduction or body weight reduction and blood pressure changes in placebo-controlled trials in SGLT2i treatment.

A. Association between HbA1c change from baseline and placebo-corrected SBP change from baseline.

B. Association between HbA1c change from baseline and placebo-corrected DBP change from baseline.

C. Association between weight change from baseline and placebo-corrected SBP change from baseline.

D. Association between weight change from baseline and placebo-corrected DBP change from baseline.

The size of circles is proportional to the weight of each study in the meta-regression.

*Analyses were adjusted for age, sex, BMI and duration of diabetes.

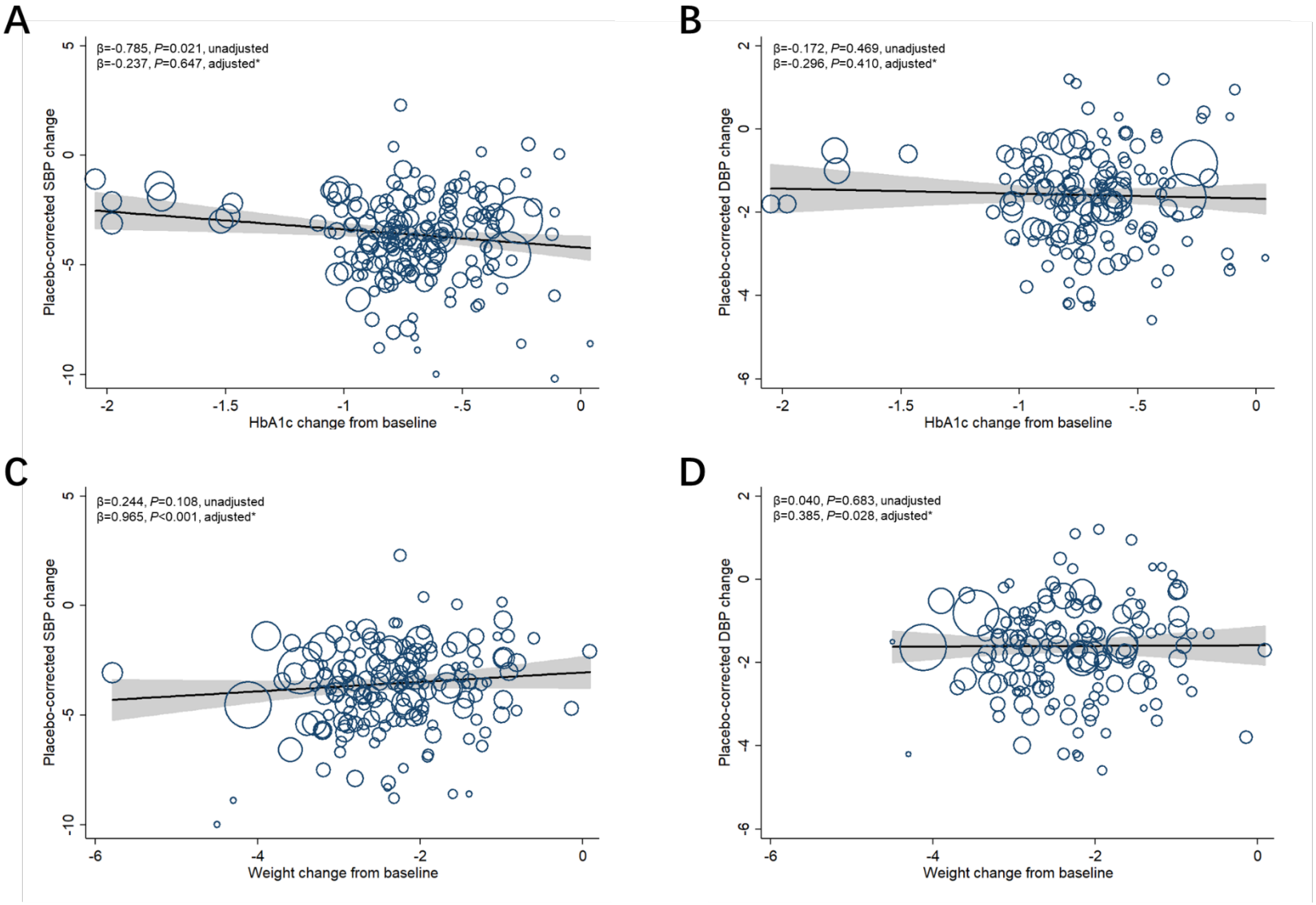
A
β=-0.785, P=0.021, unadjusted
β=-0.237, P=0.647, adjusted*
Placebo-corrected SBP change
HbA1c change from baseline
B
β=-0.172, P=0.469, unadjusted
β=-0.296, P=0.410, adjusted*
Placebo-corrected DBP change
HbA1c change from baseline
C
β=0.244, P=0.108, unadjusted
β=0.965, P<0.001, adjusted*
Placebo-corrected SBP change
Weight change from baseline
D
β=0.040, P=0.683, unadjusted
β=0.385, P=0.028, adjusted*
Placebo-corrected DBP change
Weight change from baseline

Figure S5. Meta-regression analysis of the associations between HbA1c reduction or body weight reduction and blood pressure changes in SGLT2i monotherapy.

A. Association between HbA1c change from baseline and SBP change from baseline.

B. Association between HbA1c change from baseline and DBP change from baseline.

C. Association between weight change from baseline and SBP change from baseline.

D. Association between weight change from baseline and DBP change from baseline.

The size of circles is proportional to the weight of each study in the meta-regression.

*Analyses were adjusted for age, sex, BMI and duration of diabetes.

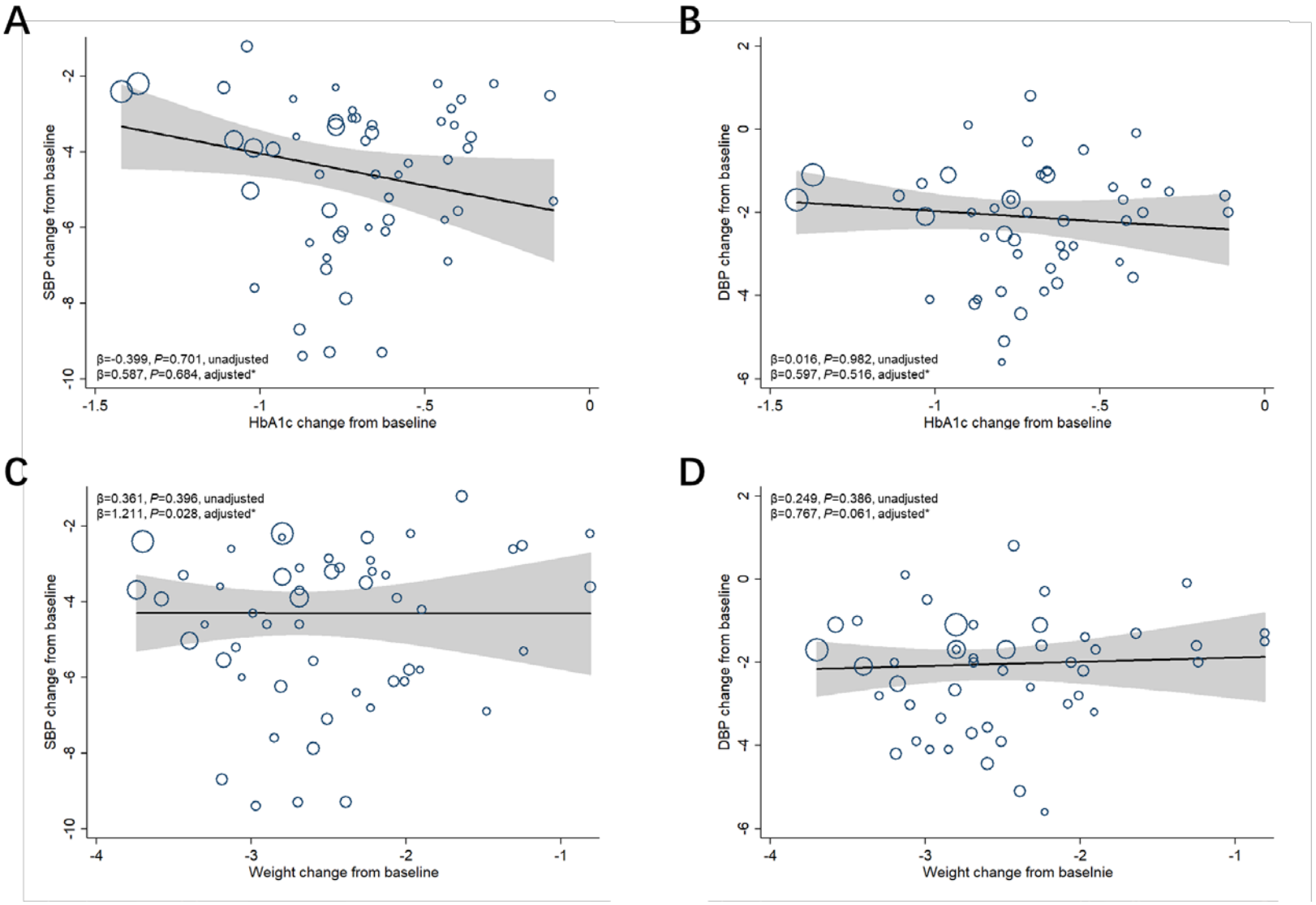
A
SBP change from baseline
-2
-4
-6
-8
-10
β=-0.399, P=0.701, unadjusted
β=0.587, P=0.684, adjusted*
-1.5
-1
-.5
0
HbA1c change from baseline
B
DBP change from baseline
2
0
-2
-4
-6
β=0.016, P=0.982, unadjusted
β=0.597, P=0.516, adjusted*
-1.5
-1
-.5
0
HbA1c change from baseline
C
SBP change from baseline
-2
-4
-6
-8
-10
β=0.361, P=0.396, unadjusted
β=1.211, P=0.028, adjusted*
-4
-3
-2
-1
Weight change from baseline
D
DBP change from baseline
2
0
-2
-4
-6
β=0.249, P=0.386, unadjusted
β=0.767, P=0.061, adjusted*
-4
-3
-2
-1
Weight change from baselnie

Figure S6. Meta-regression analysis of the associations between HbA1c reduction or body weight reduction and blood pressure changes in SGLT2i add-on therapy.

A. Association between HbA1c change from baseline and SBP change from baseline.

B. Association between HbA1c change from baseline and DBP change from baseline.

C. Association between weight change from baseline and SBP change from baseline.

D. Association between weight change from baseline and DBP change from baseline.

The size of circles is proportional to the weight of each study in the meta-regression.

*Analyses were adjusted for age, sex, BMI and duration of diabetes.

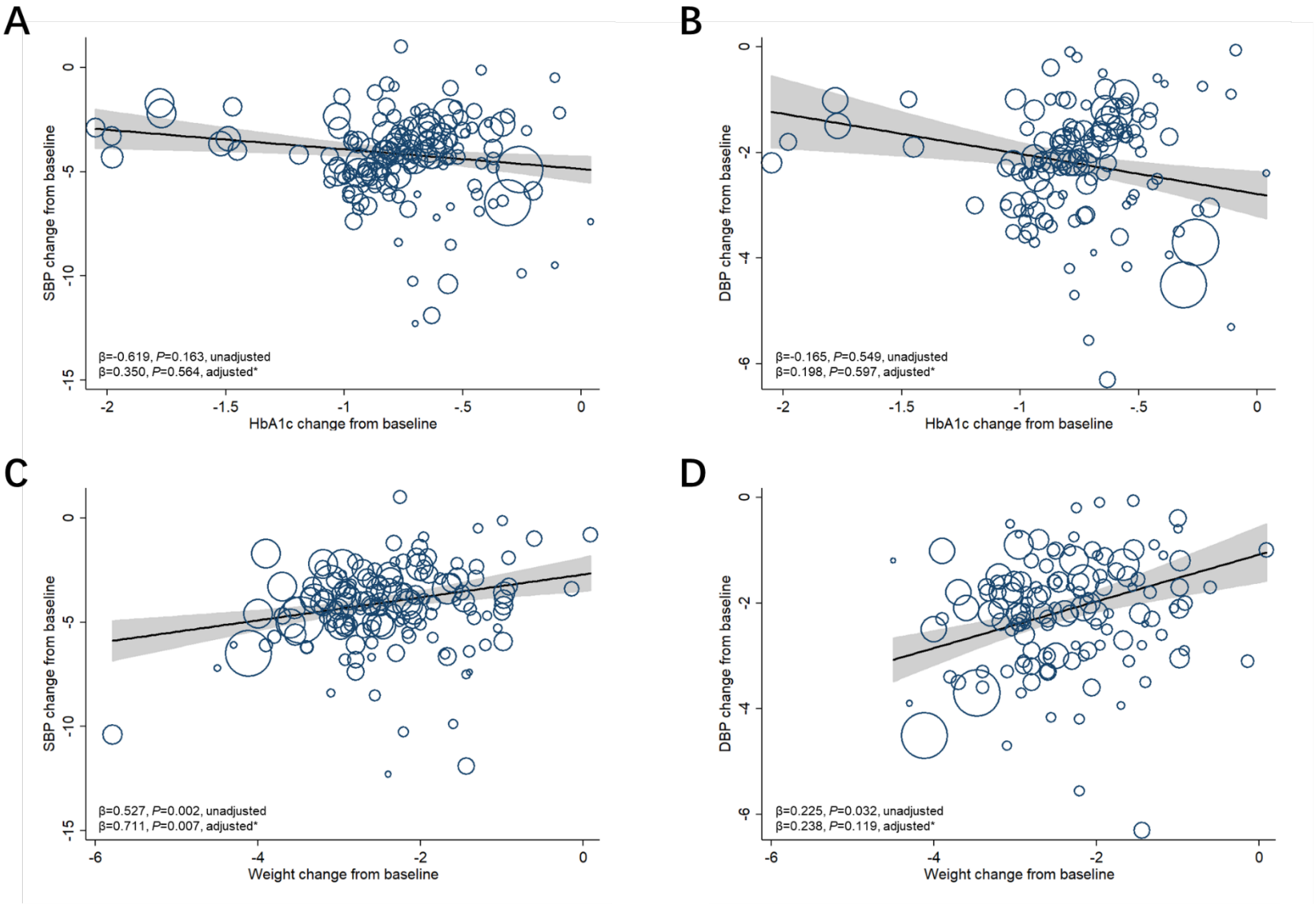
A
SBP change from baseline
0
-5
-10
-15
β=-0.619, P=0.163, unadjusted
β=0.350, P=0.564, adjusted*
-2
-1.5
-1
-.5
0
HbA1c change from baseline
B
DBP change from baseline
0
-2
-4
-6
β=-0.165, P=0.549, unadjusted
β=0.198, P=0.597, adjusted*
-2
-1.5
-1
-.5
0
HbA1c change from baseline
C
SBP change from baseline
0
-5
-10
-15
β=0.527, P=0.002, unadjusted
β=0.711, P=0.007, adjusted*
-6
-4
-2
0
Weight change from baseline
D
DBP change from baseline
0
-2
-4
-6
β=0.225, P=0.032, unadjusted
β=0.238, P=0.119, adjusted*
-6
-4
-2
0
Weight change from baseline

Figure S7. Meta-regression analysis of the associations between body weight reduction and blood pressure changes in all merged data

A. Association between weight change from baseline and SBP change from baseline.

B. Association between weight change from baseline and DBP change from baseline.

The size of circles is proportional to the weight of each study in the meta-regression.

*Analyses were adjusted for age, sex, BMI, duration of diabetes and HbA1c change from baseline.

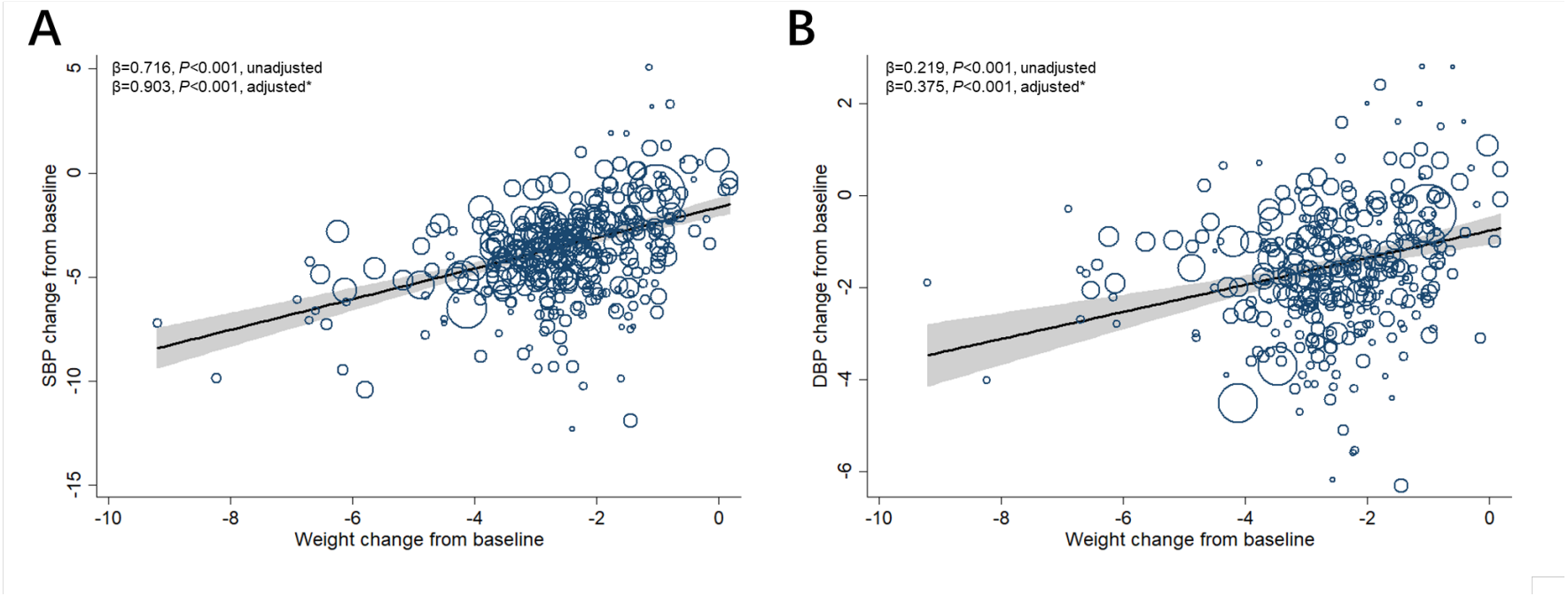

Figure S8. Funnel plot of included studies in GLP-1RA treatment.

Funnel plots of SBP changes (A) and DBP changes (B) in GLP-1RA studies.

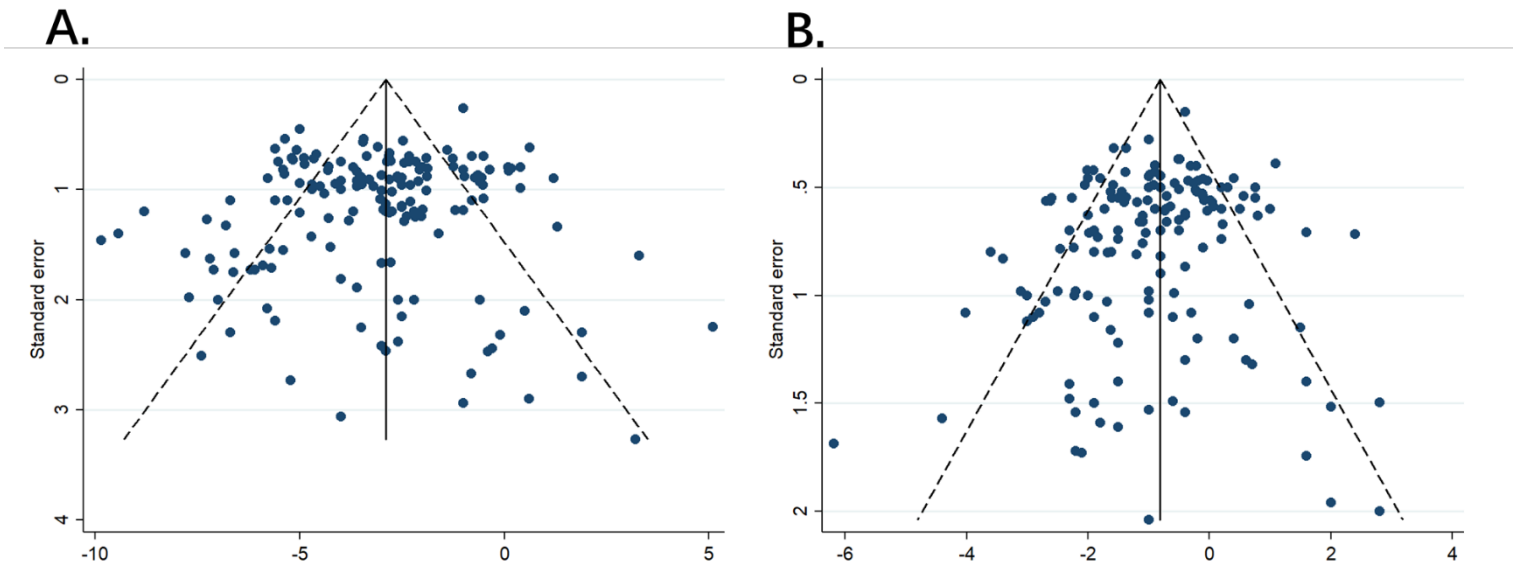

Figure S9. Funnel plot of included studies in SGLT2i treatment.

Funnel plots of SBP changes (A) and DBP changes (B) in SGLT2i studies.